https://ijpp.com

Indian Journal of Physiology and Pharmacology

Article in Press

Original Article

Comparing the efficacy and safety of sitagliptin versus glimepiride in combination with metformin in geriatric type 2 diabetes mellitus patients

Keerthi Rajan[1], Zoya Khan[1], Gargi Gupta[1], Kauser Usman[2], Kamal Kumar Sawlani[2], Wahid Ali[3], Sartaj Hussain[4], Suyog Sindhu[1], Rakesh Kumar Dixit[1]

Departments of [1]Pharmacology and Therapeutics, [2]Medicine, [3]Pathology, King George's Medical University, Lucknow, Uttar Pradesh, [4]Department of Pharmacology, All India Institute of Medical Sciences, Jammu, Jammu and Kashmir, India.

***Corresponding author:**
Keerthi Rajan,
Department of Pharmacology and Therapeutics, King George's Medical University, Lucknow, Uttar Pradesh, India.

drkeerthirajanmkgmu@gmail.com

Received: 19 September 2025
Accepted: 25 September 2025
Epub Ahead of Print: 26 February 2026
Published:

DOI
10.25259/IJPP_598_2025

Quick Response Code:

ABSTRACT

Objectives: Type 2 diabetes mellitus (T2DM) is a growing public health concern, particularly among the geriatric population, where disease management becomes complex due to age-related physiological changes and comorbidities. Although metformin remains the first-line therapy, additional agents such as sulfonylureas (e.g. glimepiride) and Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. sitagliptin) are often required for adequate glycaemic control. This study aims to evaluate and compare the safety and efficacy of sitagliptin and glimepiride as add-on therapies to metformin in elderly patients with T2DM from the North Indian population.

Materials and Methods: This randomised, prospective, interventional, active-controlled study was conducted over 1 year at King George's Medical University, Lucknow, following ethical approval. A total of 60 geriatric patients (≥60 years) with newly diagnosed or uncontrolled T2DM on metformin were randomised into two groups: Group A received metformin (500 mg BD) + glimepiride (1 mg OD), and Group B received metformin (500 mg BD) + sitagliptin (100 mg OD). Baseline and follow-up evaluations were conducted at 4, 8 and 12 weeks, assessing clinical and biochemical parameters including glycated hemoglobin (HbA1c), fasting blood glucose (FBG), lipid profile, weight, body mass index (BMI) and blood pressure (BP). Statistical analyses included Chi-square test, unpaired *t*-tests and Mann–Whitney U-test.

Results: Both treatment groups showed significant improvements in glycaemic parameters over 12 weeks. However, the reduction in HbA1c was not significantly different between the groups ($P = 0.7$). While reductions in FBG were observed in both groups, the intergroup difference was not statistically significant. Lipid profile parameters remained largely unchanged in both groups, though a non-significant trend toward improved low-density lipoprotein-cholesterol levels was seen in the sitagliptin group ($P = 0.15$). Notably, the sitagliptin group maintained significantly lower weight and BMI throughout the study ($P < 0.001$ at all time points). No significant differences were observed in systolic or diastolic BP. Safety evaluation was limited due to the lack of time.

Conclusion: Sitagliptin, when combined with metformin, demonstrated better weight management compared to glimepiride in elderly patients with T2DM, with no significant impact on other parameters. These findings support the preferential use of sitagliptin over glimepiride as an add-on therapy to metformin in geriatric T2DM patients, particularly for those at risk of comorbidities. Further long-term studies are warranted to validate these results and assess safety profiles comprehensively.

Keywords: Combination, Diabetes mellitus, Dipeptidyl-peptidase IV inhibitors, Drug therapy, Geriatric, Glimepiride, Glycated haemoglobin A, Hypoglycaemia, Metformin, Sitagliptin, Sulphonylurea compounds, Type 2

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterised by persistent hyperglycaemia, resulting from insulin resistance and impaired pancreatic beta-cell function.[1] It has become a major global health issue, strongly associated with ageing, sedentary lifestyles and obesity. In India, T2DM affects approximately 9.3% of the population, with prevalence rising to about 14% in individuals over 60 years of age. Globally, over 460 million people live with diabetes, and this number is expected to surpass 700 million by 2045.[2] In India alone, nearly 77 million individuals are affected.[3,4] As the elderly population continues to grow, the burden of T2DM in this demographic is expected to increase significantly.[5,6]

Managing T2DM in older adults is particularly challenging due to late diagnosis, the presence of multiple comorbidities and age-related physiological changes such as reduced renal function and heightened sensitivity to medications.[7] Treatment strategies must balance glycaemic control with the minimisation of adverse effects such as hypoglycaemia and weight gain, which are more dangerous in elderly individuals.[8] Pathophysiologically, T2DM develops through a combination of insulin resistance and beta-cell dysfunction, with additional contributions from impaired incretin activity, notably the Glucagon-like peptide-1 (GLP-1) pathway.[9] Chronic hyperglycaemia leads to serious complications, making early and effective treatment crucial.[10] Metformin is the first-line therapy for T2DM due to its efficacy, affordability and safety.[11] However, many patients require additional medications, such as sulfonylureas (e.g. glimepiride) or DPP-4 inhibitors (e.g. sitagliptin), when metformin alone is insufficient. Glimepiride stimulates insulin secretion but carries a higher risk of hypoglycaemia and weight gain, especially in elderly patients.[12] In contrast, sitagliptin enhances incretin activity, improving glucose control with a lower risk of hypoglycaemia and weight neutrality.[13]

Combination therapies are commonly used to enhance glycaemic control and improve adherence. While glimepiride with metformin remains effective and affordable, the risk of hypoglycaemia is a concern. Sitagliptin with metformin offers a safer alternative for elderly patients, reducing the risk of hypoglycaemia and avoiding weight gain.[14,15] Overall, individualised treatment approaches are essential for elderly T2DM patients, prioritising both efficacy and safety. Comparative studies between glimepiride-metformin and sitagliptin-metformin combinations are vital to optimise therapeutic strategies and improve outcomes in the geriatric population.[16]

MATERIALS AND METHODS

This is an age- and sex-matched randomised, prospective, interventional, active-controlled study with parallel group assignment. The study was started after ethical clearance from the Institutional Ethics Committee, KGMU (Ref code: XXIII–PGTSC-IIA/P13). The duration of the study was 1 Year. The work was conducted in the Department of Pharmacology and Therapeutics in collaboration with the Department of Medicine, King George's Medical University, Lucknow. Patients registered in the outpatient department of the Department of Medicine, King George's Medical University, Lucknow, who are diagnosed to be a case of T2DM as defined by the International Diabetes Federation (IDF).[17]

Sample size

There is no such kind of data published on comparative efficacy of sitagliptin and glimepiride as add-on therapy to metformin in geriatric type 2 diabetes mellitus patients, so assuming a pilot study, we take a sample size of 30 for each group, based on the sample size calculation by Lancaster, Dodd and Williamson for a pilot study.[18]

Inclusion criteria

Patients with >60 year of age, newly diagnosed patients with T2DM as defined by the IDF guidelines 2021, patients who either newly diagnosed/drug naïve T2DM patients, patients with uncontrolled T2DM on metformin monotherapy (fasting plasma glucose level of ≥126 mg/dL and ≤200 mg/dL and/or 2 h postprandial plasma glucose ≥200 mg/dL and/or glycosylated haemoglobin [HbA1c] levels ≥7.5% and ≤10% at screening) and willing to give written informed consent were included in the study.

Exclusion criteria

Patient not willing to give informed consent, patients with type I diabetes mellitus, patients with history of hypersensitivity to any of the used drugs, pregnant and lactating females, cardiac failure patients, liver and kidney dysfunction or severe anaemia patients, patients requiring insulin for glycaemic control and/or history of insulin usage during 3 months preceding enrolment and patients with serious cardiovascular disease (NYHA class I-IV CHF or history of MI or stroke) or cerebrovascular conditions within 6 months before enrolment were excluded from the study.

- Group A (n = 30): Patients receiving METFORMIN 500 mg BD + GLIMEPIRIDE 1 mg O.D.
- Group B (n = 30): Patients receiving METFORMIN 500 mg BD + SITAGLIPTIN 100 mg O.D.

Study method

After taking written informed consent, patients were enrolled in the study. Socio-demographic details of the patients, such as age, gender, marital status, socio-economic status, family history of diabetes, duration of diabetes, treatment history of patients, comorbidities and complications, were recorded in the case record form. Investigations done related to the study were recorded in the investigation record form.

Biochemical estimation

Patients were called after overnight fasting, and 5 mL of venous blood was drawn from the antecubital vein by a standard venepuncture method and divided into three parts. One part (1.5 mL) was kept in a fluoride vial for fasting glucose estimation, the second part (1.5 mL) was kept in a K3 Ethylenediaminetetraacetic acid vial, and the third part (2 mL) was kept in a plain vial. Patient name, patient ID, age, sex and date of the collection were noted on each vial. Fasting plasma glucose, HbA1c and lipid profile estimation were done.

Follow-up

Patients were followed up for 12 weeks. The primary outcome measure is change in HbA1c (at baseline, 12 weeks). The secondary outcome measures are change in fasting blood glucose (FBG), total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), weight, body mass index (BMI) and systolic and diastolic blood pressure (BP) (at baseline, 4 weeks, 8 weeks and 12 weeks).

Statistical analysis

Data were entered in Excel and analysed using STATA version 14.2, and graphs were depicted using Microsoft Excel/Statistical Package for the Social Sciences. Continuous variables such as the HbA1C and liver function test (LFT) values were summarised as Mean ± Standard deviation or median with interquartile range based on normality. Categorical variables were summarised as proportions along with a 95% confidence interval. Chi-square test was used to compare the outcomes across the study groups. Comparison of continuous variables across both the groups was done using an unpaired *t*-test or Mann–Whitney U-test based on normality. An additional difference in difference analysis was done to compare across the groups. $P < 0.05$ was considered statistically significant.

RESULTS

This 12-week randomised controlled trial investigated the efficacy and safety of sitagliptin versus glimepiride, both in combination with metformin, in geriatric patients (≥60 years) with type 2 diabetes mellitus (T2DM). A total of 60 participants were equally randomised into two treatment groups: Sitagliptin (100 mg once daily) plus metformin (stable dose) and glimepiride (1 mg daily) plus metformin (stable dose). Baseline characteristics, including age and gender distribution, were well-matched between the two groups, ensuring a robust comparative analysis [Table 1].

Demographic characteristics

The primary efficacy outcome, HbA1c [Table 2] demonstrated a statistically significant reduction in both groups [Figure 1]; however, difference in difference analysis between groups showed that the change between groups is not significant ($P = 0.7$).

While both groups showed a reduction in FBG [Table 3] over the study period, the differences between the groups were not statistically significant at any time point [Figure 2]. Regarding lipid profiles, no statistically significant differences were observed between the two treatment groups in total cholesterol [Figure 3 and Table 4], triglycerides, HDL-cholesterol, LDL-cholesterol (LDL-C), or VLDL-cholesterol levels throughout the 12-week study.

Table 1: Demographic characteristics

Characteristics	Glimepiride+ Metformin (*n*=30) Frequency (%)	Sitagliptin+ Metformin (*n*=30) Frequency (%)	*P*-value
Age			
61–70	23 (50.0)	23 (50.0)	1.00
>70	7 (50.0)	7 (50.0)	
Sex			
Male	11 (45.8)	13 (54.2)	0.60
Female	19 (52.8)	17 (47.2)	
Residence			
Rural	12 (40.0)	5 (16.7)	0.04
Urban	18 (60.0)	25 (83.3)	
Physical activity			
Yes	14 (46.7)	13 (43.3)	0.79
No	16 (53.3)	17 (56.7)	
Diet			
Mixed	21 (70.0)	13 (43.3)	0.03
Veg	9 (30.0)	17 (56.7)	

P-value was calculated using chi-square test and < 0.05 is considered statistically significant.

Table 2: HbA1c distribution across the study groups.

Characteristic	Glimepiride+ Metformin	Sitagliptin+ Metformin	*P*-value
Baseline	7.9±0.5	7.4±0.3	<0.001
Week 12	7.1±0.4	6.6±0.2	<0.001
Change in HbA1C	0.79±0.12	0.80±0.15	0.7

P-value was calculated using unpaired t-test and <0.05 is considered statistically significant. HbA1C: Glycated hemoglobin

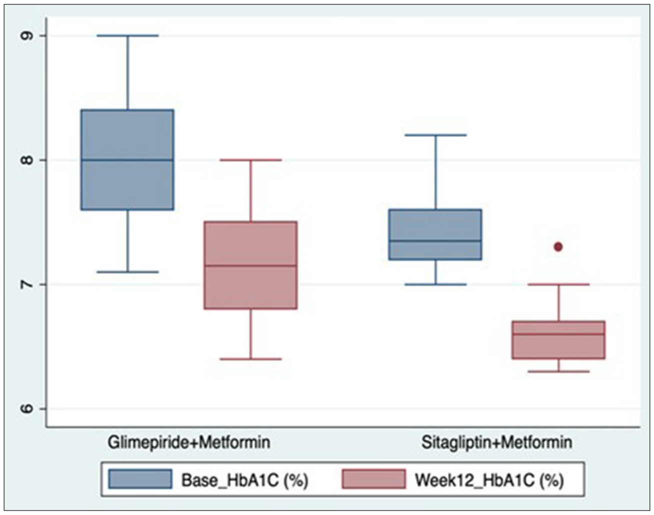

Figure 1: HbA1c distribution. Red dot indicates outlier.

Table 3: Fasting blood glucose distribution.

Characteristic	Glimepiride+ Metformin	Sitagliptin+ Metformin	*P*-value
Baseline	126.3±30.3	125.4±16.4	0.88
Week 4	118.8±28.1	116.8±15.5	0.72
Week 8	112.4±25.2	111±14.7	0.78
Week 12	106.3±22.6	105.9±14.1	0.94

P-value was calculated using unpaired t-test and <0.05 is considered statistically significant.

Table 4: Total cholesterol distribution.

Characteristic	Glimepiride+ Metformin	Sitagliptin+ Metformin	*P*-value
Baseline	132.0±28.9	136.2±50.6	0.69
Week 4	131.1±28.7	130.6±45.9	0.96
Week 8	130.3±28.5	128.0±44.7	0.81
Week 12	129.2±28.6	120.9±34.4	0.31

P-value was calculated using unpaired t-test and <0.05 is considered statistically significant.

Table 5: Weight distribution.

Characteristic	Glimepiride+ Metformin	Sitagliptin+ Metformin	*P*-value
Baseline	75.49±5.78	66.23±9.86	<0.001
Week 4	75.86±5.78	65.61±9.56	<0.001
Week 8	76.14±5.96	65.28±9.42	<0.001
Week 12	76.45±6.07	64.95±9.30	<0.001

P-value was calculated using unpaired t-test and <0.05 is considered statistically significant.

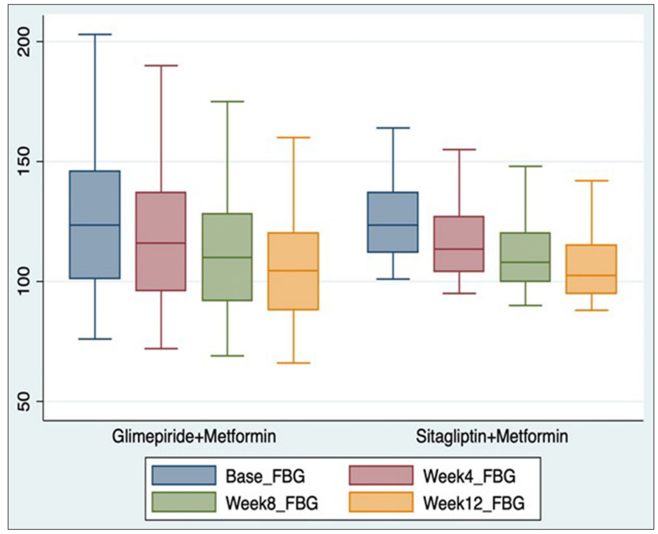

Figure 2: Fasting blood glucose (FBG) distribution.

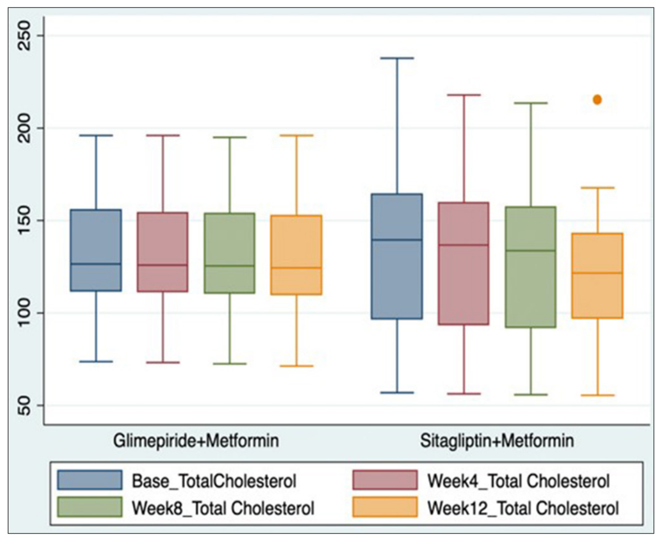

Figure 3: Total cholesterol distribution. Orange dot indicates outlier.

Table 6: Body mass index distribution.

Characteristic	Glimepiride+ Metformin	Sitagliptin+ Metformin	*P*-value
Baseline	26.56±1.97	24.64±3.39	0.009
Week 4	26.71±1.97	24.39±3.33	0.002
Week 8	26.80±2.03	24.28±3.27	0.001
Week 12	26.93±2.08	24.16±3.26	<0.001

P-value was calculated using unpaired t-test and <0.05 is considered statistically significant.

Interestingly, significant differences were observed in weight [Table 5] and BMI [Table 6]. The sitagliptin + metformin group maintained a lower mean weight and BMI throughout the study, with statistically significant differences at all time points ($P < 0.001$). Systolic and diastolic BP did not differ [Figures 4 and 5].

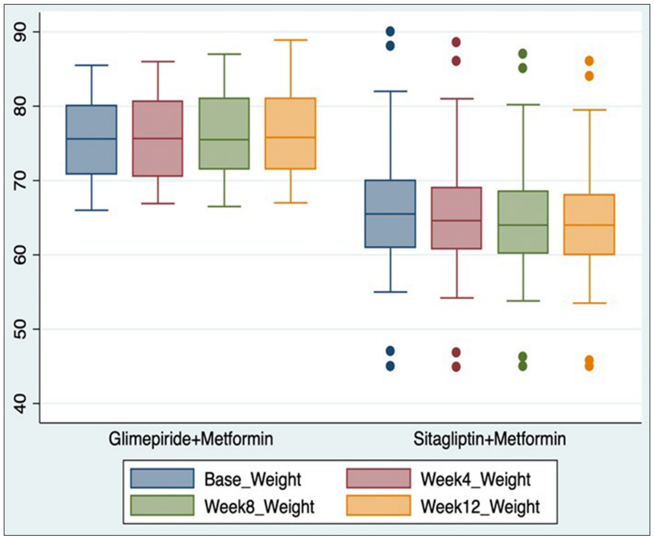

Figure 4: Body weight distribution. Dots indicate outliers.

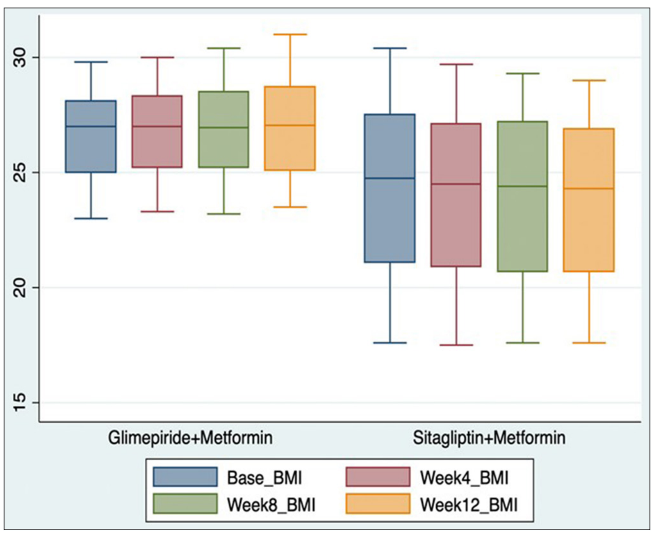

Figure 5: Body mass index (BMI) distribution.

DISCUSSION

Diabetes mellitus remains a major global health issue, with India at its epicentre. Effective T2DM management requires a combination therapy targeting both insulin resistance and beta-cell dysfunction. Metformin remains the first-line agent, but when additional control is needed, sulfonylureas like glimepiride are widely used, particularly in India, despite the availability of newer agents.[13] Our study demonstrated a reduction in HbA1c [Figure 1] with both sitagliptin + metformin and glimepiride + metformin in the geriatric population; however, there is not much difference between the groups. Furthermore, the significant results with weight and BMI align with previous studies and meta-analyses, which have shown that DPP-4 inhibitors like sitagliptin provide comparable glycaemic control to sulfonylureas but with significantly lower risks of weight gain.[19] Trials by Arechavaleta *et al*. and Bourdel-Marchasson *et al*. also support these findings, highlighting sitagliptin's safer profile in older adults.[20,21] FBG changes were not significantly different between groups. Lipid profiles remained stable in both groups, consistent with the generally neutral metabolic effects of DPP-4 inhibitors and sulfonylureas.[19] The significant difference observed in weight and BMI-favouring the sitagliptin group-is consistent with literature showing sulfonylurea-induced weight gain and the weight-neutral or modest weight loss effects associated with sitagliptin.[21] There were no significant differences in systolic or diastolic BP between groups, aligning with the neutral cardiovascular profile typically observed with these drug classes. Sitagliptin improves glucose homeostasis by enhancing glucose-dependent insulin secretion and suppressing glucagon, leading to lower hypoglycaemia risk and better postprandial control. In contrast, glimepiride stimulates insulin release regardless of glucose levels, increasing the risk of hypoglycaemia and weight gain. Overall, our study supports the use of sitagliptin over glimepiride as a safer, effective second-line agent in combination with metformin for elderly T2DM patients, emphasising better HbA1c control, lower hypoglycaemia risk and avoidance of weight gain without significant impacts on lipid profiles or BP. Limitations of our study include the relatively short duration of 12 weeks limits the assessment of long-term efficacy and safety. The sample size of 60 due to pilot study participants may limit the statistical power to detect smaller but potentially clinically significant differences in some parameters, such as lipid profiles and BP. The study lacks detailed information on adverse events like hypoglycaemia due to shorter duration and a smaller sample size, which is crucial for a comprehensive safety comparison. A more robust study with a larger sample size may give more reliable data on the comparison of safety between the drugs in the elderly population.

CONCLUSION

Based on our study findings, we have put forth the following recommendations: Given the similar HbA1c reduction and the lack of weight gain observed in the sitagliptin + metformin group, clinicians should consider sitagliptin as a preferred second-line agent to metformin in geriatric patients with T2DM who require additional glycaemic control but are at risk of weight gain or where weight neutrality is desired. Due to the known higher risk of hypoglycaemia associated with sulphonylureas like glimepiride, its use in elderly patients should be approached with caution, particularly in those with comorbidities, polypharmacy or cognitive impairment who may be less able to recognise or manage hypoglycaemic episodes. Future research should focus on longer-term studies extending beyond 12 weeks to evaluate the sustained efficacy of sitagliptin and glimepiride in this population, including their impact on diabetes-related complications, cardiovascular outcomes and the incidence of adverse events, particularly hypoglycaemia. While this study provides valuable comparative data, treatment decisions should always be individualised based on the patient's specific clinical profile, comorbidities, preferences and tolerance to medications. Regular monitoring of glycaemic control, weight and potential adverse effects is crucial for both treatment strategies.

Ethical approval: The research/study was approved by the Institutional Review Board at King George's Medical University, approval number XXIII–PGTSC-IIA/P13, dated 23rd January 2024.
Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.
Financial support and sponsorship: Nil.
Conflicts of interest: There are no conflicts of interest.
Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, *et al*. Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci 2020;21:6275.
2. Magliano D, Boyko EJ. IDF diabetes atlas. 10th edition. Brussels: International Diabetes Federation; 2021.
3. Mathur P, Leburu S, Kulothungan V. Prevalence, awareness, treatment and control of diabetes in India from the countrywide national NCD monitoring survey. Front Public Health 2022;10:478157.
4. Anjana RM, Deepa M, Pradeepa R, Mahanta J, Narain K, Das HK, *et al*. Prevalence of diabetes and prediabetes in 15 states of India: Results from the ICMR-INDIAB population-based cross-sectional study. Lancet Diabetes Endocrinol 2017;5:585-96.
5. Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of type 2 diabetes: Indian scenario. Indian J Med Res 2007;125:217-30.
6. Laosa O, Topinkova E, Bourdel-Marchasson I, Vellas B, Izquierdo M, Paolisso G, *et al*. Long-term frailty and physical performance transitions in older people with type-2 diabetes. The MIDFRAIL randomized clinical study. J Nutr Health Aging 2025;29:100512.
7. Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, *et al*. Diabetes in older adults. Diabetes Care 2012;35:2650-64.
8. American Diabetes Association. 11. Older adults: Standards of medical care in diabetes-2022. Diabetes Care 2022;45(Suppl 1):195-207.
9. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. Med Clin North Am 2004;88:787-835, ix.
10. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, *et al*. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. BMJ 2000;321:405-12.
11. Kumar S. Comparison of safety and efficacy of glimepiride-metformin and vildagliptin- metformin treatment in newly diagnosed type 2 diabetic patients. Indian J Endocrinol Metab 2021;25:326-31.
12. Rosenstock J, Raccah D, Kadowaki T. Sulfonylureas in type 2 diabetes mellitus. Diabetes Obes Metab 2010;12:104-17.
13. Prasanna Kumar KM, Seshadri K, Aravind SR, Deb P, Modi KD, Gopal RA, *et al*. Real-world observational study of glimepiride and metformin fixed-dose combination along with insulin in the management of type 2 diabetes mellitus: Indian experience. Cureus 2021;13:e13020.
14. Ballav C, Gough SC. Safety and efficacy of sitagliptin-metformin in fixed combination for the treatment of type 2 diabetes mellitus. Clin Med Insights Endocrinol Diabetes 2013;6:25-37.
15. Devarajan TV, Venkataraman S, Kandasamy N, Oomman A, Boorugu HK, Karuppiah SK, *et al*. Comparative evaluation of safety and efficacy of glimepiride and sitagliptin in combination with metformin in patients with type 2 diabetes mellitus: Indian multicentric randomized trial - START Study. Indian J Endocrinol Metab 2017;21:745-50.
16. The GRADE Study Research Group. Glycemia reduction in type 2 diabetes - glycemic outcomes. N Engl J Med 2022;387:1063-74.
17. International Diabetes Federation. IDF clinical practice recommendations for managing Type 2 diabetes in primary care. Belgium: International Diabetes Federation; 2019;12.
18. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: Recommendations for good practice. J Eval Clin Pract 2004;10:307-12.
19. Monami M, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and hypoglycemia risk: A meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 2013;102:124-32.
20. Arechavaleta R, Seck T, Chen Y, Krobot KJ, O'Neill EA, Duran L, *et al*. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: A randomized, double-blind, non-inferiority trial. Diabetes Obes Metab 2011;13(2):160-168.
21. Bourdel Marchasson I, Doucet J, Bauduceau B, Berrut G, Blickle JF, Brocker P, *et al*. Key priorities in managing glucose control in older people with diabetes. J Nutr Health Aging 2009;13:685-91.

How to cite this article: Rajan K, Khan Z, Gupta G, Usman K, Sawlani KK, Ali W, *et al*. Comparing the efficacy and safety of sitagliptin versus glimepiride in combination with metformin in geriatric type 2 diabetes mellitus patients. Indian J Physiol Pharmacol. doi: 10.25259/IJPP_598_2025