Section: Pharmacology

Original Research Article

A COMPARATIVE STUDY OF SAFETY AND EFFICACY OF METFORMIN WITH GLIMEPIRIDE VS. METFORMIN WITH SITAGLIPTIN IN TYPE 2 DIABETES MELLITUS PATIENTS

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Abstract

Metformin and sulfonylureas (SU) are commonly used oral antidiabetic drugs. However, SUs are associated with a higher incidence of hypoglycemia and weight gain, eventually necessitating transition to alternative agents or insulin therapy. Sitagliptin supplementation in type 2 diabetes has demonstrated sustained benefits in short-, medium-, and long-term biomarkers of metabolic control, along with improvements in low-density lipoprotein cholesterol levels and reduced insulin requirements. Patients aged between 30 and 60 years of both sexes and those taking metformin only, with inadequate glycemic control (HbA1c >7 and <10) were included in the study. Patients were diagnosed based on their Fasting Blood Glucose (FBG) values and patients with above 126 mg/dl and below 250 mg/dl were selected. Fifty patients were randomly assigned to one of the two following groups: Group A: 50 subjects (On Metformin 500 mg + Glimepiride 1 mg), Group B: 50 subjects (On Metformin 500 mg + Sitagliptin 100 mg). Each patient was asked to visit the OP every 2 weeks for a period of 6 months for evaluation and to obtain medication supplies and also to report adverse effects, if any. All patients were followed up for one month after the study to monitor side effects. In this study, 54 patients were males and 46 patients were females, and from these patients, 42 were pre-hypertensive, 34 patients had family history of diabetes and 22 patients had obesity indicating that T2DM may be associated with hypertension, genetic factors and obesity. The mean reduction in FBG in group A was 39 mg/dl and in group B was 42mg/dl. The difference between the two groups was 3 mg/dl during 6 months which was not significant ($p>0.05$).

The mean reduction in HbA1c was 1.3% in 6 months period. The difference between the groups was 0.41% which was significant ($p<0.05$). The body weight increased in group A with a mean increase of 1.7 kg ($p>0.05$) which was not significant. In group B the body weight decreased with a mean change of 2.62 kg ($p<0.05$) with 6 months of therapy which was significant and the mean BMI reduced with a mean change of 1.06 kg/m2 ($p<0.05$) which was also significant. This indicates that metformin 500 mg + sitagliptin 100 mg reduced the BMI. Overall adverse effects occurred in 17 (34%) patients in the group A and in 8 (16%) patients in the group B. 9 patients complained of hypoglycemic symptoms like palpitations and sweating. Among them, 8 (16%) patients belonged to group A and 1 (2%) patient was from group B. No single case of severe hypoglycemia with coma, alteration in mental state, hospitalization or death was reported. Long-term blood glucose control (HbA1c) was better achieved with metformin 500 mg + sitagliptin 100 mg.

INTRODUCTION

Diabetes, a metabolic disorder prevalent worldwide, is responsible for millions of deaths each year.[1] It is characterized by elevated levels of glycated hemoglobin (HbA1c), indicating inadequate glycemic control and an increased risk of cardiovascular disease, nephropathy and

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retinopathy.[2] Effective control of HbA1c levels in patients with type 2 diabetes is crucial for optimizing outcomes and preventing associated complications.[3] The American Diabetes Association recommends keeping HbA1c levels below 7.0% (53 mmol/mol) to mitigate adverse health consequences.[4]

As diabetes progresses, the need for combination therapy often arises due to worsening glycemic control.[5] The treatment landscape for type 2 diabetes mellitus (T2DM) has evolved with the introduction of novel antidiabetic agents, including dipeptidyl peptidase-4 inhibitors (DPP4i), sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 (GLP-1), and more significantly with insulin analogues.[6,7] While DPP4i offers moderate efficacy and a favorable safety profile, sulfonylureas, particularly modern variants such as glimepiride, have long been preferred as effective oral antidiabetic agents due to their efficacy, safety and cost-effectiveness, particularly as the first addition to metformin in Indian clinical settings.[7,8]

Metformin and sulfonylureas (SU) are commonly used oral antidiabetic drugs. However, SUs are associated with a higher incidence of hypoglycemia and weight gain, eventually necessitating transition to alternative agents or insulin therapy.[9,10] Sulfonylureas, including glimepiride, are commonly used to control blood sugar levels but are associated with side effects such as frequent hypoglycemia and weight gain. Dipeptidyl peptidase-4 (DPP-4) inhibitors, which are also incretin-based therapies, have emerged as important adjunctive treatments for type 2 DM, providing efficacy and tolerability when added to metformin therapy.[11] They improve endogenous incretin function and support glucose homeostasis without increasing the risk of hypoglycemia or weight gain.[12]

The addition of sitagliptin, a DPP-4 inhibitor, to the treatment of patients with poorly controlled type 2 diabetes receiving insulin with or without metformin has been shown to reduce HbA1c levels and reduce (or) control the need for insulin therapy.[13] Sitagliptin supplementation in type 2 diabetes has demonstrated sustained benefits in short-, medium-, and long-term biomarkers of metabolic control, along with improvements in low-density lipoprotein cholesterol levels and reduced insulin requirements.[14] Its diverse effects, including anti-inflammatory effects and modulation of monocytes and T lymphocytes, suggest potential beyond glycemic reduction, with additional benefits such as prevention of weight gain, reduced insulin doses and improved cardiovascular risk profiles.[15,16]

While sitagliptin has been compared with various therapies, including pioglitazone, liraglutide, dulaglutide, canagliflozin, glipizide, and glimepiride, a direct comparison of sitagliptin with glimepiride, particularly in the background of metformin combination therapy, has not been widely reported.[17] Our study included patients diagnosed with T2DM who were unable to achieve glycemic control with metformin alone. They received metformin + glimepiride or metformin + sitagliptin according to the inclusion criteria.

MATERIALS AND METHODS

Study Design: This was a prospective, randomized, open-label, interventional study.

Study Location: Outpatient Department, Department of General Medicine, GGH, Guntur, Andhra Pradesh.

Ethics Approval: The study received approval from the Institutional Ethics Committee and informed consent was obtained from all patients in the local language before the study after a detailed explanation of the study procedure. The entire procedure, benefits and likely side effects of the drugs were explained to the patients. The study was noninvasive. The drugs used in the study were safe. They were not life-threatening to the patient and did not pose any serious adverse events and the patients were asked to stop taking the medication immediately if any severe allergic reaction to the medication occurred.

Duration of Study: The study lasted for over a period of one year.

Sampling Method: Consecutive sampling method was used for the study.

Sample size: The sample size was 100 patients who met the study criteria (50 patients in each group).

Inclusion Criteria

Age between 30 and 60 years of both sexes and patients taking metformin only, with inadequate glycemic control (HbA1c >7 and <10). Patients were diagnosed based on their FBG values and patients with FBG above 126 mg/dl and below 250 mg/dl were included in the study.

Exclusion Criteria

Patients with known hypersensitivity to either metformin, glimepiride or sitagliptin, patients with type 1 diabetes mellitus, diabetic ketoacidosis, who have already taken these drugs, with blood pressure > 140/90, participating in another study currently or within the last 6 months, women who are pregnant, breastfeeding or planning to become pregnant during the proposed study period, patients with clinically significant cardiovascular, hepatic, pulmonary, neurological, renal or psychiatric disorders or clinically significant laboratory abnormalities (if laboratory values exceed established thresholds), patients with a history or examination findings of alcohol dependence, alcohol or drug abuse, or suspected abuse were excluded from the study.

Group Allocation: Fifty patients in each group were randomly assigned to one of the following groups:[8,17]

Group A: 50 subjects (On Metformin 500 mg + Glimepiride 1 mg)

Group B: 50 subjects (On Metformin 500 mg + Sitagliptin 100 mg)

Dose: Group ”A” patients received 1 mg of glimepiride along with 500 mg of metformin and group ”B” patients received 100 mg of sitagliptin

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along with 500 mg of metformin. Each patient was asked to come to the OP every 2 weeks for a period of 6 months for evaluation and to obtain medication supplies and to report adverse effects, if any. At each visit, the following data were collected from the enrolled patients. All patients were followed up for one month after the study to monitor side effects.[17]

Parameters Studied: Physical examination (height, weight, general BMI examination), laboratory tests (FBG, HbA1c) were done.

Statistical Analysis: The results of the study were statistically analyzed at the end of 6 months using the paired Student t-test and the significance of the results was tested using a probability value of 0.05. After applying the "t" test, the obtained t-value was compared with the "t" value in the t-table at a probability of 0.05 at 49° degrees of freedom to evaluate whether the results are significant or not.

RESULTS

In this study, 54 patients were males and 46 patients were females, and 42 patients were pre-hypertensive, 34 patients had family history of diabetes and 22 patients had obesity indicating that T2DM may be associated with hypertension, genetic factors and obesity.

Table 1: Age wise distribution in each group.

Age (yrs)	Metformin + Glimepiride (Group A)	Metformin + Sitagliptin (Group B)
41-45	9	13
46-50	14	11
51-55	12	14
56-60	15	12
Total	50	50

The numbers of patients were more in 56-60 years of age group.

Table 2: Gender wise distribution in each group

Sex	Metformin + Glimepiride (Group A)	Metformin + Sitagliptin (Group B)	Total
Males	28(56%)	26(52%)	54(54%)
Females	22(44%)	24(48%)	46(46%)

Table 3: Metabolic Disorders

Metabolic Disorder	Metformin + Glimepiride (Group A)	Metformin + Sitagliptin (Group B)	Total
Pre-hypertension	18(36%)	24(48%)	42(42%)
Family history of diabetes	18(36%)	16(32%)	34(34%)
Obesity	18(36%)	24(48%)	42(42%)

Table 4: Efficacy

Parameter	Metformin + Glimepiride (Group A)			Metformin + Sitagliptin (Group B)		
	Before	After	p-value	Before	After	p-value
FBG (mg/dl)	179.0±22.5	140 ± 20.7	< 0.001	180.4±24.5	138.8± 19.6	< 0.001
HbA1c (%)	7.85±0.75	6.9±0.71	< 0.001	7.9±0.89	6.59±0.6	< 0.001
Bodyweight (Kg)	69.24±7.11	70.94± 7.5	> 0.05	69.92±8.04	67.36±7.44	> 0.05
BMI (kg/m2)	27.9± 2.95	28.29± 3.0	> 0.05	28.66± 3.31	27.6± 3.14	< 0.05

The mean reduction in FBG with metformin 500 mg + glimepiride 1 mg (Group A) was 39 mg/dl during the 6 months of study period. In metformin 500 mg + sitagliptin 100 mg (Group B), the mean reduction in FBG during 6 months of study was 42 mg/dl. The difference between the two groups was 3 mg/dl during 6 months which was not significant (p>0.05). The mean reduction in HbA1c was 1.3% in 6 months period. The difference between both the groups was 0.41% which was significant (p<0.05).

The body weight increased in Group A with a mean increase of 1.7 kg (p>0.05) which was not significant. In Group B the body weight decreased with a mean change of 2.62 (p<0.05) with 6 months of therapy which was significant. This indicates that metformin 500 mg + sitagliptin 100 mg reduced bodyweight.

In Group A, the BMI increased with a mean change of 0.4 kg/m2 (p>0.05) which was insignificant. In Group B, the mean BMI decreased with a mean change of 1.06 kg/m2 (p<0.05) which was significant. This indicates that metformin 500 mg+ sitagliptin 100 mg decreased BMI.

Safety Results:

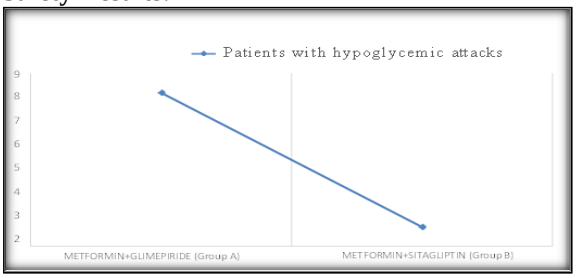

Figure 1: Patients with hypoglycemic attacks in each group

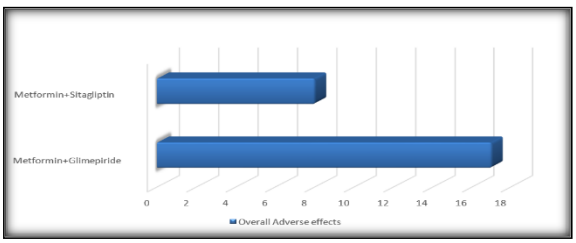

Figure 2: Total treatment related adverse effects in each group

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During the 6-month therapy, both the combinations of drugs were well tolerated. Overall adverse effects occurred in 17 (34%) patients in the metformin + glimepiride group and 8 (16%) patients in the metformin + sitagliptin group. 9 patients complained of hypoglycemic symptoms like palpitations and sweating. Among them, 8 (16%) patients belonged to metformin + glimepiride group and 1(2%) patient was from metformin + sitagliptin group. No single case of severe hypoglycemia with coma, alteration in mental state, hospitalization or death was reported. 9 (18%) patients complained of upper respiratory tract infections and nasopharyngitis in metformin + glimepiride group. 2 (4%) patients reported nausea & headache and 5 (10%) patients complained of dizziness in metformin + sitagliptin group. All adverse effects were transient and patients were given symptomatic treatment without any alteration in the administration of the study treatment.

DISCUSSION

In this study, two drug combinations, namely metformin + glimepiride and metformin + sitagliptin, were selected because glimepiride and metformin are low-cost drugs and are most commonly prescribed in tertiary care hospitals. Although sitagliptin is more expensive, some studies suggest it is safer and more effective than glimepiride.[18] They (metformin, glimepiride) are also readily available. Glimepiride has strong binding properties to the sulfonylurea receptor 1 (SUR1), resulting in rapid association and dissociation dynamics.[8] Beyond its primary action on the pancreas, glimepiride exhibits extra pancreatic activity, alleviating insulin resistance and increasing glucose utilization via glucose transporter 4.[19] This dual mechanism of action provides effective blood sugar control while minimizing the likelihood of hypoglycemia or weight gain. In particular, glimepiride exhibits increased selectivity for β-cell SUR1 receptors, preserving the protective mechanism of ischemic preconditioning.[19] Randomized clinical trials have confirmed that second- and third-generation sulfonylureas, including glimepiride, have no increased risk of all-cause mortality, cardiovascular mortality, myocardial infarction, or stroke. In addition, a meta-analysis comparing sulfonylureas to non-sulfonylurea agents found that glimepiride had the lowest overall mortality rate among all sulfonylureas.[20]

Dipeptidyl peptidase-4 (DPP-4) inhibitors, which are also incretin-based therapies, have emerged as important adjunctive treatments for type 2 DM, providing efficacy and tolerability when added to metformin therapy.[11] They improve endogenous incretin function and support glucose homeostasis without increasing the risk of hypoglycemia or weight gain.[12]

The addition of sitagliptin, a DPP-4 inhibitor, to the treatment of patients with poorly controlled type 2 diabetes receiving insulin with or without metformin has been shown to reduce HbA1c levels and reduce (or) control the need for insulin therapy.[13] Sitagliptin supplementation in type 2 diabetes has demonstrated sustained benefits in short-, medium-, and long-term biomarkers of metabolic control, along with improvements in low-density lipoprotein cholesterol levels and reduced insulin requirements.

The results of this study highlight the comparative safety and effectiveness of combination therapies of metformin with both sitagliptin and glimepiride. Over a six-month period, both treatment regimens resulted in significant reductions in fasting blood glucose (FBG) levels in the 100 participants. Importantly, these therapeutic interventions were well tolerated and fewer adverse events were reported in the metformin + sitagliptin group compared to the metformin + glimepiride group. Notably, the incidence of hypoglycemic symptoms was lower in the sitagliptin group, indicating a superior safety profile of this treatment modality. These results are consistent with previous research, as reported by Xiao, et al,[21] which also observed a lower incidence of symptomatic hypoglycemia and fewer side effects in patients who received sitagliptin compared to those who received glimepiride. Furthermore, the greater reduction in body weight observed in the sitagliptin group underlines the favorable safety profile compared to glimepiride.

Furthermore, our study showed a more significant decrease in HbA1c levels in the sitagliptin group compared to the glimepiride group, which is consistent with the results of studies by J Kesavadev, et al.[17] This suggests that sitagliptin provides better glycemic control compared to glimepiride and may reduce the risk of long-term complications associated with poorly controlled diabetes. In contrast to some previous studies that reported comparable safety profiles and efficacy between glimepiride and sitagliptin, our results indicate a clear discrepancy.

In particular, glimepiride was associated with a higher incidence of adverse events and a less pronounced reduction in HbA1c levels compared to sitagliptin in our study. This discrepancy may be due to differences in study design, patient demographics, or duration of treatment, highlighting the need for further investigation.

The results of this study support the preferred use of metformin + sitagliptin as a treatment regimen for patients with type 2 diabetes, providing superior glycemic control, fewer side effects, and potential benefits such as weight loss. However, additional research, including large-scale clinical trials with extended follow-up periods, is needed to validate these results and elucidate the long-term effects of these treatment modalities on diabetic complications and patient outcomes. Such comprehensive examinations will help to optimize therapeutic strategies and improve quality.

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CONCLUSION

Long-term blood glucose control (HbA1c) was better achieved with metformin + sitagliptin. Because diabetes is a long term, chronic disease, metformin + sitagliptin may be preferable to metformin + Glimepiride.

REFERENCES

1. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of Type 2 diabetes - globalburden of disease and forecastedtrends. J Epidemiol Glob Health. 2020 Mar;10(1):107-11. doi: 10.2991/jegh.k.191028.001, PMID 32175717, PMCID PMC7310804.
2. Bash LD, Selvin E, Steffes M, Coresh J, Astor BC. Poor glycemic control in diabetes and the risk of incident chronic kidney disease even in the absence of albuminuria and retinopathy: Atherosclerosis Risk in Communities (ARIC) Study. Arch Intern Med.2008 Dec 8;168(22):2440-7.doi: 10.1001/archinte.168.22.2440, PMID 19064828.
3. Sugandh F, Chandio M, Raveena F, Kumar L, Karishma F, Khuwaja S et al.Advances in the management of diabetes mellitus: A focus on personalizedmedicine. Cureus. 2023 Aug 18;15(8):e43697. doi: 10.7759/cureus.43697, PMID 37724233, PMCID PMC10505357.
4. Sherwani SI, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c test in diagnosis and prognosis of diabeticpatients. Biomark Insights. 2016 Jul 3;11:95-104. doi: 10.4137/BMI.S38440, PMID 27398023, PMCID PMC4933534.
5. Xie X, Wu C, Hao Y, Wang T, Yang Y, Cai P et al.Benefits and risks of drug combination therapy for diabetes mellitus and its complications: a comprehensive review. Front Endocrinol (Lausanne). 2023 Dec 19;14:1301093. doi: 10.3389/fendo.2023.1301093, PMID 38179301, PMCID PMC10766371.
6. Deacon CF. Dipeptidyl peptidase 4 inhibitors in the treatment of type 2 diabetes mellitus. Nat Rev Endocrinol.2020 Nov;16(11):642-53. doi: 10.1038/s41574-020-0399-8. PMID 32929230.
7. Yin R, Xu Y, Wang X, Yang L, Zhao D. Role of dipeptidyl peptidase 4inhibitors in antidiabetictreatment. Molecules. 2022 May 10;27(10):3055. doi: 10.3390/molecules27103055, PMID 35630534, PMCID PMC9147686.
8. Devarajan TV, Venkataraman S, Kandasamy N, Oomman A, Boorugu HK, Karuppiah SKP et al.Comparative evaluation of safety and efficacy of glimepiride and sitagliptin in combination with metformin in patients with type 2 diabetes mellitus: Indian multicentricrandomized trial - START study. Indian J Endocrinol Metab.2017 Sep-Oct;21(5):745-50. doi: 10.4103/ijem.IJEM_176_17, PMID 28989886, PMCID PMC5628548.
9. Scheen AJ. Sulphonylureas in the management of type 2 diabetes: to be or not to be? Diabetes Epidemiol Manag. 2021;1:100002. doi: 10.1016/j.deman.2021.100002.
10. Kalra S, Bahendeka S, Sahay R, Ghosh S F, Orabi A, Ramaiya K, Al Shammari S, Shrestha D, etal., Consensus Recommendations on Sulfonylurea and Sulfonylurea Combinations in the Management of Type 2 Diabetes Mellitus - International Task Force. Indian J Endocrinol Metab. 2018;22(1):132-157. doi: 10.4103/ijem.IJEM_556_17. PMID: 29535952; PMCID: PMC5838894.
11. Sola D, Rossi L, Schianca GP, Maffioli P, Bigliocca M, Mella R et al.Sulfonylureas and their use in clinical practice. Arch Med Sci.2015 Aug 12;11(4):840-8. doi: 10.5114/aoms.2015.53304. PMID 26322096, PMCID PMC4548036.
12. Kim W, Egan JM. The role of incretins in glucosehomeostasis and diabetestreatment. Pharmacol Rev.2008 Dec;60(4):470-512.doi: 10.1124/pr.108.000604, PMID 19074620.
13. Shankar RR, Bao Y, Han P, Hu J, Ma J, Peng Y et al.Sitagliptin added to stable insulin therapy with or without metformin in Chinese patients with type 2 diabetes. J Diabetes Investig.2017 May;8(3):321-9. doi: 10.1111/jdi.12585. PMID 27740719, PMCID PMC5415484.
14. Giampietro O, Giampietro C, Bartola LD, Masoni MC, Matteucci E. Sitagliptin as add-on therapy in insulin deficiency: biomarkers of therapeutic efficacy respond differently in type 1 and type 2 diabetes. Drug Des Devl Ther.2013;7:99-104. doi: 10.2147/DDDT.S38346. PMID 23439744, PMCID PMC3576885.
15. Lee YS, Jun HS. Anti-inflammatoryeffects of GLP-1-basedtherapies beyond glucosecontrol. Mediators Inflamm.2016;2016:3094642. doi: 10.1155/2016/3094642. PMID 27110066, PMCID PMC4823510.
16. Tsalamandris S, Antonopoulos AS, Oikonomou E, Papamikroulis GA, Vogiatzi G, Papaioannou S et al.The role of inflammation in diabetes: currentconcepts and futureperspectives. Eur Cardiol.2019 Apr;14(1):50-9. doi: 10.15420/ecr.2018.33.1, PMID 31131037, PMCID PMC6523054.
17. Kesavadev J, Babu Sadasivan Pillai P, Shankar A, Krishnan G, Jothydev S. SITAGLIPTIN 100 MG VS. Glimepiride 1-3 MG asan ADD-ON toinsulinandmetforminin TYPE 2 diabetes. Endocrine connections publish [ahead of print], published on Oct 5, 2017 as doi:10.1530/EC-17-0100.
18. Srivastava S, Saxena GN, Keshwani P, Gupta R. Comparing the efficacy and safety profile of sitagliptin versus glimepiride in patients of type 2 diabetes mellitus inadequately controlled with metformin alone. J Assoc Physicians India. 2012 Mar;60:27-30. PMID 22799111.
19. Basit A, Riaz M, Fawwad A. Glimepiride: evidence-based facts, trends, and observations (GIFTS). [corrected]. Vasc Health Risk Manag.2012;8:463-72. doi: 10.2147/HIV.S33194. Erratum in: Vasc Health Risk Manag.2013;9:1. PMID 23028231, PMCID PMC3448454
20. Rados DV, Pinto LC, Remonti LR, Leitão CB, Gross JL. Correction: The Association between Sulfonylurea Use and All-Cause and Cardiovascular Mortality: a Meta-Analysis with Trial Sequential Analysis of Randomized Clinical Trials. PLOS MedPLOS Med. 2016;13(6):e1002091. doi: 10.1371/journal.pmed.1002091. PMID 27340828'
21. Dong Xiao lei. et al. Effect of fasting plasma glucose level on red blood cell deformation and immune function in type 2 diabetic patients. Chin J Diabetes. 2015;23:827-31.

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