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ORIGINAL RESEARCH

Effect of dapagliflozin as fourth drug in type ii diabetes mellitus patients with poorly controlled glycemic status on triple drug therapy

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Abstract

Background: The worldwide pandemic, diabetes is managed by keeping the patient's glycemic index stable. The first-line treatment for diabetes is metformin; however, when metformin is insufficient, people need to take additional oral hypoglycemic agents (OHAs). A third OHA might be introduced if dual therapy doesn't work. Insulin is usually advised if triple therapy proves to be futile as well. Some people, though, reject insulin and would rather use a different OHA. Proposed as a fourth add-on medication, dapagliflozin's effectiveness requires additional clinical research.

Methods and Materials: This single arm prospective observational study enrolled 140 type 2 diabetes patients with uncontrolled hyperglycemia (HbA1c >7%) on triple drug therapy who refused insulin. Dapagliflozin was added, and patients were monitored over nine months.

Results: Key findings included significant reductions in HbA1c, fasting, and post-prandial blood sugar levels, with 53.6% achieving the target HbA1c (<7%) by the final follow-up. Treatment outcomes were associated with various baseline factors. UTIs were reported in 14.3% of patients, but this was not significantly linked to treatment success.

Conclusion: The findings of the study show that it is a useful strategy to attain targeted treatment goal without posing any additional risk due to use of fourth drug, However, its long-term impact on level of glycemic control needs to be assessed carefully.

Keywords: Diabetes, Insulin, Dapagliflozin, Glycemic Index.

Introduction

Diabetes is a global pandemic that has silently affected more than 500 million people worldwide and has affected almost every tenth adult[1]. There is an alarming increase in the incidence and prevalence of diabetes mellitus (DM) in Asian Indians[2]. Lifestyle, particularly dietary and physical activity status of an individual plays an important role in the pathogenesis and progression of diabetes. With the growing socioeconomic and technological changes, the changing lifestyle and physical activity of people throughout the world has witnessed a phenomenal increase in prevalence of diabetes and impaired glucose tolerance in adults [3,4,5,6,7.]

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Goal of any diabetic treatment is attainment of glycemic control as uncontrolled diabetes could pose various microvascular, macrovascular, and neuropathic issues, such as nephropathy, retinopathy and neuropathy . As per 2023, American Diabetes Association (ADA) guidelines, achieving glycated hemoglobin (HbA1c) level<7% is the targeted goal of treatment strategies for diabetes [8]. In a more graver form, it may also trigger cardiovascular events like myocardial infarction and stroke. Diabetes management follows a systematic stepwise approach starting with non-medical strategies centered around lifestyle changes and interventions, followed by patient centric pharmacological interventions beginning with use of oral hypoglycemic agents. Metformin is the first-line treatment through oral hypoglycemic agents[9], however, a large proportion of patients do not respond to metformin alone and require add-on treatment. Such patients are placed on dual therapy with the addition of another oral hypoglycemic agent that includes a combination of metformin and sulfonylureas are recommended for patients in whom metformin monotherapy fails to produce optimum decline in blood glucose levels [10,11,12]. A third OHA can also be added as a rescue when even dual therapy fails to achieve the targeted glycemic control. Failure to achieve glycemic control even after triple-drug therapy failure is an issue of concern and calls for intervention through insulin therapy [13]. However, a number of times, patients are reluctant to take insulin and insist on trial of another OHA. To cater to the need of such patients, Dapagliflozin has been proposed as fourth add-on drug to triple therapy[14,15,16]. However, the efficacy of this drug as fourth add on drug is still under scrutiny and requires substantial clinical evidence to assess whether it can be used as an alternative to compelling need for insulin therapy.

Hence, the present study was proposed as a single arm prospective observational study to assess the efficacy of Dapagliflozin as a fourth drug in type 2 diabetes mellitus patients with uncontrolled hyperglycemia who are already on triple drug therapy and refusing insulin.

Materials and methods

Study Site: Department of Medicine, Integral Institute of Medical Sciences and Research (IIMSR), Lucknow.

Study Design: Before-after.

Study period: Eighteen months, starting from September, 2022 to March, 2024.

Study Population: All patients of type 2 Diabetes mellitus who were inadequately controlled inspite of taking triple drug anti diabetic regimen for three months and who were reluctant to take insulin. All patients were using Metformin (500 to 2000 mg) + Glimepiride (2 to 4 mg) + Sitagliptin (100 mg) prior to intervention.

Sample Size: 140 patients

Inclusion Criteria

Type 2 diabetes mellitus Patients of both sexes (male and female) on maximum doses of 3 oral anti-diabetic agents having inadequate response (>7%).

Patients between 30 to 65 years who were inadequately controlled on 3 drug therapy.

Exclusion Criteria

Newly diagnosed cases of type 2 diabetes

Type 1 diabetes

Gestational diabetes

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Patients with eGFR <60ml/min/1.73mm^2
Patients with recurrent UTI and patients with history of diabetic keto acidosis and other comorbidities(cardiac, hepatic, renal diseases,stroke)
Patient not giving consent

Approvals and Permissions
Approval for the study was obtained from the Institutional Ethics Committee. Informed consent was obtained from all the patients enrolled in the study.

Methodology: Patients data, medical history and dietary preferences were recorded ; they were screened for blood glucose , HbA1c, lipid and renal profile .Then, started on dapagliflozin 10 mg for 12 weeks with dietary and lifestyle counselling with HbA1c and blood sugar monitored at 1,3,6 and 9 months.

Data Management and Statistical Analysis
Data s collected was fed into computer using Microsoft Excel 2017 version. Data analysis was performed using IBM SPSS software version 25.Data has been represented as numbers and percentages for discrete/categorical variables. Continuous data has been represented using mean±standard deviation as the central tendency. Chi-square for categorical and Independent samples t-tests for continuous parametric variables were used for comparisons.
Paired comparisons of mean values were made using Repeat Measures ANOVA. A **p** value ≤0.05 was considered statistically significant.

Results
The present study was aimed to assess the effect of Dapagliflozin as a fourth drug in type 2 Diabetes mellitus patients with uncontrolled hyperglycemia who are already on triple drug therapy and refusing insulin. For this purpose, a total of 140 eligible patients were enrolled in the study. Table 1 shows the general profile and characteristics of study population.

Table 1: General profile and characteristics of study population (n=140)

SN	Characteristic	Statistic
1.	Mean age±SD(Range)in years	55.56±10.63(33-80)
2.	Male:Female	67(47.9%):73(52.1%)
3.	Mean BMI±SD(Range)kg/m^2	25.70±4.95(15.06- 38.34)
4.	Mean AC±SD(Range)cm	81.20±10.11(55-111)
5.	Occupation Agriculture/Farmer Business Service Labour/Skilled labour Self-employed Professional Teacher Housewife Retired	 20(14.3%) 32(22.9%) 13(9.3%) 5(3.6) 1(0.7%) 8(5.7%) 43(30.7%) 18(12.9%)
6.	H/o Hypertension	28(20.0%)
7.	H/o Dyslipidemia	11(7.9%)
8.	H/o CAD	0
9.	H/o CKD	0
10.	H/o Metabolic syndrome	0
11.	Diet	

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	Vegetarian Mixed	37(26.4%) 103(73.6%)

Table 2: Diabetic profile of study population at enrolment (n=140)

SN	Characteristic	Statistic
1.	Time since diagnosis <1year 1-2years 2.1-5Years	 21(15.0%) 101(72.1%) 18(12.9%)
2.	Mean HbA1c±SD(Range)%	8.84±1.52(7.0-14.0)
3.	Mean FBS±SD(Range)(mg/dl)	212.78±41.59(121-324)
4.	Mean PPBS±SD(Range)(mg/dl)	360.01±64.44(214-576)

Majority (n=101; 72.1%) of patients had diagnosis of diabetes mellitus for 1-2 years followed by those who had this diagnosis for <1 year (15%) and 2.1-5 years (12.9%) respectively Glycated haemoglobin (HbA1C) levels ranged from 7 to 14% with a mean of 8.84±1.52%. Fasting blood sugar levels ranged from 121 to 324 mg/dl with a mean of 212.78±41.59 mg/dl while post-prandial blood sugar levels ranged from 214 to 576 mg/dl with a mean of 360.01±64.44 mg/dl (Table 2; Fig. 1).

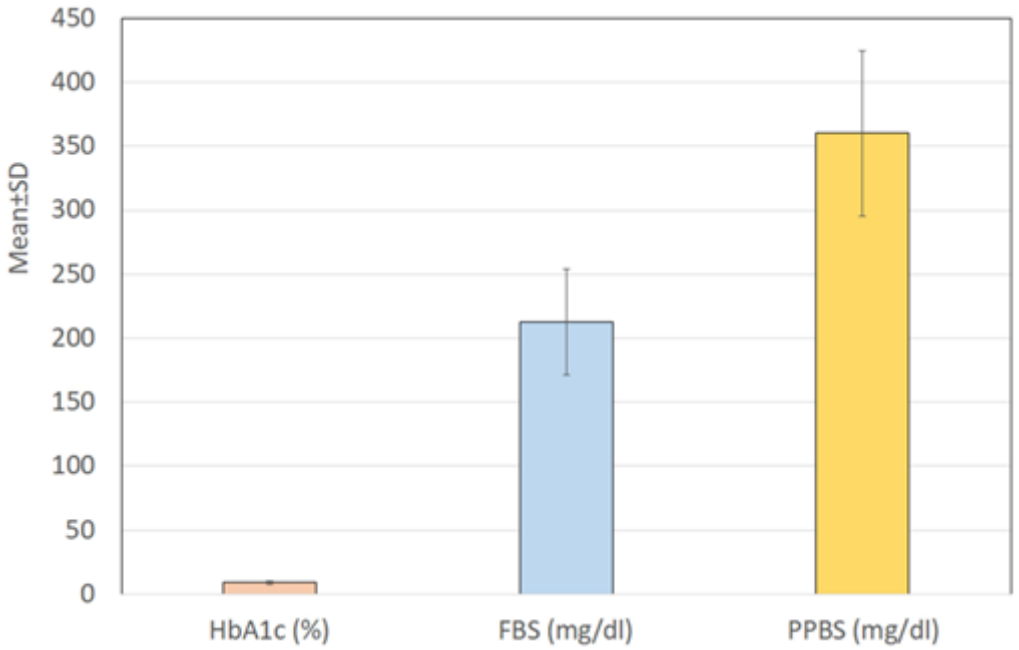

Fig. 1: Mean HbA1C, fasting and post-prandial blood sugar levels in study population

Table 3: Follow-up glycemic status (n=140)

SN	Parameter	Mean	SD
First FU(1month)			
1.	HbA1c(%)	8.24	1.64
2.	FBS(mg/dl)	164.14	58.76
3.	PPBS(mg/dl)	279.67	113.05
No. of patients achieving HbA1c ≤7% at follow-up(%)		34(24.3%)	
Second FU(3months)			
1.	HbA1c(%)	8.03	1.59
2.	FBS(mg/dl)	159.29	57.68

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3.	PPBS(mg/dl)	272.03	110.27
No. of patients achieving HbA1c ≤7% at follow-up(%)		41(29.3%)	
Third FU(6months)			
1.	HbA1c(%)	7.77	1.57
2.	FBS(mg/dl)	152.56	55.87
3.	PPBS(mg/dl)	262.28	107.33
No. of patients achieving HbA1c ≤7% at follow-up(%)		56(40.0%)	
Fourth FU(9months)			
1.	HbA1c(%)	7.52	1.59
2.	FBS(mg/dl)	146.66	55.01
3.	PPBS(mg/dl)	253.94	105.67
No. of patients achieving HbA1c ≤7% at follow-up(%)		75(53.6%)	
p <0.001 for all mean values (Repeat measures ANOVA)			

At first, second, third and final follow-up intervals, mean HbA1c levels were 8.24±1.64, 8.03±1.59, 7.77±1.59 and 7.52±1.59 % respectively, thereby showing a significant declining trend (p<0.001) .

At first, second, third and final follow-up intervals, mean fasting blood sugar levels were 164.14±58.76, 159.29±57.68, 152.56±55.87 and 146.66±55.01 mg/dl respectively, thereby showing a significant declining trend (p<0.001).

At first, second, third and final follow-up intervals, mean post-prandial blood sugar levels were 279.67±113.05, 272.03±110.27, 262.28±107.33 and 253.94±105.67 mg/dl respectively, thereby showing a significant declining trend (p<0.001).

Percentage of patients achieving targeted HbA1c levels was 24.3%, 29.3%, 40% and 53.6% respectively at first, second, third and final follow-up intervals.(Table 3)

Table 4: Evaluation of change in glycemic parameters at different follow ups as compared to baseline (n=140)

SN	Parameter	At enrolment		At FU		Change		Significance of change (Paired 't'-test)	
		Mean	SD	Mean	SD	Mean	SD	't'	'p'
First FU									
1.	HbA1c (%)	8.84	1.51	8.24	1.64	-0.60	0.88	8.105	<0.001
2.	FBS(mg/dl)	212.28	41.59	164.14	58.76	-48.14	56.91	10.01	<0.001
3.	PPBS(mg/dl)	360.01	64.44	279.67	113.05	-80.34	92.04	10.327	<0.001
Second FU									
1.	HbA1c (%)	8.84	1.51	8.03	1.59	-0.86	0.88	10.780	<0.001
2.	FBS(mg/dl)	212.28	41.59	159.29	57.68	-52.99	56.10	11.176	<0.001
3.	PPBS(mg/dl)	360.01	64.44	272.03	110.27	-87.98	89.74	11.60	<0.001
Third FU									
1.	HbA1c (%)	8.84	1.51	7.77	1.57	-1.07	0.90	13.963	<0.001
2.	FBS(mg/dl)	212.28	41.59	152.56	55.87	-59.72	54.50	12.965	<0.001
3.	PPBS(mg/dl)	360.01	64.44	262.28	107.33	-97.73	87.13	13.271	<0.001
Fourth/Final FU									
1.	HbA1c (%)	8.84	1.51	7.52	1.59	-1.32	0.96	16.280	<0.001
2.	FBS(mg/dl)	212.28	41.59	146.66	55.01	-65.62	53.87	14.41	<0.001
3.	PPBS(mg/dl)	360.01	64.44	253.94	105.67	- 106.07	85.23	14.725	<0.001

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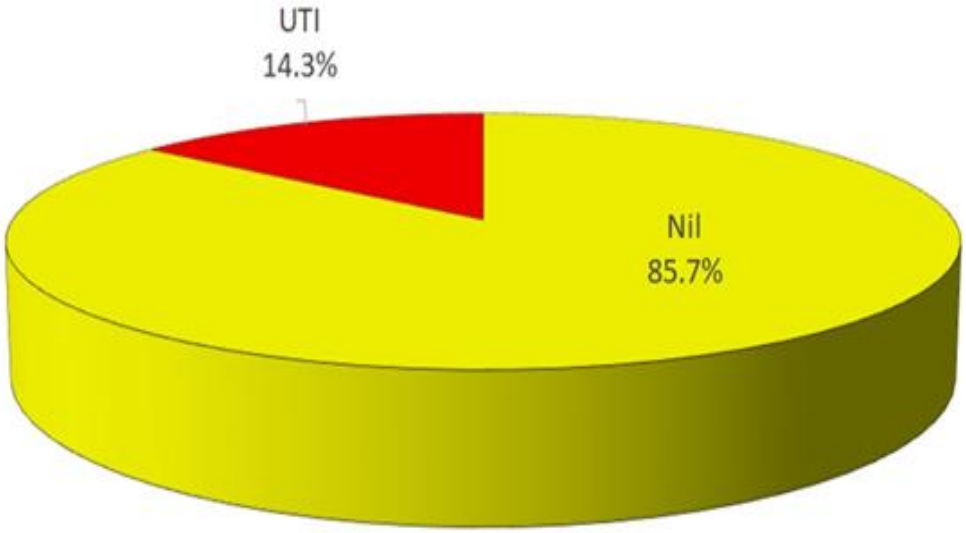
Mean reduction in HbA1c levels as compared to baseline were 0.60±0.88, 0.86±0.88, 1.07±0.90 and 1.32±0.96 % respectively at first, second, third and final follow-ups. A significant change in mean HbA1c levels as compared to baseline was observed from the first follow-up itself ($p<0.001$).

Mean reduction in fasting blood sugar levels as compared to baseline were 48.14±56.91, 52.99±56.10, 59.72±54.50 and 65.62±53.87 mg/dl respectively at first, second, third and final follow-ups. A significant change in mean fasting blood sugar levels as compared to baseline was observed from the first follow-up itself ($p<0.001$)

Mean reduction in post-prandial blood sugar levels as compared to baseline were 80.34±92.04, 87.98±89.74, 97.73±87.13 and 106.07±85.23 mg/dl respectively at first, second, third and final follow-ups. A significant change in mean post-prandial blood sugar levels as compared to baseline was observed from the first follow-up itself ($p<0.001$)(Table4).

Table 5: Adverse effects till final assessment (n=140)

SN	Variable	No.	%
1.	No adverse effect	120	85.7
2.	Urinary tract infection(UTI)	20	14.3



Most of the patients (n=120; 85.7%) did not experience any adverse effect. Adverse effects were experienced by only 20 (14.3%) patients. UTI was the adverse effect noted in all these cases (Table 5).

Discussion

The goal of diabetes treatment is glycemic control to prevent complications like nephropathy, retinopathy, and cardiovascular events. Management starts with lifestyle changes and progresses to pharmacological interventions, beginning with metformin. If needed, dual or triple oral hypoglycemic therapies are used, with insulin as a last resort. Dapagliflozin is proposed as a fourth drug option, though its efficacy needs more clinical evidence.

This study was a single-arm, prospective observational study of 140 type 2 diabetes patients on triple therapy who refused insulin. It assessed Dapagliflozin's efficacy and used lifestyle and dietary counseling. The study showed significant glycemic improvements, though with limitations such as lack of a control group.

Patients had a mean age of 55.56 years, a mean BMI of 25.70 kg/m², and a majority were females and housewives/business owners. Most had a short diabetes duration and no severe

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comorbidities, with lipid and renal profiles within normal ranges. The study observed significant HbA1c and blood sugar declines, with a success rate of 53.6%. UTIs were the main adverse effect.

Significant treatment associations were found with occupation, baseline dyslipidemia, HbA1c, blood sugar, lipid, and renal profiles. Limitations included the absence of a control group and difficulty isolating the effects of lifestyle interventions. Further studies are recommended to evaluate Dapagliflozin's long-term efficacy and safety.

Conclusion

The study evaluated Dapagliflozin as a fourth drug in 140 type 2 diabetes patients with uncontrolled hyperglycemia (HbA1c >7%), who were already on triple therapy and refused insulin. Patients received baseline evaluations and follow-ups at 1, 3, 6, and 9 months, with dietary and lifestyle counselling.

At enrolment, mean HbA1c, Fasting and post-prandial blood sugar levels were 8.84±1.52%, 212.78±41.59 mg/dl and 360.01±64.44 mg/dl respectively.

At the final assessment, mean reduction in HbA1C, fasting blood sugar and post-prandial blood sugar levels was 1.32±0.96%, 65.62±53.87 mg/dl and 106.07±85.23 mg/dl respectively. All the three parameters showed a significant reduction from baseline.

UTI was noted in 14.3% of patients. The study concludes that adding Dapagliflozin is effective and safe, but long-term effects and economic considerations, including higher costs compared to insulin therapy, warrant further investigation. Proper counseling is recommended to encourage insulin use where needed.

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