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Evaluation of safety and efficacy of glimepiride and sitagliptin in combination with metformin in patients with type 2 diabetes mellitus: Analytical study

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Abstract
Aim: To evaluate and compare safety and efficacy of glimepiride and sitagliptin in combination with metformin in patients with type 2 diabetes mellitus (T2DM).
Methods: This prospective analytical study was carried out in the Department of Pharmacology at Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar from November 2019 to May 2020. A total of 300 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 = 190) or sitagliptin 50 mg/metformin 500 mg twice daily (sitagliptin group, n = 110) for 15 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 15 weeks, there was a statistically significant difference in the mean HbA1c reduction in glimepiride group (0.39%) as compared to sitagliptin group (0.31%) (P = 0.001). Mean reduction in FPG and PPG was also statistically significant in the glimepiride group as compared to the sitagliptin group (P = 0.007). There was no significant difference in terms of change in BMI (0.09±0.43kg/m^2 vs. 0.11±0.34kg/m^2) in glimepiride and sitagliptin groups, respectively, (P = 0.611) 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 hypoglycaemia.

Keywords: T2DM patients, glycemic parameters, BMI, HbA1c

Introduction
Diabetes mellitus, a common chronic disease, affected an estimated population of 415 million in 2015. 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 the prevention of diabetes related complications; improvement in glycaemic control is of the prime importance. Thus far, different oral anti-hyperglycemic agents are available to achieve euglycemia. Reports have shown that about 60% of the diabetes patients do not achieve their therapeutic targets when on monotherapy making dual therapy a necessity to achieve glycaemic control [2] During trial of mono or dual therapy for optimal efficacy, tolerability and safety of the patients is of prime importance. A drug combination which is efficacious and is with less adverse effects should be chosen for the treatment of T2DM [3] Oral drug classes such as metformin, sulphonylurea, thiazolidinedione, alpha glucosidase inhibitors and DPP IV inhibitors are available which significantly lower the HbA1c level and are routinely used in the management of diabetes. Sulphonylureas are associated with weight gain and hypoglycaemia, thiazolidinedione causes fluid retention and metformin in many patients leads to gastrointestinal irritation [4] the drugs of class dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) are equally efficacious as compared to other anti-diabetic agents and also has very limited adverse effects. Sulphonylurea are associated with weight gain and hypoglycaemia, thiazolidinedione causes fluid retention and metformin in many Patients leads to gastrointestinal irritation [5] Sitagliptin which is a DPP-4 inhibitors is orally active and routinely prescribed as monotherapy or as anadd on therapy. Safety and efficacy of sitagliptin is well established for the treatment of T2DM.[6] The aim 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.

Material and Methods
This prospective analytical study was carried out in the Department of Pharmacology at Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar from November 2019 to May 2020. Participants of either sex aged between 20 and 70 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 haemoglobin [HbA1c] levels ≥7.5% and ≤10% at screening) were eligible for participation in the study.
A total of 380 T2DM participants were screened of which,

300 patients were randomized to receive glimepiride 1 mg or 2 mg/sustained-release metformin 1000 mg once daily (glimepiride group, n = 190) or sitagliptin 50 mg/ metformin 500 mg twice daily (sitagliptin group, n = 110) both as fixed dose combinations (FDCs) for 15 weeks, with no dose adjustment during the entire period of study.

Demographic details including age, sex, the current and past medical history, 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 5 weeks and at end of 15 weeks. HbA1c and all other screening tests were conducted at baseline and 15 weeks post-study treatment. 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. We were also instructed to follow physical activity as advised by the investigator. The FPG and PPG were measured by collecting venous blood samples. The patient's weight and BMI were also recorded. At the end of 15 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. The primary outcome was change in HbA1c from baseline up to 15 weeks. The secondary outcomes included change in FPG, PPG, and BMI from baseline up to 15 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 analysis

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2010) and then exported to data editor page of SPSS version 19 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics included computation of percentages and means. Test applied for the analysis was student t-test. The level confidence interval and p-value were set at 95% and 5%.

Results

Table 1: baseline parameter

Parameter	Glimepiride N=190	Sitagliptin N=110
Gender		
Male	110 (57.90)	70 (63.64)
Female	80 (42.10)	40 (36.36)
Age (years), (mean±SD)	52.1±7.89	49.65±8.69
Blood pressure		
SBP (mm of Hg)	129.4±7.41	130.1±7.2
DBP (mm of Hg)	79.8±6.79	79.8±6.93
Body weight (kg), (mean±SD)	65.25±9.59	65.65±9.55
BMI (kg/m^2), (mean±SD)	24.59±2.71	24.61±2.73
Mean duration of diabetes (months)	42.36	37.51
Duration of diabetes		
Newly diagnosed	61 (32.11)	43 (39.10)
<5 years	79 (41.58)	34 (30.90)
5-10 years	35 (18.40)	23(20.90)
>10 years	15 (7.89)	10 (9.10
Co morbid conditions		
Hypertension	61 (32.10)	32 (29.10)
Asthma and wheezing	22 (11.58)	10(9.10)
Other illness	11 (5.78)	6(5.46)
Blood glucose parameters		
HbA1c (%)	7.81±0.42	7.81±0.52
FPG (mg/dl)	151.51±18.37	151.59±19.98
PPG (mg/dl)	275.11±28.72	269.39±30.49

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

Table 2: Efficacy of parameter

Parameter	Mean±SD						p -value
	Glimepiride group (n=190)			Sitagliptin group (n=110			
	Baseline	End of study	Mean difference	Baseline	End of study	Mean difference	
HbA1c (%)	7.81±0.42	7.42±0.41	−0.39±0.23	7.81±0.52	7.50±0.57	−0.31±0.22	0.031*
FPG (mg/dl)	151.51±18.37	138.40±15.88	−13.11±12.22	151.59±19.98	143.54±20.21	−8.05±15.46	0.047*
PPG (mg/dl)	275.11±28.72	251.90±24.32	−23.21±22.76	269.39±30.49	256.28±30.77	−13.11±28.24	0.017*

Test applied: t-test

Table 3: Symptoms suggestive of hypoglycaemia

Symptoms	Glimepiride group N (%)	Sitagliptin group N (%)	P (between group difference)
Dizziness	11 (5.78)	5 (4.54)	0.780*
Sweating	10 (5.26)	5 (4.54)	1.000*
Chills	11 (5.78)	4 (3.64)	0.667*

Table 4: Change in body mass and body weight

Parameter	Mean ± SD						
	Glimepiride group (n=190)			Sitagliptin group (n=110)			P-value
	Baseline	End of study	Mean difference	Baseline	End of study	Mean difference	
Body weight (kg)	65.25±9.59	65.42±8.73	0.17±0.77	65.65±9.55	65.89±8.66	0.24±0.71	0.518*
BMI (kg/m2)	24.59±2.71	24.68±2.89	0.09±0.43	24.61±2.73	24.72±2.81	0.11±0.34	0.611*

Test applied: t-test

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 [7] However, sulfonylureas have been a part of the therapeutic armamentarium for T2DM since 1950 and are one of the most potent oral antidiabetic agents.[8] 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 [9, 10] Glimepiride has unique binding characteristics with the sulfonylurea receptor 1 (SUR1) resulting in the fast association and dissociation [11]. Due to its extrapancreatic activity, glimepiride reduces insulin resistance and improves glucose utilization through glucose transporter 4.[11] This dual mode of action of glimepiride results in a potent glycemic reduction with minimal risk of hypoglycemia or weight gain [11] It has a greater selectivity for β-cell SUR1 receptors and thereby does not impair the protective ischemic preconditioning [12, 13] 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 [14]. In a meta-analysis comparing sulfonylurea with a nonsulfonylurea agent, glimepiride had the lowest all-cause mortality among all sulfonylureas.[15] 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 [9]. 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 15 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 = 0.007). 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 [9, 16]. 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. 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* [17]. 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.[18] 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 [19].

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 ove0r 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 [20]. 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.[21] 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.[22] Low-dose glimepiride has also demonstrated effective plasma glucose reduction with no reports of hypo glycemia or weight gain.[23] Low-dose glimepiride, due to its peripheral insulin sensitizing effect, does not cause down regulation of the insulin receptors and thus may prevent unnecessary hyper insulinemia and cell function failure [24].

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.[25] 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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