Original Article

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

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Abstract

Background and Objective: Modern sulfonylureas like glimepiride offer effective glycemic control with extrapancreatic benefits and good tolerability. The objective of the present study was to evaluate and compare safety and efficacy of glimepiride and sitagliptin in combination with metformin in patients with type 2 diabetes mellitus (T2DM). **Methods:** In this open-label, randomized, comparative, multicenter study, a total of 305 T2DM patients who were either drug naïve or uncontrolled on metformin were randomized to glimepiride 1 or 2 mg/sustained-release metformin 1000 mg once daily (glimepiride group, $n = 202$) or sitagliptin 50 mg/metformin 500 mg twice daily (sitagliptin group, $n = 103$) for 12 weeks. Primary endpoint was change in glycosylated hemoglobin (HbA1c). Secondary endpoints were change in fasting plasma glucose (FPG), postprandial plasma glucose (PPG), body mass index (BMI) and to assess overall safety profile. **Results:** At 12 weeks, there was a statistically significant difference in the mean HbA1c reduction in glimepiride group (0.42%) as compared to sitagliptin group (0.30%) ($P = 0.001$). Mean reduction in FPG and PPG was also statistically significant in the glimepiride group as compared to the sitagliptin group ($P = 0.008$). There was no significant difference in terms of change in BMI (0.07 ± 0.39 kg/m^2 vs. 0.08 ± 0.31 kg/m^2) in glimepiride and sitagliptin groups, respectively, ($P = 0.644$) between both the groups. The incidences of hypoglycemic events were also comparable among both the groups. **Conclusion:** In T2DM patients, glimepiride/metformin combination exhibited significant reduction in glycemic parameters as compared to sitagliptin/metformin combination. Moreover, there was no significant difference between both the groups in terms of change in BMI and incidence of hypoglycemia.

Keywords: Glimepiride, metformin, modern sulfonylurea, sitagliptin, type 2 diabetes mellitus

Introduction

Diabetes mellitus, a common chronic disease, affected an estimated population of 415 million in 2015.[1] India, an epicenter of diabetes, had 69.2 million diabetic patients in 2015. This is projected to increase to 123.5 million in 2040.[1]

For effective management of type 2 diabetes mellitus (T2DM), combination therapy, which addresses both insulin resistance and beta-cell dysfunction, is essential.[2] Metformin is widely accepted as the first-line oral agent for T2DM. When metformin alone is insufficient, the choice of second-line treatment has remained a challenge. Despite a plethora of new agents, sulfonylureas are still the most accepted second-line add-on to metformin, especially in Indian clinical settings.[3,4] Modern sulfonylureas, such as glimepiride and modified release gliclazide backed by a large body of evidence, experience, and outcome data, are preferred over conventional ones like glibenclamide.[5] Glimepiride is the only sulfonylurea approved by the United States Food and Drug Administration for the

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treatment of T2DM as monotherapy as well as in combination with metformin or insulin.[6] Glimepiride possesses beneficial properties such as optimal insulin secretion, extrapancreatic effects, beta-cell friendly nature, weight neutral effects, and less risk of hypoglycemia.[6-10] Moreover, glimepiride also has potent antioxidative, anti-inflammatory, and angiogenic properties and is considered safe in patients with cardiovascular disease because of its lack of detrimental effects on ischemic preconditioning.[11,12]

The objective of this study was to compare the efficacy and safety of glimepiride or sitagliptin in combination with metformin in newly diagnosed/drug naïve or metformin uncontrolled T2DM patients in India.

Methods

Participants

Participants of either sex aged between 18 and 65 years who were either newly diagnosed/drug naïve T2DM patients or those uncontrolled on metformin monotherapy (fasting plasma glucose [FPG] level of ≥126 mg/dL and ≤200 mg/dL and/or 2 h postprandial plasma glucose [PPG] ≥200 mg/dl and/or glycosylated hemoglobin [HbA1c] levels ≥7.5% and ≤10% at screening) were eligible for participation in the study. The other eligibility criteria included women of childbearing potential who agreed not to become pregnant and use an appropriate contraceptive method, participants willing to sign informed consent form and comply with the study visit as per protocol and perform 5-point home blood glucose monitoring as per protocol, participants willing to provide audiovisual recording of the consent process, and participants agreeing to follow recommended diet plan and physical activity instructions throughout the study.

Patients with type 1 diabetes or secondary forms of diabetes, patients requiring insulin for glycemic control and/or history of insulin usage during 3 months preceding enrollment, pregnant or lactating women, and patients who were currently on a combination therapy with 2 or more oral antidiabetic agents were excluded from the study. Patients with clinically significant renal or hepatic disease, patients with congestive heart failure requiring pharmacological treatment, patients with history of unstable angina, acute coronary syndrome within the past 6 months, patients on antituberculosis treatment, patients on any other treatment for chronic ailments such as HIV, hepatitis B, hepatitis C, and chronic kidney failure, and patients with history of allergy to any of the investigational product/s, chronic alcoholism, planned surgical intervention during the expected study duration, and history of any surgical interventions during 3 months before enrollment were also excluded from the study.

Study design

This prospective, open-label, randomized, comparative multicenter study was conducted at 6 centres of Apollo Hospitals in India according to Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol and informed consent form were approved by the Ethics Committee of the respective hospital which participated in the study. A total of 379 T2DM participants were screened of which, 305 patients were randomized to receive glimepiride 1 mg or 2 mg/sustained-release metformin 1000 mg once daily (glimepiride group, n = 202) or sitagliptin 50 mg/metformin 500 mg twice daily (sitagliptin group, n = 103) both as fixed dose combinations (FDCs) for 12 weeks, with no dose adjustment during the entire period of study. Block randomization technique with block size of 6 was followed using the statistical software.

Demographic details including the current and past medical history, date of diagnosis, concomitant medications, and physical assessment, including height, weight, body mass index (BMI), and vitals, were recorded at the time of screening. FPG and PPG were monitored at baseline and subsequently every 4 weeks and at end of 12 weeks. HbA1c and all other screening tests were conducted at baseline and 12 weeks post-study treatment. In addition, the patients after thorough training on using the glucometer for self-monitoring of blood glucose were given a glucometer instruction sheet, glucometer, and glucometer strips to perform a 5-point home-based glucose monitoring once a week, on every Sunday. The patients were advised to measure blood glucose using glucometer whenever there were symptoms of fatigue/sweating/giddiness/blurred vision and were further advised to take 2 teaspoons of sugar if the glucose value was <70 mg/dL and were also advised to call the study coordinator immediately. After consultation with dietician, the patients were provided with a diet plan to follow till the next visit and were also instructed to follow physical activity as advised by the investigator. During the follow-up visit, the FPG and PPG were measured by collecting venous blood samples. The patient's vital parameters as well as weight were also recorded. In each follow-up visit, the patient diary was reviewed for occurrence of instances of symptoms suggestive of hypoglycemia, study drug compliance, and results of the home blood glucose monitoring. At the end of 12 weeks of treatment, the patients were advised to attend a follow-up visit wherein the patient's FPG, PPG, HbA1c, hematology, clinical chemistry including renal function test, liver function test and lipid profile, urinalysis, pregnancy test for female patients, and vitals including height and weight were recorded.

Study outcomes

The primary outcome was change in HbA1c from baseline up to 12 weeks. The secondary outcomes included change in FPG, PPG, and BMI from baseline up to 12 weeks. Important safety outcomes included number of patients with episodes of symptomatic/biochemical hypoglycemic events, and number of serious adverse events reported in each group.

Statistical methods

Continuous data were reported using the following descriptive statistics: number of observations (n), mean, standard deviation, minimum, and maximum. Mean and standard deviation were presented with minimum and maximum values. For analyzing

continuous data, Student's *t*-test was carried out. Categorical data were presented using frequency (*n*) with percentage (%), and comparison was done using Chi-square test. All *P* values for efficacy analyses were calculated at 0.05 level of significance. All statistical analyses were performed using SPSS for Windows, Version 10.0 SPSS Inc. Chicago, USA.

Results

Baseline parameters: of the 379 T2DM participants screened, 74 were excluded from the study. Of the 305 randomized participants, 276 completed the 12-week study (184 in glimepiride group and 92 in sitagliptin group) and 29 participants were either dropouts or lost to follow-up. Complete disposition of study participants is given in Figure 1.

The baseline blood glucose parameters including HbA1c, FPG, and PPG were similar in both the groups. Other baseline parameters such as BMI, systolic blood pressure, and diastolic blood pressure were comparable in both groups. The demographic and baseline characteristics are summarized in Table 1. Out of the total evaluable study population, 93 (33.7%) were newly diagnosed T2DM patients and 183 (66.3%) patients diagnosed to have T2DM with their glycemic parameters remaining uncontrolled with metformin monotherapy.

Efficacy

At 12 weeks, both treatment groups exhibited an improvement in HbA1c from baseline, which was statistically significant (Student's *t*-test, $P = 0.001$). However, the mean reduction in HbA1c from baseline in the glimepiride group was significantly more as compared to the sitagliptin group (0.42 ± 0.24% vs. 0.30 ± 0.20% respectively, Student's *t*-test $P = 0.001$) [Figure 2]. The mean reduction in FPG (12.41 ± 13.21 mg/dl) and PPG (21.01 ± 21.88 mg/dl) from baseline up to 12 weeks was statistically significant in the glimepiride group, $P = 0.001$. The sitagliptin group also resulted in a statistically significant reduction in FPG (7.45 ± 15.36 mg/dl) and PPG (12.09 ± 28.22 mg/dl) from baseline up to 12 weeks, $P = 0.001$. However, the mean reduction in FPG (12.41 vs. 7.45 mg/dl) and PPG (21.01 vs. 12.09 mg/dl) was significantly more in the glimepiride group as compared to sitagliptin group, respectively, $P = 0.008$ [Figure 3]. The efficacy parameters from baseline to end of study are depicted in Table 2.

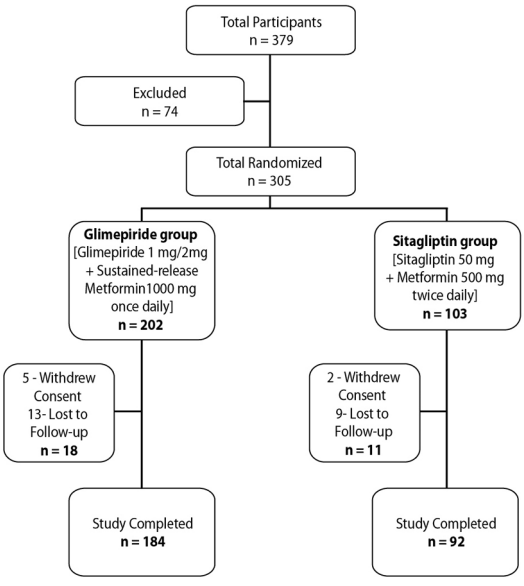

Figure 1: Disposition of study participants

Safety

Both the groups had a comparable safety profile during the study. A total of 42 participants reported episodes of symptoms

Table 1: Baseline parameters

Parameter	Glimepiride group (*n*=184)	Sitagliptin group (*n*=92)
Gender, *n* (%)		
Male	104 (56.5)	59 (64.1)
Female	80 (43.5)	33 (35.9)
Age (years), mean±SD	50.3±8.79	48.75±9.41
Blood pressure (mean±SD)		
SBP (mm of Hg)	130.4±9.29	129.1±8.8
DBP (mm of Hg)	79.9±6.36	79.9±7.51
Body weight (kg), mean±SD	64.05±9.68	64.72±9.65
BMI (kg/m^2), mean±SD	24.64±2.99	24.34±2.64
Mean duration of diabetes (months)	41.48	35.54
Duration of diabetes, *n* (%)		
Newly diagnosed	55 (29.9)	38 (41.3)
<5 years	75 (40.8)	29 (31.5)
5-10 years	42 (22.8)	18 (19.6)
>10 years	12 (6.5)	7 (7.6)
Comorbid conditions, *n* (%)		
Hypertension	63 (34.2)	28 (30.4)
Asthma and wheezing	18 (9.8)	6 (6.5)
Other illness	10 (5.4)	5 (5.4)
Blood glucose parameters (mean±SD)		
HbA1c (%)	7.96±0.48	7.96±0.56
FPG (mg/dl)	152.01±19.27	152.55±20.88
PPG (mg/dl)	271.21±29.82	267.38±31.26

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SD: Standard deviation, HbA1c: Glycosylated hemoglobin, FPG: Fasting plasma glucose, PPG: Postprandial plasma glucose

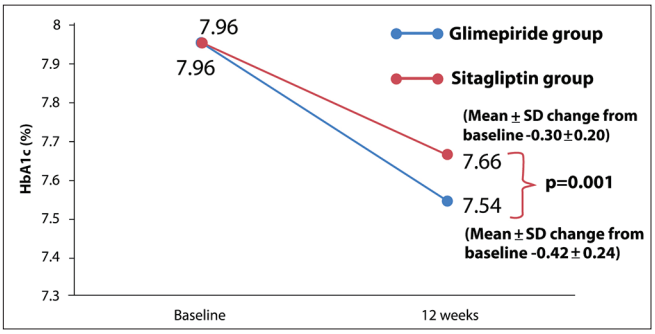

Figure 2: Change in glycosylated hemoglobin from baseline to end of study

Table 2: Efficacy parameters (*n*=276)

Parameters	Mean±SD						*P* (between group difference)
	Glimepiride group (*n*=184)			Sitagliptin group (*n*=92)			
	Baseline	End of study	Mean difference	Baseline	End of study	Mean difference	
HbA1c (%)	7.96±0.48	7.54±0.43	−0.42±0.23	7.96±0.56	7.66±0.56	−0.30±0.20	0.001*
FPG (mg/dl)	152.01±19.27	139.60±16.38	−12.41±13.21	152.55±20.88	145.10±20.36	−7.45±15.36	0.008*
PPG (mg/dl)	271.21±29.82	250.20±25.42	−21.01±21.88	267.38±31.26	255.29±30.96	−12.09±28.22	0.008*

By Student's *t*-test. *Significant. SD: Standard deviation, HbA1c: Glycosylated hemoglobin, FPG: Fasting plasma glucose, PPG: Postprandial plasma glucose

Table 3: Symptoms suggestive of hypoglycemia

Symptoms	Glimepiride group (*n*=184), *n* (%)	Sitagliptin group (*n*=92), *n* (%)	*P* (between group difference)
Dizziness	9 (4.9)	4 (4.3)	0.840*
Sweating	10 (5.4)	5 (5.4)	1.000*
Chills	10 (5.4)	4 (4.3)	0.698*

By Chi-square test. *Not significant

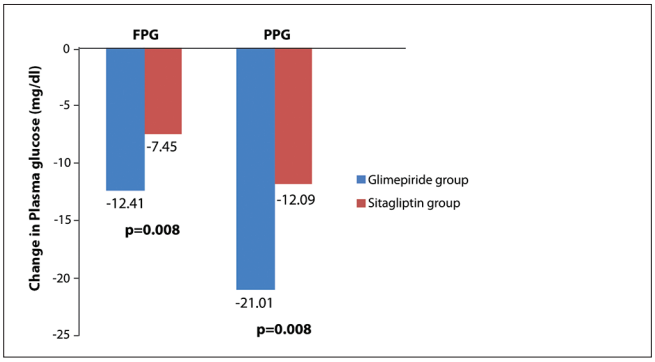

Figure 3: Change in fasting plasma glucose and postprandial plasma glucose from baseline to end of study

suggestive of hypoglycemia, i.e., dizziness, sweating, or chills. The incidences of hypoglycemic symptoms were comparable in both the groups [Table 3]. Of these, 20 were confirmed by glucometer readings. The patients themselves managed most of these episodes by consuming sugar or carbohydrate rich food without the necessity for seeking medical help. No severe hypoglycemia or symptoms related to severe hypoglycemia was recorded as per the patient's diary in both the groups. The change in body weight; glimepiride group (0.15 ± 0.97 kg) and sitagliptin group (0.22 ± 0.82 kg) and BMI; glimepiride group (0.07 ± 0.39 kg/m^2) and sitagliptin group (0.08 ± 0.31 kg/m^2) from baseline to end of study was similar in both the groups [Table 4]. None of the patients had any serious adverse event during the study.

Discussion

Management of T2DM has changed dramatically with the introduction of newer antidiabetic agents including dipeptidyl peptidase-4 inhibitors (DPP4i), sodium-glucose co-transporter 2 inhibitors, glucagon-like peptide-1 (GLP-1) analogs, and insulin analogs. DPP4i are a well-established class of oral agents having moderate efficacy with a good overall safety profile including low risk of hypoglycemia and weight neutrality.[13] However, sulfonylureas have been a part of the therapeutic armamentarium for T2DM since 1950 and are one of the most potent oral antidiabetic agents.[14] Due to good efficacy, safety, and cost-effectiveness, sulfonylureas, especially modern ones like glimepiride, are the most preferred first add-on to metformin in Indian clinical settings.[5,15]

Glimepiride has unique binding characteristics with the sulfonylurea receptor 1 (SUR1) resulting in the fast association and dissociation.[16] Due to its extrapancreatic activity, glimepiride reduces insulin resistance and improves glucose utilization through glucose transporter 4.[16] This dual mode of action of glimepiride results in a potent glycemic reduction with minimal risk of hypoglycemia or weight gain.[16] It has a greater selectivity for β-cell SUR1 receptors and thereby does not impair the protective ischemic preconditioning.[17,18] A meta-analysis with trial sequential analysis of randomized clinical trials confirmed that second- and third-generation sulfonylureas including glimepiride were not associated with increased all-cause and cardiovascular mortality, myocardial infarction, or stroke.[19] In a meta-analysis comparing sulfonylurea with a nonsulfonylurea agent, glimepiride had the lowest all-cause mortality among all sulfonylureas.[20] The South Asian Federation of Endocrine Societies consensus statement also emphasized that modern sulfonylureas should be preferred over the older ones due to better cardiovascular outcomes, less hypoglycemia, and less weight gain.[5]

In our study, drug naïve T2DM patients or T2DM patients uncontrolled on metformin monotherapy were randomized to receive an FDC of glimepiride 1 mg or 2 mg/sustained-release metformin 1000 mg once daily or sitagliptin 50 mg/metformin 500 mg twice daily over 12 weeks. The glimepiride group exhibited a significantly greater reduction in HbA1c as compared to sitagliptin group (P = 0.001). The reductions in FPG and PPG were also found to be significantly more in the glimepiride group (P = 0.008). Sulfonylureas are always blamed for causing hypoglycemia in T2DM patients which is more evident in older sulfonylureas as compared to the modern ones like glimepiride.[5,21] However, in our study, the incidences of symptomatic hypoglycemia were similar among the glimepiride and sitagliptin groups. Moreover, there was no evidence of severe hypoglycemic events in both the groups.

Table 4: Change in body weight and body mass index

Parameters	Mean±SD						*P* (between group difference)
	Glimepiride group (*n*=184)			Sitagliptin group (*n*=92)			
	Baseline	End of study	Mean difference	Baseline	End of study	Mean difference	
Body weight (kg)	64.05±9.68	64.20±9.58	0.15±0.97	64.72±9.65	64.94±9.57	0.22±0.82	0.530*
BMI (kg/m2)	24.64±2.99	24.71±3.03	0.07±0.39	24.34±2.64	24.42±2.61	0.08±0.31	0.644*

By Student's t-test. *Not significant. SD: Standard deviation, BMI: Body mass index

Both therapies showed comparable safety profile and were generally well tolerated.

These results are consistent with prior studies comparing glimepiride and sitagliptin or other DPP4i as add on to metformin. In a study by Srivastava *et al*.,[22] there were greater glycemic benefits (HbA1c, FPG, and PPG) with glimepiride as compared to sitagliptin with 36% of patients in glimepiride group and 12% of patients in sitagliptin group achieving the target HbA1c. In a similar study, there were greater reductions in HbA1c among glimepiride group (0.44%) versus sitagliptin group (0.25%) with higher percentage of patients on glimepiride reaching the HbA1c target of <7% and statistically nonsignificant effects on weight with glimepiride.[23] In a systematic review and meta-analysis comparing glimepiride/metformin versus any DPP4i/metformin combination, the glimepiride/metformin combination resulted in a 12% greater reduction in HbA1c, 0.21 mmol/L greater reduction in FPG with significantly fewer dropouts, and 20% reduced risk of requiring rescue treatment. There was a between group difference of 2.1 kg in weight, which was not considered as clinically relevant. This study suggested that there is greater effectiveness with the glimepiride/metformin combination with good safety profile, which makes it a preferential choice of treatment for many uncontrolled T2DM patients.[24]

A study comparing different classes of oral antidiabetic agents (sulfonylurea, thiazolidinedione or DPP4i) as second-line therapies to metformin monotherapy among ~20,000 patients revealed that in routine clinical practice, adding a DPP4i to metformin resulted in an increased, earlier requirement for treatment intensification as compared to a sulfonylurea or a thiazolidinedione over 5 years. Moreover, the addition of sulfonylurea resulted in 0.3%–0.5% greater reduction in HbA1c with a slight reduction in body weight of 0.2 kg from baseline. The weight reduction seen with sulfonylurea was attributed to therapeutic patient education, lifestyle changes, and using it in combination with metformin.[25] Similar findings were seen in a 104 weeks study wherein glimepiride resulted in a mean HbA1c reduction of 0.36% versus linagliptin which resulted in a mean HbA1c reduction of 0.16% as add on to metformin.[26]

Another observational cohort study (ZODIAC-39) involving ~3000 patients suggested that strict glycemic control can be maintained with a sulfonylurea/metformin combination without relevant changes in weight over 5 years. Out of the different sulfonylurea/metformin combinations studied, glimepiride/metformin combination resulted in 0.1 kg weight gain, gliclazide/metformin combination resulted in 3.9 kg weight gain, and glibenclamide/metformin combination resulted in 3.3 kg weight gain.[27] Low-dose glimepiride has also demonstrated effective plasma glucose reduction with no reports of hypoglycemia or weight gain.[28] Low-dose glimepiride, due to its peripheral insulin sensitizing effect, does not cause downregulation of the insulin receptors and thus may prevent unnecessary hyperinsulinemia and β-cell function failure.[29]

Sulfonylureas as second-line agents have shown good glycemic control and better quality-adjusted life-years (QALYs) comparable to other newer agents such as DPP4i and GLP-1 receptor agonists but at lower cost with the longest time to insulin dependence.[30] All these studies, including the results of our study, suggest that modern sulfonylureas like glimepiride are an important strategic tool to manage T2DM. This study had several limitations. First the two doses of glimepiride 1 mg or 2 mg were used in FDC. The daily frequency of dose administration was different for both the groups. Lastly, the duration of treatment period was short.

Conclusion

In T2DM patients, glimepiride/metformin combination exhibited significant reduction in glycemic parameters as compared to sitagliptin/metformin combination. Both glimepiride and sitagliptin were well tolerated with no significant between group difference in weight and low propensity for hypoglycemia. Hence, given the good efficacy, safety profile, less hypoglycemic risk, weight neutrality, extrapancreatic effects and many pleiotropic benefits, glimepiride is still a rational choice as an add on to metformin in T2DM patients. Modern sulfonylureas like glimepiride thus are still an important second-line option after metformin in this era of newer antidiabetic agents.

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Conflicts of interest

There are no conflicts of interest.

References

1. International Diabetes Federation. IDF Diabetes. 7th ed. Brussels, Belgium: International Diabetes Federation; 2015. Available from: Http://www.diabetesatlas.org. [Last accessed on 2017 Feb 10].
2. LaSalle JR, Cross LB. Oral combination therapy with thiazolidinediones in type 2 diabetes. Am J Manag Care 2006;12:S369-81.
3. Acharya KG, Shah KN, Solanki ND, Rana DA. Evaluation of antidiabetic prescriptions, cost and adherence to treatment guidelines: A prospective, cross-sectional study at a tertiary care teaching hospital. J Basic Clin Pharm 2013;4:82-7.
4. Lim PC, Chong CP. What's next after metformin? Focus on sulphonylurea: Add-on or combination therapy. Pharm Pract (Granada) 2015;13:606.
5. Kalra S, Aamir AH, Raza A, Das AK, Azad Khan AK, Shrestha D, *et al.* Place of sulfonylureas in the management of type 2 diabetes mellitus in South Asia: A consensus statement. Indian J Endocrinol Metab 2015;19:577-96.
6. Basit A, Riaz M, Fawwad A. Glimepiride: Evidence-based facts, trends, and observations (GIFTS). [corrected]. Vasc Health Risk Manag 2012;8:463-72.
7. Müller G, Satoh Y, Geisen K. Extrapancreatic effects of sulfonylureas – A comparison between glimepiride and conventional sulfonylureas. Diabetes Res Clin Pract 1995;28 Suppl: S115-37.
8. Moon JS, Ha KS, Yoon JS, Lee HW, Lee HC, Won KC, *et al.* The effect of glargine versus glimepiride on pancreatic β-cell function in patients with type 2 diabetes uncontrolled on metformin monotherapy: Open-label, randomized, controlled study. Acta Diabetol 2014;51:277-85.
9. Bugos C, Austin M, Atherton T, Viereck C. Long-term treatment of type 2 diabetes mellitus with glimepiride is weight neutral: A meta-analysis. Diabetes Res Clin Pract 2000;50 Suppl 1:S47.
10. Holstein A, Plaschke A, Egberts EH. Lower incidence of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. Diabetes Metab Res Rev 2001;17:467-73.
11. Nakamura I, Oyama J, Komoda H, Shiraki A, Sakamoto Y, Taguchi I, *et al.* Possible effects of glimepiride beyond glycemic control in patients with type 2 diabetes: A preliminary report. Cardiovasc Diabetol 2014;13:15.
12. Mocanu MM, Maddock HL, Baxter GF, Lawrence CL, Standen NB, Yellon DM. Glimepiride, a novel sulfonylurea, does not abolish myocardial protection afforded by either ischemic preconditioning or diazoxide. Circulation 2001;103:3111-6.
13. Abrahamson MJ. Should sulfonylureas remain an acceptable first-line add-on to metformin therapy in patients with type 2 diabetes? Yes, they continue to serve us well! Diabetes Care 2015;38:166-9.
14. Makkar BM, Gupta D, Gainda A. Clinical trials to clinical practice: Role of sulfonylureas in today's practice. Medicine Update. New Delhi, India: Jaypee Brothers Medical Publishers PVT LTD; 2013. p. 393-8.
15. Thacker H, Shah S, Chadha M, Kovil R, Chawla M, Gupta S, *et al.* 2193-PUB management of type 2 diabetes in Western India: Attitudes and practices among physicians leading the forefront of diabetes care. New Orleans, Louisiana, USA: ADA; 2016.
16. Briscoe VJ, Griffith ML, Davis SN. The role of glimepiride in the treatment of type 2 diabetes mellitus. Expert Opin Drug Metab Toxicol 2010;6:225-35.
17. Geisen K, Végh A, Krause E, Papp JG. Cardiovascular effects of conventional sulfonylureas and glimepiride. Horm Metab Res 1996;28:496-507.
18. Klepzig H, Kober G, Matter C, Luus H, Schneider H, Boedeker KH, *et al.* Sulfonylureas and ischaemic preconditioning; a double-blind, placebo-controlled evaluation of glimepiride and glibenclamide. Eur Heart J 1999;20:439-46.
19. Varvaki Rados D, Catani Pinto L, Reck Remonti L, Bauermann Leitão C, Gross JL. The association between sulfonylurea use and all-cause and cardiovascular mortality: A meta-analysis with trial sequential analysis of randomized clinical trials. PLoS Med 2016;13:e1001992.
20. Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: A meta-analysis of randomized clinical trials. Diabetes Obes Metab 2013;15:938-53.
21. van Dalem J, Brouwers MC, Stehouwer CD, Krings A, Leufkens HG, Driessen JH, *et al.* Risk of hypoglycaemia in users of sulphonylureas compared with metformin in relation to renal function and sulphonylurea metabolite group: Population based cohort study. BMJ 2016;354:i3625.
22. 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;60:27-30.
23. Kumar S, Pathak AK, Saikia D, Kumar A. Efficacy, safety and treatment satisfaction of glimepiride vs. Sitagliptin in combination with metformin in type 2 diabetes mellitus. J Clin Diagn Res 2015;9:FC07-10.
24. Amate JM, Lopez-Cuadrado T, Almendro N, Bouza C, Saz-Parkinson Z, Rivas-Ruiz R, *et al.* Effectiveness and safety of glimepiride and iDPP4, associated with metformin in second line pharmacotherapy of type 2 diabetes mellitus: Systematic review and meta-analysis. Int J Clin Pract 2015;69:292-304.
25. Mamza J, Mehta R, Donnelly R, Idris I. Important differences in the durability of glycaemic response among second-line treatment options when added to metformin in type 2 diabetes: A retrospective cohort study. Ann Med 2016;48:224-34.
26. Gallwitz B, Rosenstock J, Rauch T, Bhattacharya S, Patel S, von Eynatten M, *et al*. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: A randomised, double-blind, non-inferiority trial. Lancet 2012;380:475-83.
27. Schrijnders D, Wever R, Kleefstra N, Houweling ST, van Hateren KJ, de Bock GH, *et al*. Addition of sulphonylurea to metformin does not relevantly change body weight: A prospective observational cohort study (ZODIAC-39). Diabetes Obes Metab 2016;18:973-9.
28. George J. Starting with low dose sulfonylurea and metformin in early stage type 2 diabetes mellitus. Indian J Endocrinol Metab 2015;19:309.
29. Bermúdez-Pirela VJ, Cano C, Medina MT, Souki A, Lemus MA, Leal EM, *et al*. Metformin plus low-dose glimeperide significantly improves homeostasis model assessment for insulin resistance (HOMA (IR)) and beta-cell function (HOMA (beta-cell)) without hyperinsulinemia in patients with type 2 diabetes mellitus. Am J Ther 2007;14:194-202.
30. Zhang Y, McCoy RG, Mason JE, Smith SA, Shah ND, Denton BT. Second-line agents for glycemic control for type 2 diabetes: Are newer agents better? Diabetes Care 2014;37:1338-45.