Sitagliptin 100 mg vs glimepiride 1–3 mg as an add-on to insulin and metformin in type 2 diabetes (SWIM)

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Abstract

Objective: To compare the effect of sitagliptin (100 mg) vs glimepiride (1–3 mg) as add-on therapy in Indian type 2 diabetes (T2DM) patients on treatment with insulin and metformin (SWIM study).

Research design and methods: This 24-week, controlled, open-label study randomized T2DM patients ($n = 440$) receiving a stable dose of metformin and insulin combination therapy to sitagliptin (100 mg) or glimepiride (1–3 mg) as add-on therapy. Baseline HbA1c was ≥7.3% and ≤8.5%. After a 6-week titration period for glimepiride (dose titrated every 2 weeks by 1 mg up to a maximum of 3 mg daily), patients were continued for 18 weeks on their respective tolerable doses of glimepiride (ranging from 1 mg to 3 mg) or sitagliptin (100 mg) along with metformin and insulin.

Results: Greater reductions in HbA1c and TDD of insulin were achieved with sitagliptin compared to glimepiride. HbA1c targets and reductions in TDD were achieved by more patients on sitagliptin than on glimepiride. Reductions in both body weight and BMI were also noted among patients on sitagliptin when compared to those on glimepiride, and more hypoglycemic events occurred with glimepiride treatment than with sitagliptin.

Conclusions: Sitagliptin (100 mg), when compared to glimepiride (1–3 mg), bestowed beneficial effects to T2DM patients in terms of achieving greater glycemic control and also brought significant reductions in total daily dose of insulin required, bodyweight, BMI and hypoglycemic events. Overall, the results suggest that sitagliptin (100 mg) is a superior agent over glimepiride (1–3 mg) as an add-on to insulin–metformin therapy among Asian Indians with T2DM.

Key Words
- glimepiride
- insulin
- metformin
- sitagliptin
- type 2 diabetes

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Introduction

As diabetes mellitus is a chronic metabolic disease, combination therapy usually becomes necessary during the course of treatment due to progressive worsening of blood glucose control. With disease advancement, many patients will require insulin therapy due to inadequate glycemic control with oral agents (1). Metformin and sulfonylureas (SU) are the most commonly used oral antidiabetic agents. However, SU have a greater tendency to cause hypoglycemia and weight gain and hence, many patients will eventually require to be shifted to another class of oral antidiabetic agents or insulin therapy (2, 3).

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DPP-4 inhibitors are a class of oral antidiabetic drugs which enhance the function of endogenous incretin and help with glucose homoeostasis without increasing the risk of hypoglycemia and weight gain (4). Addition of sitagliptin, a DPP-4 inhibitor for treatment of type 2 diabetes mellitus (T2DM) in patients poorly controlled on insulin with or without metformin, has been shown to reduce HbA1c and delay the need for insulin therapy (5). Sitagliptin as add-on therapy in T2DM has reported to provide persistent beneficial effects on short-term, intermediate-term and long-term biomarkers of metabolic control, as well as on low-density lipoprotein cholesterol levels and insulin requirement (6). Due to multiple actions of sitagliptin such as anti-inflammatory effect and effect on monocytes and T-lymphocytes, the clinical usefulness of the addition of sitagliptin in T2DM could be beyond glycemic reduction. Secondary effects like prevention of weight gain, reduction in insulin dose, improved cardiovascular risk profile, etc., may be expected from the addition of sitagliptin to diabetes treatment (7, 8).

Although sitagliptin has been compared to therapies like pioglitazone (9), liraglutide (10), dulaglutide (11), canagliflozin (12), glipizide (13) and glimepiride (with background metformin monotherapy) (14, 15), a vis-à-vis comparison of sitagliptin vs glimepiride (a sulfonylurea) with background therapy of metformin and insulin has not been reported. This 24-week open-label, randomized, parallel-group study was conducted to compare the efficacy of **s**itagliptin (100 mg) vs glimepiride (1–3 mg) as add-on therapy in Indian T2DM patients on treatment with insulin and metformin (SWIM study).

Research design and methods

Subjects and study design

This prospective, open-label, randomized, parallel-group study (Clinical Trial Registration No. NCT01341717) was conducted at our comprehensive diabetes care center and was an investigator initiated proposal supported by Merck & Co. The study was approved by Independent Ethics Committee, Jothydev's Diabetes Research Centre and written informed consent was obtained from all study participants. The study was conducted in accordance with the guidelines on good clinical practice and with ethical standards for human experimentation established by the Declaration of Helsinki.

Inclusion criteria

- >T2DM patients (n=440) of either gender between 25 years and 60 years of age.
- Receiving metformin (≥1000 mg) and >10 IU of total daily dose (TDD) of biphasic or basal regimens of insulin.
- Baseline HbA1c of ≥7.3% and ≤8.5%.

Exclusion criteria

- >Upper age limit was restricted to 60 years considering the age-related decline in hepatic and renal functions, increase in half-life, particularly of glimepiride which will have more chances of inducing hypoglycemia in the elderly population.
- Patients with type 1 diabetes, history of pancreatitis, creatinine clearance ≤50 mL/min, chronic liver and kidney diseases, serum glutamate transaminase and prothrombin time ≥2.5× upper limit of normal, uncontrolled thyroid disorders, cardiac failure, hemochromatosis, autoimmune disorders and on systemic corticosteroids intake, were excluded.
- Patients with BMI >40 kg/m^2 and those using acarbose, pioglitazone or short-acting insulin analogs at the time of run-in phase were excluded.

The primary hypothesis for this study was that sitagliptin (100 mg) is non-inferior to glimepiride (1–3 mg) in reducing the HbA1c after 24 weeks of therapy from baseline with a non-inferiority margin of 0.3%. The primary analysis was based on the per-protocol (PP) dataset (all randomized subjects who completed study as per study protocol). Safety analyses were conducted on the intent-to-treat (ITT) dataset (all randomized subjects who received one or more doses of study drug). All statistical tests were interpreted at a two-sided significance level of 5%, and all CIs were interpreted at a two-sided confidence level of 95%.

Assuming no difference between sitagliptin and glimepiride in HbA1c-lowering efficacy and a common S.D. of 1.0% with respect to change in A1C, it was estimated that 176 subjects per treatment group (total 352) provided 80% power to demonstrate the non-inferiority of sitagliptin (100 mg) with glimepiride (1–3 mg). Sample size was based on a one-tailed α of 0.025 for non-inferiority comparison. Assuming a dropout rate of over 20% over 24 weeks, it was planned to enroll 440 patients (220 in each of the two groups).

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Treatment randomization and baseline characteristics A total of 810 patients were screened of which 370 subjects were excluded because of non-fulfillment of inclusion and exclusion criteria and the remaining 440 patients were enrolled in the study. Enrolled patients were randomized in 1:1 ratio using a computer-generated stratified block design with stratification for gender (male and female) to receive either sitagliptin (100 mg) ($n=219$) or glimepiride (1–3 mg) ($n=221$) (Fig. 1). Randomization was generated at the beginning of the study and provided in sealed envelopes for each study subject. After enrollment, study subjects were assigned a serial number in a chronological order and only after having assigned the study number to the enrolled subject, the sealed envelope for the subject number and concerned gender was opened to reveal the treatment allocation.

During the run-in period, compliance to optimal diet, exercise, treatment with insulin and metformin (≥1000 mg), and stable treatment with statin and antihypertensives were ensured. Patients were free to withdraw at will at any time. Study withdrawal criteria were safety or compliance issues at the discretion of the investigator, such as frequent hypoglycemia episodes during study, major protocol deviation which may have influence on study outcomes, lack of effectiveness of therapy assessed at week 12 (no reduction in HbA1c from baseline), any significant change in systemic treatment which could interfere with glycemic control, voluntary donation of blood by study subject or participation of the subject in other therapeutic trials during the study.

The demography and baseline characteristics of the enrolled patients are presented in Table 1. The two groups (sitagliptin and glimepiride) were similar with respect to the demography (except for BMI), insulin schedule, duration of diabetes and baseline HbA1c. The PP (all randomized subjects who completed the study as per study protocol) included 213 patients on sitagliptin (100 mg) and 205 patients on glimepiride (1–3 mg) therapy.

Treatment

Titration period (6-week period after randomization) During the titration period, patients randomized to glimepiride had their glimepiride daily dose titrated every 2 weeks by 1 mg up to a maximum of 3 mg daily (Table 2). The median daily dose of metformin was 1000 mg in both study groups. The criteria for insulin dose titration were target fasting plasma glucose (FPG) values between 70 mg/dL and 125 mg/dL, without hypoglycemia. The TDD of insulin was reduced by 20%

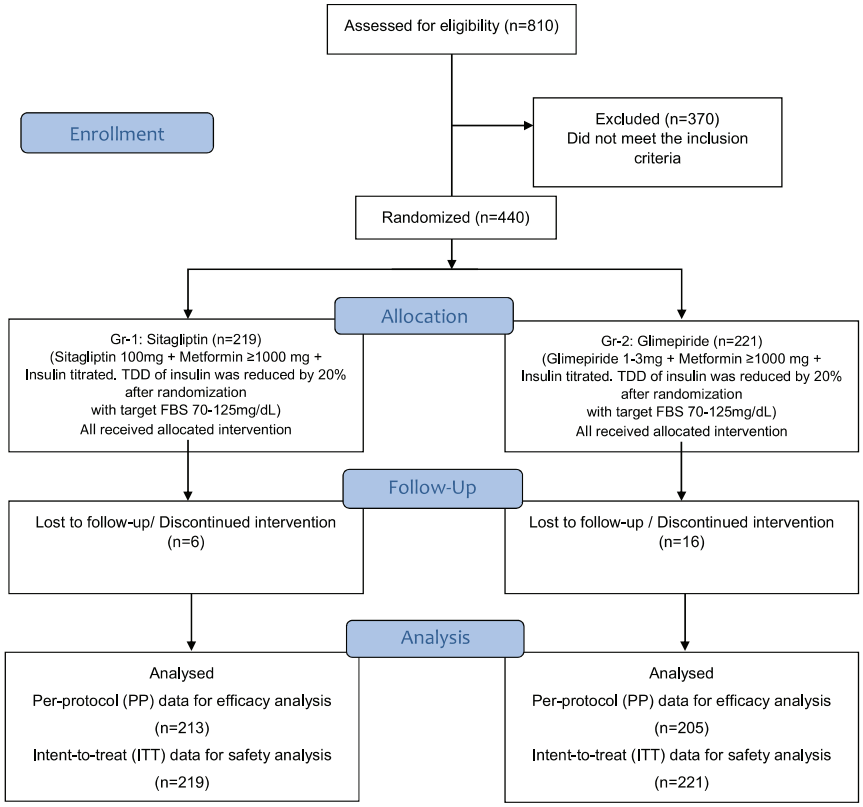

Figure 1
Study flow diagram.

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Table 1 Demography and baseline data of patients enrolled (ITT dataset).

ITT dataset	Sitagliptin (100 mg) (*n* = 219) No. (%)	Glimepiride (1–3 mg) (*n* = 221) No. (%)	*'P'* χ^2 test
Gender			
Male	103 (47.03)	113 (51.13)	0.39
Female	116 (52.97)	108 (48.87)	
Insulin regimen			
Basal	116 (52.97)	108 (48.87)	0.39
Biphasic	103 (47.03)	113 (51.13)	
	Mean (S.D.)	**Mean** (S.D.)	*'P'* (*'t'* test)
Age (years)	51.09 (6.58)	50.11 (7.83)	0.16
BMI (kg/sq m)	26.02 (3.32)	25.15 (3.69)	0.01
Hb (g%)	13.03 (1.42)	12.99 (1.58)	0.78
Duration of DM (years)	14.96 (7.33)	15.67 (7.20)	0.30
HbA1c			
%	7.96 (63)	7.91 (63)	0.08
mmol/mol eq	0.33 (3.6)	0.35 (3.8)	

after randomization to minimize the risk of hypoglycemia due to the addition of sitagliptin (100 mg) or glimepiride (1–3 mg). Thereafter, insulin dose was held constant, or reduced in the case of hypoglycemia. Patients randomized to sitagliptin received a single daily dose of 100 mg for the entire study period.

Maintenance period (18-week period after the titration period) During the maintenance period, dosages of all oral drugs were held constant and insulin doses were titrated to achieve target FPG between 70 mg/dL and 125 mg/dL, without hypoglycemia (based on investigator's discretion or >3 episodes per month). Patients were followed up after 2, 4, 6, 12, 16, 20 and 24 weeks after randomization. Patients continued receiving their concurrent lipid-lowering agents, antihypertensive agents and other medications without making any changes.

Study end points and assessments

The primary objective of the study was to confirm the efficacy of metformin + insulin + 100 mg sitagliptin combination therapy over metformin + insulin + 1–3 mg glimepiride combination therapy in controlling glycemia with respect to changes observed in HbA1c after 24 weeks of administration. Secondary end points assessed were change from baseline in insulin TDD (calculated as 30-day geometric mean) at 24 weeks, proportion of patients achieving an HbA1c targets of <6.5% (16) and <7.0% (17) at 24 weeks, changes in body weight and BMI at 24 weeks and episodes of hypoglycemia during the study period. Hypoglycemia was assessed by a questionnaire and supplemented by plasma glucose values (wherever available). Other secondary end points like changes from baseline in C-peptide levels and lipid profile (total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol) were also assessed. Clinical assessments and compliance assessments were done at all visits.

Safety and tolerability were assessed by physical examinations, vital signs, 12-lead electrocardiograms and different laboratory parameters comprising serum chemistry (creatinine, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total proteins, albumin and globulin). Data of adverse events such as hypoglycemia, abdominal pain, nausea, vomiting and diarrhea were collected throughout the study; their severity and relationship with any of the drugs under study were determined by the investigator. Hypoglycemic events were categorized as per American Diabetes Association's recommendations as follows: Asymptomatic hypoglycemia (an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤70 mg/dL), Documented symptomatic hypoglycemia (an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤70 mg/dL), Probable symptomatic hypoglycemia (an event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤70 mg/dL), Relative hypoglycemia (an event during which a person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets those as indicative of hypoglycemia, but with a measured plasma glucose concentration >70 mg/dL) and Severe hypoglycemia (an event requiring assistance of another

Table 2 Glimepiride dosages during the titration period.

Glimepiride dose	No. of patients taking respective doses of glimepiride during 0–6 weeks of study (%)			
	Week 0	Week 2	Week 4	Week 6
1 mg	204 (99.51)	31 (15.12)	32 (15.61)	35 (17.07)
2 mg	1 (0.49)	174 (84.88)	52 (25.37)	32 (15.61)
3 mg	0 (0)	0 (0)	121 (59.02)	138 (67.32)

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person to actively administer carbohydrates, glucagon or take other corrective actions) (18). All blood estimations were performed at the clinical and biochemistry laboratory of the hospital by technicians blinded to the treatments received by the subject.

Analytical methods adopted for measuring clinical parameters C-peptide was measured by the electrochemiluminescence immunoassay method by using fully automated Roche Cobas e 411 analyzer. HbA1C was estimated using the BioRad D10 cation exchange HPLC analyzer. Blood glucose estimations, lipid profile and serum parameters were assessed using the Selectra Pro S Fully automated clinical chemistry analyzer. Blood glucose and cholesterol were determined using enzymatic assay based on the Trinder end point reaction, triglycerides by the enzymatic method (GPO-PAP), LDL cholesterol by the direct enzymatic method (PVS/PEGME), HDL cholesterol by the direct enzymatic method (liquid), creatinine by the enzymatic method (Creatinine PAP), total bilirubin by the Malloy Evelyn modified method, alanine aminotransferase and aspartate aminotransferase by the IFCC method without pyridoxal phosphate (P-5′-P), total proteins by the Biuret end point method and albumin by the colorimetric Bromocresol green method.

Statistical analyses

The demography and the baseline data were compared between the two groups using unpaired '*t*' test for measurement data and chi-square test for discrete data. Continuous data were compared between the two groups using an unpaired '*t*' test, whereas discrete data were compared using a chi-square test. Primary end point of change in HbA1c from baseline at 24 weeks was analyzed using an ANCOVA model, including treatment as a fixed effect, baseline HbA1c as covariate and stratification factors (gender, insulin regimen (basal or biphasic), duration of T2DM (<5, 5–15 and 15–60 years) and age groups (25–40, 41–50 and >50 years)) as random factors. Baseline-adjusted means and their two-sided 95% CIs are presented. Odds ratio (OR) were computed for proportion of patients achieving target HbA1c in the two groups. 95% CIs of the OR are presented. Patients requiring increased insulin doses were compared using the proportion test and the reductions in insulin doses were compared between the two groups using the unpaired '*t*' test.

Results

Primary end points

Change in HbA1c (%) at 24 weeks Table 3 shows the HbA1c values (adjusted for baseline HbA1c) at baseline, 24 weeks and change from baseline. The two groups had similar HbA1c values at baseline ($P=0.36$). The ANCOVA results show significant differences in the change in HbA1c with sitagliptin (100 mg) and glimepiride (1–3 mg) ($P<0.001$), with greater reductions in HbA1c seen with sitagliptin regimen compared to glimepiride regimen. There was no significant effect of baseline HbA1c ($P=0.86$), age of the patients ($P=0.202$), duration of diabetes ($P=0.455$) and insulin regimen ($P=0.099$) on the change in HbA1c. However, there was a significant effect of gender ($P=0.002$) on the change in HbA1c at 24 weeks.

Patients achieving HbA1c (%) target At 24 weeks, the patients achieving target HbA1c of <7.0% with sitagliptin (100 mg) (59.62%) were significantly higher ($z=3.594$, O.R.=2.043, 95% CI=1.384–3.017, $P=0.0003$) compared to glimepiride (1–3 mg) (41.95%) therapy. Similarly, for a target HbA1c of <6.5% at 24 weeks, the percentage of patients attaining the target HbA1c was higher ($z=3.871$, O.R.=2.895, 95% CI=1.690–4.960, $P=0.0001$) with sitagliptin (25.82%) than with glimepiride (10.73%) therapy (Fig. 2).

Secondary end points

Change in insulin TDD (IU/day) Table 4 shows the proportion of patients in sitagliptin (100 mg) and glimepiride (1–3 mg) groups requiring a change in insulin dose (30-day geometric mean) at the end of 24 weeks. Compared to glimepiride, a greater proportion of patients on sitagliptin had a reduction in insulin dose ($P<0.0001$). Also, more patients on glimepiride required an increase in insulin dose ($P<0.0001$) compared to sitagliptin (36.10% vs 17.84%). The mean reduction in insulin TDD with sitagliptin was 39.38%, whereas with glimepiride, it was 31.74% ($P=0.003$).

Body weight (kg) A mean decrease in body weight of −0.30 (1.79) kg was observed with sitagliptin (100 mg) at 24 weeks, whereas with glimepiride (1–3 mg), there was an increase in the body weight by 0.54 (1.86) kg (Table 5). Thus, patients in the sitagliptin group had a decrease in

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Table 3 HbA1c (%) values and change from baseline values (PP dataset).

	Sitagliptin (100 mg) ($n=213$)				Glimepiride (1–3 mg) ($n=205$)				'P'
	N	Mean	S.D.	95% CI	*N*	Mean	S.D.	95% CI	
HbA1c values									
Baseline	213	7.78 (62) Range (7.0–8.5)	0.56 (6.1)	7.92 (63) to 8.01 (64)	205	7.83 (62) Range (7.0–8.5)	0.45 (4.9)	7.85 (62) to 7.94 (63)	0.36
24 weeks	213	7.08 (54)	1.01 (11)	6.95 (52) to 7.21 (55)	205	7.52 (59)	1.02 (11.1)	7.39 (57) to 7.65 (60)	<0.0001
Change from baseline in HbA1c at 24 weeks									
All patients	213	−0.70 (−9.6)	0.15 (1.6)	−0.78 (−11) to −0.61 (−8.2)	205	−0.31 (−4.2)	0.15 (1.6)	−0.40 (−5.6) to −0.22 (−2.7)	<0.001
Gender									
Male	101	−0.97 (−10.6)	0.16 (1.7)	−1.15 (−12.6) to −0.79 (−8.6)	105	−0.58 (−6.3)	0.13 (1.4)	−0.76 (−8.3) to −0.40 (−4.4)	<0.01
Female	112	−0.79 (−8.6)	0.14 (1.5)	−0.97 (−10.6) to −0.62 (−6.8)	100	−0.18 (−2.0)	0.13 (1.4)	−0.37 (−4.0) to 0.00005 (0.1)	<0.01
Duration of DM (years)									
<5	30	−0.80 (−8.7)	0.23 (2.5)	−1.26 (−13.8) to −0.34 (−3.7)	37	−0.39 (−4.3)	0.21 (2.3)	−0.80 (−8.7) to −0.02 (−0.2)	<0.01
5–15	112	−0.78 (−8.5)	0.12 (1.3)	−1.02 (−11.1) to −0.55 (−6.0)	103	−0.32 (−3.5)	0.10 (1.1)	−0.52 (−5.7) to −0.11 (−1.2)	<0.05
>15	71	−0.38 (−4.2)	0.17 (1.9)	−0.71 (−7.8) to −0.06 (−0.7)	65	−0.29 (−3.2)	0.13 (1.4)	−0.55 (−6.0) to −0.02 (−0.2)	<0.05
Age group (years)									
25–40	15	−0.60 (−6.6)	0.28 (3.1)	−1.15 (−12.6) to −0.05 (−0.5)	20	−0.44 (−4.8)	0.26 (2.8)	−0.95 (−10.4) to −0.07 (−0.8)	<0.05
41–50	68	−0.55 (−6.0)	0.16 (1.7)	−0.86 (−9.4) to −0.23 (−2.5)	64	−0.36 (−3.9)	0.16 (1.7)	−0.66 (−7.2) to −0.05 (−0.5)	>0.05
>50	130	−0.86 (−9.4)	0.09 (1.0)	−1.04 (−11.4) to −0.68 (−7.4)	121	−0.25 (−2.7)	0.09 (1.0)	−0.42 (−4.6) to −0.07 (−0.7)	<0.05

All values for HbA1c expressed as % (mmol/mol eq).

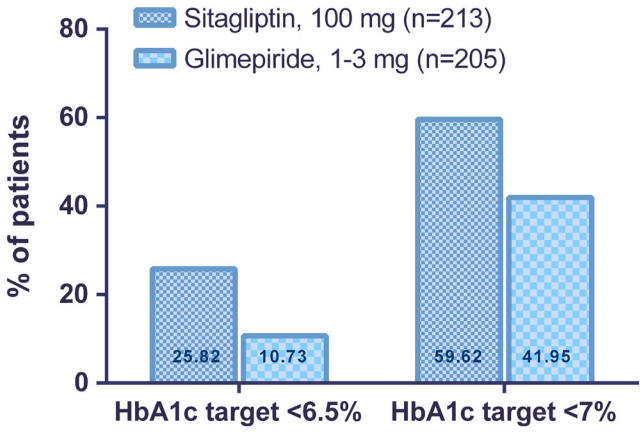

Figure 2
Percentage of patients achieving HbA1c target of <6.5% and <7.0% at 24 weeks.

BMI, whereas those in glimepiride group had an increase in BMI ($P=0.002$).

Other clinical parameters The changes in C-peptide levels observed after 24 weeks were similar with sitagliptin (100 mg) and glimepiride (1–3 mg). In addition, no differences were observed among the two treatments with respect to other clinical parameters such as total cholesterol, LDL cholesterol and triglycerides at 24 weeks (Table 6).

Safety Table 7 depicts the hypoglycemia with sitagliptin (100 mg) (2.34%) and glimepiride (1–3 mg) (27.80%) groups ($P<0.0001$) with 8 (3.90%) events of severe hypoglycemia documented in the glimepiride group and none with sitagliptin.

Discussion

Type 2 diabetes is a major risk factor for developing both microvascular and macrovascular complications (19). The primary goal of treatment is to target glycemic control by maintaining the HbA1c level near 6–7% in order to decrease the incidence of microvascular and macrovascular complications without predisposing patients to hypoglycemia (20). ADA-EASD position statement states that metformin, along with lifestyle changes, should be considered first-line therapy in patients with T2DM. If diabetes remains uncontrolled with first-line therapy, medications including insulin, SU, thiazolidinediones (TZDs), gliptins, GLP-1 analogs

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Table 4 Change in insulin dose (PP dataset).

	Sitagliptin (100 mg) (n=213)	**Glimepiride** (1–3 mg) (n=205)	***P* Value**
Insulin dose change	**No. (%)**	**No. (%)**	**'*P*' (χ^2 test)**
Dose not reduced	12 (5.63)	18 (8.78)	<0.0001
Dose reduced	163 (76.53)	113 (55.12)	χ^2=21.684
Dose increased	38 (17.84)	74 (36.10)	
Insulin dose (IU/day)	**Mean (S.D.)**	**Mean (S.D.)**	**'*P*' ('*t*' test)**
Baseline	28.71 (16.80)	27.23 (17.42)	0.477
24 weeks	18.76 (14.58)	19.77 (15.19)	0.579
Change in insulin dose	**Mean (S.D.)**	**Mean (S.D.)**	**'*P*' ('*t*' test)**
Mean reduction	−9.96 (5.80)	−7.46 (5.67)	<0.0001
% reduction	−39.38 (20.52)	−31.74 (20.68)	0.003

or gliflozins may be employed (21). The use of these traditional agents may be limited, however, because of several factors. Biguanides and TZDs improve the insulin resistance, but do not address the progressive decline in beta-cell function. SU can lose their effectiveness over time, while TZDs increase the risk of fracture and cardiac failure. Hence, new treatment options are sought.

One recent approach is to target the incretin mimetic hormone GLP-1. GLP-1 is released in response to hyperglycemia, and it stimulates insulin secretion, decreases glucagon secretion, improves beta-cell function and slows the gastric emptying. GLP-1 production is reduced in patients with T2DM. Once GLP-1 is produced, it is rapidly degraded by DPP-4 (22). By blocking the enzyme with DPP-4 antagonists, e.g., Sitagliptin, the action of GLP-1 hormone is prolonged. Once the blood glucose level approaches normal, the amounts of insulin released and glucagon suppressed diminish, thus preventing an 'overshoot' and subsequent hypoglycemia which is seen with some other oral hypoglycemic agents (23, 24).

This prospective, open-label, randomized, parallel-group study was conducted at a specialty diabetes care center in Southern India in 440 T2DM patients with inadequate glycemic control. The incretin-based therapies like GLP-1 agonists and DPP-4 inhibitors are being reported to be particularly effective in Asian patients with T2DM (25). This could be due to genetic factors, possibly greater incidence of insulin deficiency rather than insulin resistance in Asians. The possible cause of this has been suggested as an underlying GLP-1 insufficiency (26).

Study revealed that, in both the arms, the addition of sitagliptin (100 mg) vs glimepiride (1–3 mg) provided meaningful and statistically significant HbA1c-lowering efficacy, with greater reductions observed in patients with sitagliptin than glimepiride. The findings are consistent with those reported in some recent studies (10, 14, 15). In addition, more patients with the sitagliptin-based therapy achieved the HbA1c targets of <6.5% or <7% after 24 weeks compared to glimepiride-based therapy.

The % reduction in insulin dose achieved with sitagliptin (100 mg) was also greater when compared to glimepiride-treated (1–3 mg) group. These improvements achieved in TDD could have been possibly due to reductions observed in hypoglycemic events and thereby considerable reductions in their defensive eating behavior. With advancing stages in T2DM, glycemic variability (GV) could be a significant risk factor contributing to endothelial damage and vascular complications and the standard deviation (S.D.) around a mean glucose value measured over a 24-h period using the continuous glucose monitoring (CGM) system is probably the most appropriate tool for assessing intraday GV (27). An Indian data on T2DM subjects assessing GV showed increasing S.D. with increasing TDD of insulin (28). In this context, the reduction in TDD achieved with sitagliptin holds greater significance and point toward the need of a further in-depth study by employing more advanced technologies like CGM. The increasing utilization of insulin is also a cause for concern due its suggested role in carcinogenesis (29, 30) and hence, achieving a lower TDD with sitagliptin should be considered truly beneficial.

Patients in the sitagliptin (100 mg) group were found to achieve greater weight loss compared to

Table 5 Body weight and BMI (PP dataset).

	Sitagliptin (100 mg) (n=213)	**Glimepiride** (1–3 mg) (n=205)	**'*t*' test**
	Mean (S.D.)	Mean (S.D.)	'*P*'
Body weight (kg)			
Baseline	67.31 (10.22)	64.03 (11.12)	0.002
24 weeks	67.01 (10.40)	64.64 (11.00)	0.024
Change from baseline	−0.30 (1.79)	0.54 (1.86)	<0.0001
BMI (kg/sq m)			
Baseline	26.02 (3.32)	25.15 (3.69)	0.012
24 weeks	25.83 (3.74)	25.34 (3.63)	0.181
Change from baseline	−0.20 (1.57)	0.19 (0.81)	0.002

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Table 6 Laboratory parameters (PP dataset).

	Sitagliptin (100 mg) (n = 213)	**Glimepiride** (1–3 mg) (n = 205)	**Unpaired 't' test**	
	Mean (S.D.)	Mean (S.D.)	't'	'P'
C-peptide				
Baseline	3.08 (2.81)	2.67 (2.51)	1.569	0.117
Change at 24 weeks	−0.06 (0.27)	−0.15 (1.77)	0.764	0.446
Total cholesterol (mg%)				
Baseline	137.58 (28.67)	143.57 (33.22)	−1.974	0.049
Change at 12 weeks	−4.0 (27.62)	−4.60 (32.39)	0.198	0.843
Change at 24 weeks	3.02 (32.80)	−2.86 (37.77)	1.701	0.090
Triglycerides (mg%)				
Baseline	99.58 (37.66)	100.88 (36.44)	−0.357	0.721
Change at 12 weeks	−9.44 (31.76)	−8.57 (28.80)	−0.295	0.768
Change at 24 weeks	−18.61 (31.14)	−20.19 (30.51)	0.525	0.600
LDL cholesterol (mg%)				
Baseline	70.77 (26.83)	74.20 (27.76)	−1.284	0.200
Change at 12 weeks	−1.56 (27.26)	−3.25 (27.51)	0.631	0.528
Change at 24 weeks	−7.41 (31.07)	−10.53 (30.43)	1.035	0.301
HDL cholesterol (mg%)				
Baseline	47.04 (11.79)	47.13 (11.30)	−0.079	0.937
Change at 12 weeks	−0.11 (7.50)	0.23 (4.69)	−0.556	0.578
Change at 24 weeks	−1.09 (9.08)	−0.75 (5.02)	−0.475	0.635

glimepiride-treated (1–3 mg) group. The findings reported by Amjad Abrar and coworkers (15) are similar to our findings. Aforementioned study was conducted in Pakistan where the patients have a similar profile to that of the Indian population. Significant reductions achieved in TDD with sitagliptin also suggest an insulin-sparing effect of DPP-4 inhibitors. Our results are similar to that reported by Yuji Tajiri and coworkers (31) where addition of sitagliptin to insulin reduced glycosylated hemoglobin and glucose fluctuation in Japanese patients with T2DM. This is an attractive proposition owing to the likelihood of further decreases in the risk of hypoglycemia and weight gain.

Even though our results reveal that sitagliptin (100 mg) improves glycemic control in T2DM patients poorly controlled on insulin with metformin, relative to glimepiride (1–3 mg) while reducing insulin dose, the open-label study design and the submaximal dose of glimepiride in control group should be considered as the limitations of the study. One other limitation is that the study compares two classes of drugs – Sulphonylurea and DPP4i which have different mechanisms of action, former requiring dose titration and latter having fixed dose. A more detailed investigation using a CGM would have definitely provided more insights into the extent of glycemic variations confronted by these individuals. Also, the narrow inclusion criteria and wide exclusions limit the generalization of the study results.

Conclusion

Sitagliptin (100 mg), when compared to glimepiride (1–3 mg), bestowed beneficial effects to T2DM patients in terms of achieving greater glycemic control and also brought significant reductions in TDD of insulin required, bodyweight, BMI and hypoglycemic events. On the whole, the results suggest that sitagliptin (100 mg) is a better agent over glimepiride (1–3 mg) as an add-on to insulin–metformin therapy among Asian Indians with T2DM.

Table 7 Patients having hypoglycemia during therapy.

	Sitagliptin (100 mg) (n = 213)	**Glimepiride** (1–3 mg) (n = 205)	χ^2 **test**	
	>No. (%)	No. (%)	'χ^2'	'P'
Hypoglycemia type				
Asymptomatic hypoglycemia	0	1 (0.49)		
Doc. Sympt. hypoglycemia	2 (0.94)	28 (13.65)		
Prob. Sympt. hypoglycemia	0	6 (2.93)		
Relative hypoglycemia	3 (1.41)	14 (6.83)		
Severe hypoglycemia	0	8 (3.90)		
Total patients having hypoglycemia	5 (2.34)	57 (27.80)	48.295	<0.0001

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Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
J D K researched data, and edited and reviewed the manuscript. P B S researched data, A S reviewed the manuscript, G K contributed to the discussion and edited the manuscript, and S J contributed to discussion. J D K is the guarantor of this work, and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis.

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