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Efficacy and Safety of Dapagliflozin as Adjunct Therapy in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Metformin and Sulfonylurea

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ABSTRACT

Background: Achieving adequate glycaemic control remains challenging in patients with type 2 diabetes mellitus (T2DM) receiving metformin and sulfonylurea. Dapagliflozin offers an additional glucose-lowering mechanism through inhibition of renal sodium-glucose cotransporter-2.

Aim: To evaluate the efficacy and safety of dapagliflozin as adjunct therapy in patients with T2DM inadequately controlled on metformin and sulfonylurea.

Materials and Methods: This prospective observational study included 147 patients with inadequately controlled T2DM receiving metformin and sulfonylurea. Dapagliflozin 10 mg once daily was added to the existing treatment regimen. Changes in HbA1c, fasting and postprandial blood glucose, body weight, BMI, blood pressure and laboratory safety parameters were assessed during follow-up. Adverse drug reactions were also recorded. Statistical significance was set at $p<0.05$.

Results: Mean HbA1c decreased by 0.769 percentage points, while fasting and postprandial blood glucose declined by 25.67 mg/dL and 36.49 mg/dL, respectively ($p<0.001$). Significant reductions were observed in body weight (2.27 kg), BMI (0.87 kg/m²), systolic blood pressure (4.60 mmHg) and diastolic blood pressure (2.40 mmHg) (all $p<0.001$). Renal function and haematological parameters showed no statistically significant changes. Urinary tract infections occurred in 4.1% of patients, genital infections in 3.4% and diabetic ketoacidosis was recorded in 1.4%.

Conclusion: Adjunctive dapagliflozin therapy was associated with improved glycaemic control, reduced body weight and lower blood pressure in patients inadequately controlled on metformin and sulfonylurea. Careful monitoring for adverse events, particularly infections and diabetic ketoacidosis, remains necessary.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by insulin resistance and impaired pancreatic β-cell function, resulting in persistent hyperglycaemia. Despite the availability of several glucose-lowering medications, many patients fail to achieve adequate glycaemic control with conventional treatment. The American Diabetes Association (ADA) recommends individualized treatment strategies based on glycaemic status, associated comorbidities, treatment response and the risk of adverse effects [1]. Cardiovascular risk reduction is also an important consideration when selecting antidiabetic therapy, particularly in patients with longstanding diabetes [2].

Metformin and sulfonylureas are commonly pre-

scribed oral antidiabetic agents because of their established efficacy, availability and relatively low cost. However, progressive β-cell dysfunction may reduce their effectiveness over time, necessitating additional treatment. The ADA and European Association for the Study of Diabetes (EASD) consensus report recommends treatment intensification when glycaemic targets remain unmet, with consideration of cardiovascular and renal benefits, body weight and hypoglycaemia risk [3].

Dapagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, reduces renal glucose reabsorption and promotes urinary glucose excretion through an insulin-independent mechanism. This complementary action makes it suitable for combination therapy with other glucose-lowering agents. Mathieu et al. [4] demonstrated improved glycaemic control with dapagliflozin-containing triple therapy in patients inadequately controlled on existing oral antidiabetic treatment.

The addition of dapagliflozin to metformin and sulfonylurea has shown favourable effects on glycated haemoglobin (HbA1c), body weight and fasting plasma glucose. Matthaei et al. [5] reported significant improvements in glycaemic control and body weight following dapagliflozin add-on therapy. Wilding et al. [6] also demonstrated sustained glucose-lowering efficacy in patients receiving insulin-based treatment, while Bailey et al. [7] reported improvements in glycaemic parameters when dapagliflozin was added to metformin.

Although dapagliflozin offers an additional therapeutic option, its use requires assessment of adverse effects, particularly genital infections, urinary tract infections, volume depletion and hypoglycaemia when combined with sulfonylureas. Evidence regarding its effectiveness and tolerability in routine Indian clinical settings remains relevant, especially among patients with inadequate glycaemic control despite dual oral therapy.

Therefore, the present study aimed to evaluate the efficacy and safety of dapagliflozin as an adjunct to metformin and sulfonylurea in patients with inadequately controlled T2DM, with particular emphasis on glycaemic improvement, body weight, blood pressure and adverse drug reactions.

MATERIALS AND METHODS

Study Design and Setting

The study evaluated the efficacy and safety of dapagliflozin as an adjunct to ongoing metformin and sulfonylurea therapy in patients with inadequately controlled T2DM. Patients were assessed for changes in glycaemic parameters, body weight, blood pressure and treatment-related adverse events during the study period.

Study Population

Adult patients with established T2DM who had inadequate glycaemic control despite treatment with metformin and a sulfonylurea were considered eligible for the study.

Inclusion Criteria

• Adults aged ≥18 years with diagnosed T2DM.

• Inadequate glycaemic control despite metformin and sulfonylurea therapy.

• Patients willing to participate and attend scheduled follow-up visits.

Exclusion Criteria

• Type 1 diabetes mellitus.

• Pregnancy or lactation.

• Diabetic ketoacidosis or acute metabolic complications.

• Severe renal impairment or contraindications to dapagliflozin.

• History of hypersensitivity to SGLT2 inhibitors.

• Patients with acute severe illness likely to interfere with treatment assessment.

Treatment and Follow-up

Patients receiving metformin and sulfonylurea therapy were evaluated following the addition of dapagliflozin. Clinical and laboratory parameters were assessed at baseline and during follow-up, with the principal efficacy assessment performed at 24 weeks.

Table 1: Age Distribution of Study Participants (n=147)

Age Group (Years)	Frequency (n)	Percentage (%)
40–45	23	15.6
46–50	22	15.0
51–55	23	15.6
56–60	16	10.9
61–65	19	12.9
66–70	23	15.6
71–75	21	14.3
Total	**147**	**100.0**

Outcome Measures

The primary outcome was the change in HbA1c from baseline to 24 weeks.

Secondary outcomes included changes in fasting plasma glucose, postprandial blood glucose, body weight, body mass index (BMI), systolic blood pressure and diastolic blood pressure.

Safety was evaluated by recording adverse drug reactions, including hypoglycaemia, urinary tract infections, genital mycotic infections, dehydration and diabetic ketoacidosis.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Changes in continuous parameters were assessed using appropriate paired statistical tests. Between-group comparisons, where applicable, were performed using independent-samples tests, while categorical variables were compared using the chi-square test or Fisher's exact test. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 147 patients with type 2 diabetes mellitus (T2DM), inadequately controlled on metformin and sulfonylurea, were included in the study. Dapagliflozin was added to their existing treatment regimen, and changes in glycaemic parameters, body weight, blood pressure and adverse events were assessed during follow-up.

The participants were distributed across the age groups of 40–75 years. The highest representation was observed in the 40–45, 51–55 and 66–70-year age groups, each accounting for 15.6% of the study population. The 56–60-year group had the lowest representation (10.9%).

Following dapagliflozin therapy, significant reductions were observed in HbA1c, fasting blood glucose and postprandial blood glucose (all p<0.001). The mean HbA1c reduction was 0.769 percentage points, while fasting and postprandial glucose decreased by 25.673 mg/dL and 36.490 mg/dL, respectively.

Body weight decreased by an average of 2.272 kg, accompanied by a reduction in BMI of 0.871 kg/m². Systolic and diastolic blood pressure also declined significantly, with mean reductions of 4.599 mmHg and 2.395 mmHg, respectively.

Serum creatinine, blood urea and estimated glomerular filtration rate showed no statistically significant changes during follow-up. Haemoglobin, total leukocyte count and platelet count also remained statistically unchanged.

Urinary tract infections were recorded in 6 patients (4.1%), while genital infections occurred in 5 patients (3.4%). Diabetic ketoacidosis was documented in 2 patients (1.4%). The study also recorded two events in an additional adverse-event category, although the exact nature of these events requires confirmation from the original case records.

The available data indicate that most participants did not experience the specified adverse events during follow-up. However, the occurrence of diabetic ketoacidosis requires particular attention when assessing the overall safety of dapagliflozin.

DISCUSSION

The present study evaluated the efficacy and safety of dapagliflozin as adjunct therapy in 147 patients with type 2 diabetes mellitus inadequately controlled on metformin and sulfonylurea. Following treatment, significant improvements were observed in glycaemic parameters, body weight and blood pressure. Mean HbA1c decreased by 0.769 percentage points, while fasting and postprandial blood glucose declined by 25.67 mg/dL and 36.49 mg/dL, respectively (p<0.001). These findings are consistent with those of Ferrannini et al. [8], who demonstrated significant glycaemic improvement with dapagliflozin in patients with inadequately controlled type 2 diabetes.

The reduction in HbA1c observed in the present study is comparable to the findings of Strojek et al. [9], who reported improved glycaemic control when dapagliflozin was added to glimepiride. The glucose-lowering effect of dapagliflozin is independent of insulin secretion, making it a useful addition to conventional oral antidiabetic therapy. Nauck et al. [10] also

Table 2: Changes in Glycaemic and Clinical Parameters Following Dapagliflozin Therapy (n=147)

Parameter	Mean Reduction	t-value	p-value
HbA1c (%)	0.769	16.580	<0.001
Fasting blood glucose (mg/dL)	25.673	19.140	<0.001
Postprandial blood glucose (mg/dL)	36.490	18.609	<0.001
Body weight (kg)	2.272	17.614	<0.001
BMI (kg/m²)	0.871	14.977	<0.001
Systolic blood pressure (mmHg)	4.599	10.082	<0.001
Diastolic blood pressure (mmHg)	2.395	7.300	<0.001

Table 3: Changes in Body Composition and Laboratory Safety Parameters (n=147)

Parameter	Mean Change	t-value	p-value
Whole-body fat (%)	−1.313	13.349	<0.001
Whole-body muscle (%)	+0.395	−4.936	<0.001
ALT/SGPT	−1.129	2.429	0.016
AST/SGOT	−1.871	4.939	<0.001
Serum creatinine	No significant change	−1.642	0.103
Blood urea	No significant change	1.097	0.275
eGFR	No significant change	−1.895	0.060
Haemoglobin	No significant change	−0.687	0.493
Total leukocyte count	No significant change	−1.176	0.241
Platelet count	No significant change	0.783	0.435

A significant reduction in whole-body fat percentage was observed following treatment (p<0.001), accompanied by a modest increase in muscle percentage (p<0.001). Liver enzyme levels also decreased, with statistically significant changes in ALT (p=0.016) and AST (p<0.001).

Table 4: Adverse Events Reported During Follow-up (n=147)

Adverse Event	Frequency (n)	Percentage (%)
Urinary tract infection	6	4.1
Genital infection	5	3.4
Diabetic ketoacidosis	2	1.4
Additional adverse-event category*	2	1.4

demonstrated sustained glycaemic efficacy with dapagliflozin compared with glipizide when added to metformin, along with favourable effects on body weight.

Apart from glycaemic improvement, the present study recorded a mean weight reduction of 2.27 kg and a decrease in BMI of 0.87 kg/m². Systolic and diastolic blood pressure declined by 4.60 mmHg and 2.40 mmHg, respectively. These changes may be explained by urinary glucose loss and the associated osmotic diuretic effect of SGLT2 inhibition. Wiviott et al. [11], in the DECLARE–TIMI 58 trial, demonstrated cardiovascular benefits of dapagliflozin, particularly in reducing hospitalization for heart failure. McMurray et al. [12] subsequently reported a reduction in worsening heart failure and cardiovascular death among patients with heart failure and reduced ejection fraction. Although cardiovascular outcomes were not directly assessed in the present study, the observed reductions in weight and blood pressure are relevant to the overall cardiometabolic profile of these patients.

Renal function parameters, including serum creatinine, blood urea and estimated glomerular filtration rate, showed no statistically significant changes during follow-up. Heerspink et al. [13] demonstrated that dapagliflozin reduced the risk of kidney disease progression and adverse cardiovascular outcomes in patients with chronic kidney disease. Similarly, Solomon et al. [14] reported clinical benefits in patients with heart failure and mildly reduced or preserved ejection fraction. However, the present study was not designed to evaluate long-term renal or cardiovascular outcomes, and the absence of significant laboratory changes should not be interpreted as evidence of organ protection.

Regarding safety, urinary tract infections occurred in 6 patients (4.1%), genital infections in 5 patients (3.4%) and diabetic ketoacidosis was recorded in 2 patients (1.4%). These findings indicate the need for continued monitoring during dapagliflozin therapy, particularly in patients receiving sulfonylureas. Zelniker et al. [15], in a systematic review and meta-analysis, reported cardiovascular and renal benefits associated with SGLT2 inhibitors while emphasizing the importance of evaluating treatment-related risks. The two recorded cases of diabetic ketoacidosis in the present study require confirmation and clinical review before drawing conclusions regarding treatment safety.

The study was limited by its observational design, absence of a concurrent control group and relatively short follow-up period. Although significant improvements were observed after adding dapagliflozin, these changes cannot be attributed exclusively to the drug without accounting for other treatment-related and lifestyle factors. Longer controlled studies would help establish the durability of glycaemic improvement and clarify the incidence of uncommon adverse events.

CONCLUSION

Dapagliflozin added to metformin and sulfonylurea was associated with significant reductions in HbA1c, blood glucose, body weight and blood pressure in patients with inadequately controlled type 2 diabetes mellitus. Renal and haematological parameters remained statistically unchanged during follow-up. Urinary and genital infections were reported, along with two recorded cases of diabetic ketoacidosis, emphasizing the need for appropriate safety monitoring.

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