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Glycemic Outcomes Of Dapagliflozin, Glimepiride, And Sitagliptin As Add-On Therapy To Metformin In Patients With Type 2 Diabetes Mellitus: A Prospective Observational Study

Maheshwaran A[1], Dhanapal C K[1*], Sundhararajan R[2]

[1] Department of Pharmacy, FEAT, Annamalai University, Tamil Nadu, India
[2] Department of Pharmacy, Mohamed Sathak AJ College of Pharmacy, Chennai, Tamil Nadu, India.

Abstract:

Background: Type 2 diabetes mellitus (T2DM) is a metabolic disease marked with progressive entity that cannot be managed effectively without combination therapy. Compared to randomised trials, which allow control of efficacy data, there is a dearth of real-world comparative data on second-line agents.

Objectives: The aim is to compare glycemic outcomes between dapagliflozin, glimepiride and sitagliptin as an addition to metformin in patients with T2DM.

Methods: An observational, prospective study was commissioned in a tertiary care hospital during a period of 9 months. Patients with T2DM under treatment were included by selection and maintained based on the add-on therapy administered by their treating doctor: dapagliflozin (n=40), glimepiride (n=40) or sitagliptin (n=40). The first-order outcomes were the changes in glycated haemoglobin (HbA1c), blood sugar fasting (FBS), postprandial blood sugar (PPBS). ANOVA analyses were conducted with $p<0.05$ taken as significant.

Results: Baseline results showed that groups were similar in the following domains: age, sex, years of diabetes, and glycemic indices. HbA1c levels differed significantly 9 months post-intervention in all groups, with the dapagliflozin group showing the greatest (−1.7%, $p< 0.001$) drop, then sitagliptin (−1.3), and lastly glimepiride (−0.9). The same trend was observed in FBS and PPBS where the most significant improvements could be observed in dapagliflozin.

Conclusion: Dapagliflozin has been found to have better glycemic effects than glimepiride and sitagliptin as an add-on medication to metformin in the real-life setting. Sitagliptin had intermediate levels of benefits and good toleration whereas glimepiride was no weaker but of lesser effectiveness in the management of glucose. This evidence justifies patient-specific therapeutic choices depending on their efficacy and their safety, as well as the context of the patient.

Keywords: T2DM, Dapagliflozin, Metformin, Sitagliptin, Glimepride, Observational study.

1.INTRODUCTION:

Diabetes mellitus type 2 (T2DM) has become a major health issue in the world in the 21st century. The International Diabetes Federation (IDF) 2021 report states that today there are about 537 million adults with diabetes in the world, out of which the number has reached 738 million that are expected to occur by 2045. India really is one of the leading countries in the measure of diabetes, with approximately 74 million cases. T2DM is linked with severe microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (cardiovascular disease, stroke, peripheral arterial disease) debilitations that impose significant morbidity, death, and health-intervention costs.[1][2]

Lifestyle change alongside the use of pharmacology is the basis of the T2DM management segment, which is initially metformin as it is effective, safe, and affordable [3]. Nevertheless, being progressive in nature, most patients will be in need of therapy intensification after 2-3 years of diagnosis with T2DM

[4]. The reason behind selecting second-line therapy depends on glycemic targets, comorbidities, costs, and patient-specific integrations including risk of hypoglycemia, weight and cardiovascular well-being [5, 6].

Sulfonylureas (e.g., glimepiride), dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin) and sodium–glucose cotransporter-2 (SGLT2) inhibitors (e.g., dapagliflozin) are common choices of second-line therapy [7]. The action of sulfonylureas is the enhancement of insulin secretion; these are very effective at glucose-lowering but may result in hypoglycemia and weight gain. DPP-4 inhibitors increase natural incretin hormones that portend moderate glucose reduction, without case of hypoglycemia and weight-neutrality [8]. SGLT2 inhibitors have the impact of reducing kidney glucose reabsorption, resulting in improved glycemia, reduced weight loss, and cardiovascular outcomes, but increased risks of genitourinary infections [8].

Although the effectiveness of such drugs has been proved by randomised controlled trials (RCTs), real world experience is crucial in interpreting their outcomes in the context of everyday clinical practise. Observational studies offer complementary literature to RCT results, including diverse patient populations, multiple adherences and reflect the true trends in prescribing.

The purpose of this prospective observational study was to evaluate comparative effects of dapagliflozin, glimepiride, and sitagliptin as either an add-on oral therapy compared to metformin in a T2DM population under tertiary care in an Indian hospital.

2.MATERIAL AND METHODS:

2.1 Study Design:

This prospective, observational, single-centre study was conducted in the Diabetes Outpatient Department of KVT speciality Hospital, Erukkancherry, Chennai, Tamil Nadu, India, over a span of 9 months (January- September 2024).

2.2 Ethical Considerations:

The protocol to conduct the research was approved by the Institutional Ethics Committee of KVT Multi Speciality Hospital (KVTSH-IEC), reference number of ECR/1663/Inst/TN/2022. All the participants completed an informed consent in writing before enrolment.

2.3 Criteria for patient recruitment:

Inclusion criteria

The criteria encompassed men and women aged 20-60 years with a known type 2 diabetes mellitus (T2DM) diagnosis based on the conditions of the American Diabetes Association (ADA) guidelines. Potential participants had to have a steady regimen of at least 1000 mg per day of metformin that had to be at least three months. Moreover, only participants with a glycated haemoglobin (HbA1c) of < 6.5% and an estimated glomerular filtration rate (eGFR) of >60 ml/min /1.73 m^2 were taken into consideration. Enrolment took place when patients had signed informed consent.

Exclusion Criteria

The patients were not allowed to participate in the study in case they had type 1 diabetes, chronic kidney disease (CKD), dialysis, hepatic dysfunction that was chronic or severe, pregnant or lactating. Patients whose serum creatinine was >1.3 mg/dl or more, or whose eGFR was less than 60 ml/min/1.73 m^2 were ineligible. Other exclusion criteria were diabetic keto acidosis, the history of frequent severe hypoglycemia, clinically significant psychiatric illness, using insulin, glucagon-like peptide-1 (GLP-1) receptor agonists or complementary and alternative medicines.

2.4 Sample size determination:

As per the recommendation from the statistician, the sample size was calculated from the standard formula. The calculations were made having two-sided $\alpha = 0.05$ (type 1 error) ie $Z_{1-\alpha/2} = 1.96$, Power

(1-β) = 0.80 ie $Z_{1-\beta}$ = 0.84, Standard deviation = 0.8% based on the prior clinical studies, Target difference (Δ) = 0.5%, which resulted in a sample size of 40 participants in each group.

2.5 Procedure of the study:

The eligible patients were recruited and selected in three treatment categories based on the add-on therapy that their treating professional advised. Group A was given dapagliflozin 5 mg daily state in combination with metformin, Group B was treated with glimepiride 2-4 mg in combination with metformin and Group C was treated sitagliptin 100 mg daily with metformin. Background metformin therapy was maintained at a steady dosage, and continued through the study period. Clinical and biochemical measurements, such as HbA1c, postprandial blood sugar (PPBS), fasting blood sugar (FBS), and baseline, three, six-, and nine-months patient monitoring were performed. The waiting resolution (safety outcomes) was also recorded during every follow-up visit (adverse events and hypoglycemic episodes).

2.6 Data Collection:

Baseline and 3-, 6-, and 9-month follow-up visits were used to record patient-data. The glycemic indices, comprising HbA1c, FBS, PPBS were made the main parameters of the assessment. Moreover, anthropometric data as body weight and body mass index (BMI) were collected. The safety measurements were conducted regularly during the study period, especially noting incidences of hypoglycemia, i.e. a blood glucose level lower than 70 mg/dL on record as well as any other adverse episode as reported by the participants.

2.7 Statistical Analysis:

All data were analysed with SPSS v25.0. The variables of continuous values were expressed in terms of mean ± SD. Paired t-tests were used to carry out intra-group comparisons. An ANOVA was followed with post-hoc test (Tukey) to assess inter-group differences. The p-value of less than 0.05 was regarded as significant.

3. RESULTS:

3.1 Baseline Characteristics:

The baseline characteristics of 120 patients were collected and were compared across groups. No significant difference was observed between the groups which has been tabulated in **Table 1.**

Parameter	Dapagliflozin (n=40)	Glimepiride (n=40)	Sitagliptin (n=40)	p-value
Age-wise distribution				
20-40	18 (45.0)	19 (47.5)	20(50.0)	0.90
40-60	22 (55.0)	21 (52.5)	20(50.0)	
Gender				
Male	24 (60.0%)	23 (57.5%)	22(55.0)	0.74
Female	16 (40.0%)	17 (42.5%)	18(45.0)	
Blood Pressure (BP)				
Systolic BP	128.4±8.6	129.2±9.0	127.9±8.4	0.79
Diastolic BP	81.5±6.2	82.1±6.5	81.2±6.0	0.83
Duration of Diabetes (years)	4.4±3.2	4.7±3.4	4.5±3.0	0.90
BMI (kg/m^2)	27.6±3.1	27.8±2.9	27.4±3.2	0.81
HbA1c (%)	8.1±0.6	8.2±0.5	8.0±0.6	0.63
FBS (mg/dl)	176±18	174±20	178±19	0.70
PPBS (mg/dl)	276±25	280±27	278±26	0.77

Table 1: Comparison of baseline parameters among the study group.

3.2 Changes in the glycaemic parameters within the groups over 9 months:

The three treatment groups had similar parameters of glycemia at a baseline. As of the 3rd month, the reduction in the fasting blood sugar (FBS) was observed in all groups with the highest growth in dapagliflozin (p = 0.0329), sitagliptin (p = 0.0316), and glimepiride (p = 0.0316). There was a significant decrease in postprandial blood sugar (PPBS) but not in sitagliptin at this point, but in the dapagliflozin and glimepiride groups (p=0.0161). The dapagliflozin group only (p = 0.00998) experienced significant reduction in HbA1c, whereas sitagliptin (p = 0.329) was unable to demonstrate significant reductions at 3 months or glimepiride (p = 0.452).

Two-thirds and nine-month later, the effects were yet to be seen in the glimepiride pre- and six and nine-months arms, respectively, as significant changes were observed in every glycemic index in the dapagliflozin and sitagliptin arms; glimepiride was observed to have moderate effects. Remarkably, the statistical significance of HbA1c measurements was reached in the groups using dapagliflozin and sitagliptin, but not in the glimepiride one (p = 0.141)

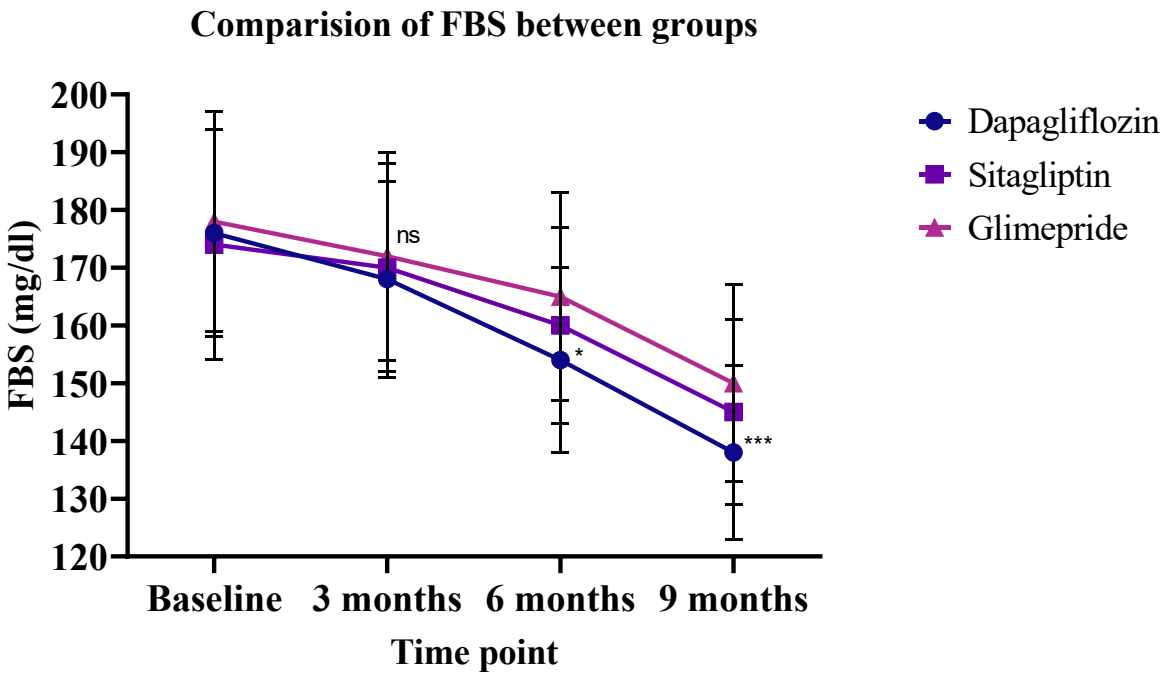
At month 9, the three treatment arms exhibited substantial and statistically significant improvement in HbA1c, FBS and PPBS as compared with baseline. The same has been represented in **Table 2.**

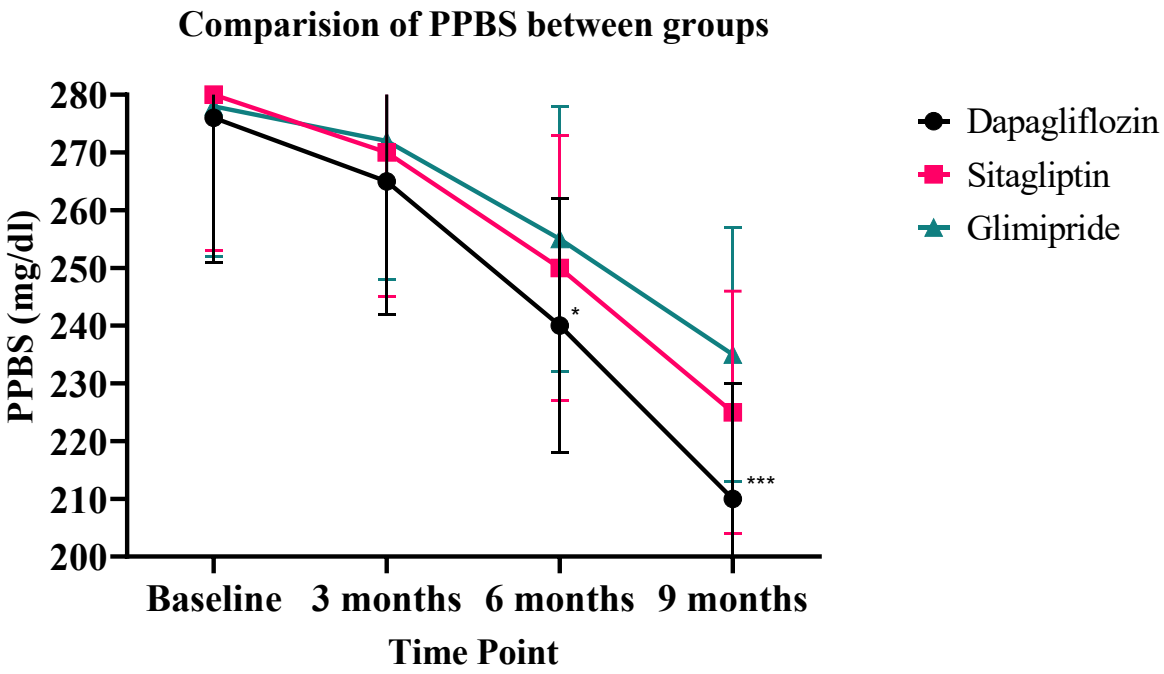
Parameter	Baseline	3 months	p-value	6 months	p-value	9 months	p-value
Group A (Metformin + Dapagliflozin)							
FBS	176±18	168±17	0.081	154±16	0.021	138±15	0.001
PPBS	276±25	265±22	0.092	240±21	0.030	210±18	0.001
HbA1c	8.1±0.6	7.9±0.7	0.089	7.4±0.6	0.028	6.9±0.5	0.001
Group B (Metformin + Sitagliptin)							
FBS	174±20	158±19	0.094	148±18	0.032	138±16	0.001
PPBS	280±27	262±23	0.101	240±22	0.041	220±22	0.001
HbA1c	8.2±0.5	7.9±0.6	0.097	7.5±0.5	0.037	7.2±0.5	0.001
Group C (Metformin + Glimipride)							
FBS	178±19	162±20	0.120	153±19	0.045	145±17	0.002
PPBS	278±26	255±26	0.128	240±22	0.050	230±21	0.003
HbA1c	8.0±0.6	7.9 ±0.5	0.141	7.8±0.6	0.048	7.5±0.4	0.004

Table 2: Measurement of glycemic indices during baseline, and 3, 6, and 9 months in patients placed in an add-on therapy to metformin. Measurements were as mean ± SD. Repeated-measures ANOVA was used to perform within-group comparisons and Bonferonni post-hoc test. Significance levels: p< 0.05, p< 0.01, p 0.001 p vs baseline.

3.3 Changes in the glycaemic parameters between the groups over 9 months:

All participants showed no statistical difference between the FBS, PPBS, or HbA1c levels of the three groups at baseline level (p > 0.05). At the 3-month follow-up, there were some minor numeric changes, which were in both directions equally in all treatment arms, and this was not statistically significant (ns). At 6 months, patients on dapagliflozin exhibited much larger changes in HbA1c, FBS, and PPBS than each of sitagliptin or glimepiride (p < 0.05), but there was no difference in sitagliptin vs. glimepiride. At 9 months, the effect of dapagliflozin was overwhelming when compared to sitagliptin or glimepiride in all glycemic parameters (p < 0.001). Moreover, sitagliptin showed greater reductions by a moderate difference compared to glimepiride at this period (p < 0.01). The comparison has been illustrated in **Figure 1**.


Comparision of FBS between groups
FBS (mg/dl)
200
190
180
170
160
150
140
130
120
ns
*
***
Baseline
3 months
6 months
9 months
Time point
Dapagliflozin
Sitagliptin
Glimepride


Comparision of PPBS between groups
PPBS (mg/dl)
280
270
260
250
240
230
220
210
200
*
***
Baseline
3 months
6 months
9 months
Time Point
Dapagliflozin
Sitagliptin
Glimipride

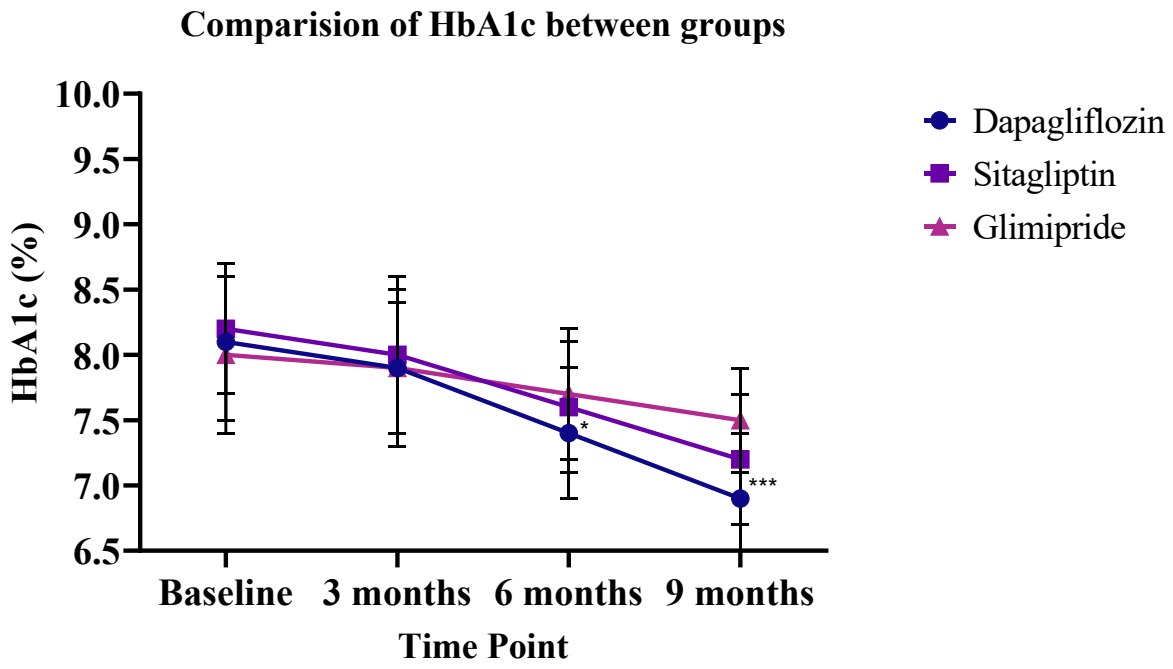


Figure 1: Glycemic index changes in patients using metformin plus dapagliflozin, sitagliptin, or glimepiride as an add on therapy over 9 months. (A) FBS (B) PPBS and (C) HbA1c. Data are expressed as mean ± SD. Post-hoc analysis was used in two-way ANOVA between-group comparisons. The significance is represented as follows: ns = not significant, $p < 0.05$, and **$p < 0.01$ and $p<0.001$.

4. DISCUSSION:

This prospective observational study aimed to determine comparative efficacy of dapagliflozin, sitagliptin, and glimepiride as add-on agents to metformin in T2DM patients. The outcomes showed that dapagliflozin presented the greatest gains in glycemic indices in 9 months followed by sitagliptin and glimepiride. These results are in line with and support both randomised controlled trials (RCTs) and real-world-based evidence.

We find the dapagliflozin experienced robust reductions in the HbA1c, FBS, and PPBS, which is in line with the results of the DECLARE-TIMI 58 trial [9], which recruited over 17,000 participants and provided significant HbA1c cutoff and cardiovascular outcomes with dapagliflozin versus placebo. Likewise, multi-centric real-life studies, like the CVD-REAL study [10], established the efficacy of SGLT2 inhibitors like dapagliflozin in both minimising glycemia and proving lower values of heart failure and cardiovascular mortality hospitalisation. Notably, our findings support such findings in a practical clinical context that highlights the fact that our glucose-lowering effect of dapagliflozin is not only when restricting to fasting level parameters but also when considering postprandial levels. This benefit mechanism is independent of insulin, forced by enhanced urinary glucose excretion, and can result in long-term glycemic control without excessive risk of hypoglycemia.

The sitagliptin exhibited moderate effects on the reduction of glycemic indices, with the strongest effect of PPBS, which is indicative of its incretin-like mechanism of action facilitating postprandial insulin revenge and inhibiting glucagon. These findings are consistent with TECOS trial [11], which demonstrated minimal HbA1c improvement (~0.30.4) /cardiovascular non-harmfulness of sitagliptin in more than 14,000 individuals. Similar effects on modest glycemic efficacy of DPP-4 inhibitors could be seen in real-world observational studies, including those by Fu et al. (2018), especially in patients whose duration of the diabetes had shorter periods. The role of sitagliptin as a safe and weight-neutral alternative, particularly when a postprandial control of glucose is a therapeutic priority, is therefore verified by our findings.

The reduction in HbA1c with glycemic regulators was lower at a significant categorization with glimepiride than either dapagliflozin or sitagliptin, which are also sulfonylureas. This is in line with the available evidence in which sulfonylureas albeit effective initially tend to decline in efficacy over time through progressive 8-cell depletion. Initial improvements observed with sulfonylureas were proved by the UKPDS (1998) although the long-term follow-up glycemic control was not favourable. Most recent comparative trials, including the CAROLINA trial in which linagliptin was compared with glimepiride [12], also demonstrated that whereas glimepiride effectively mandated HbA1c in the short-term, it did not last as well as the incretin-based therapies. We also find our results reflected in these findings, with glimepiride delivering smaller improvement but less effective than dapagliflozin or sitagliptin after 9 months follow-up.

5. CONCLUSION:

In this observation study, Dapagliftozin as add-on metformin therapy was found to have the most effective glycemic outcome related intervention on metformin in patients with type 2 diabetes in the two randomised controlled clinical trials. The positive effects of dapagliflozin were observed in a combination of fasting, postprandial, and long-term glycemic indicators, which is indicative of its independence of insulin. Sitagliptin was moderately effective with specific effect related to postprandial glucose whilst glimepiride gave relatively smaller changes which were in line with its decreasing efficacy over time. These results, consistent with evidence of large randomised controlled trials and observational studies, highlight the clinical benefit of dapagliflozin in the achievement of sustained glycemic control. They justify larger, more medium-term studies to be able to validate these observations and also investigate the outcome besides glycemia, e.g. cardiovascular and renal outcomes.

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