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Original Research Article

To Investigate the Impact of Further Treatment with SGLT 2 Inhibitors on Glycaemic Indices

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Abstract:

Background: Type 2 diabetes mellitus is a metabolic disorder characterised by elevated blood sugar levels due to the body's impaired ability to respond to insulin and decreased production of insulin. It represents over 90% of adult diabetes cases.

Aim: To investigate the impact of further treatment with SGLT-2 inhibitors on glycemic indices.

Material and Methods: A total of 50 patients, regardless of gender, aged between 18 and 70 years, who have been diagnosed with type 2 diabetes mellitus and have HbA1c levels greater than 7.0% despite treatment with metformin ± sulphonyl urea, were selected to participate in our research. These patients were then started on either Empa or Dapa, which are gliflozins, as an additional medication. It is important to note that all participants willingly agreed to be part of the study. The research excluded pregnant women, patients with systemic diseases other than diabetes, and those with a S. creatinine clearance of less than 60 ml/min.

Results: The comparison of glycemic parameters from baseline to follow-up visits at 3 months and 6 months showed significant improvements. The mean HbA1c decreased from 8.67% at baseline to 7.87% at 3 months, and further to 7.23% at 6 months. These reductions were statistically significant, with p-values of <0.001 for both time points compared to baseline. Similarly, the mean fasting blood sugar (FBS) levels decreased from 161.03 mg/dL at baseline to 141.76 mg/dL at 3 months and to 121.98 mg/dL at 6 months, with p-values <0.001 for both comparisons. The postprandial blood sugar (PPBS) levels also showed a significant reduction from 241.54 mg/dL at baseline to 201.86 mg/dL at 3 months and to 181.88 mg/dL at 6 months, again with p-values <0.001 for both comparisons. The ADR profile indicated that 20% of the patients experienced genital mycotic infections, 16% had urinary tract infections, 10% reported dehydration, and 6% experienced hypoglycemia. However, 48% of the patients did not report any adverse drug reactions, indicating a relatively manageable safety profile for the add-on SGLT2 inhibitor therapy. The correlation analysis revealed significant negative correlations between baseline HbA1c and reductions in glycemic parameters. The reduction in HbA1c had a correlation coefficient of -0.72 with a p-value of <0.001, indicating that higher baseline HbA1c levels were associated with greater reductions in HbA1c. Similarly, reductions in FBS and PPBS had correlation coefficients of -0.58 and -0.63, respectively, both with p-values <0.001.

Conclusion: SGLT-2 inhibitors are a potential new class of antidiabetic drugs that provide improved management of fasting blood sugar (FBS), postprandial blood sugar (PPBS), and glycated haemoglobin (HbA1c).

Keywords: glycosuria, HbA1c, type 2 diabetes mellitus, weight loss.

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Introduction

Type 2 diabetes mellitus is a metabolic disorder characterised by elevated blood sugar levels due to the body's impaired ability to respond to insulin and decreased production of insulin. It represents over 90% of adult diabetes cases [1,2]. Diet and exercise are essential components of treatment, with medication used to achieve desired blood sugar levels. The utilisation of existing medicines for type 2 diabetes mellitus (T2DM) is often constrained by their capacity to cause substantial negative effects. Metformin may lead to gastrointestinal symptoms such as diarrhoea and nausea and, in rare cases, lactic acidosis. On the other hand, sulphonylureas, or insulin, can cause hypoglycemia and weight gain [3]. More recent medications, such as the incretin mimetics, might cause symptoms such as nausea, vomiting, and diarrhea [4]. Achieving optimal glycemic control may be challenging, es-

pecially when using a combination of various oral medications and the addition of insulin [4,5]. The kidney plays a vital role in managing glucose levels by facilitating the absorption of glucose from the proximal tubules into the bloodstream. This is an important evolutionary adaptation for maintaining glucose balance and preserving energy. The procedure described here is responsible for the consistently high levels of glucose in the blood of people with diabetes, since they have an enhanced ability to reabsorb glucose in the kidneys [6]. Emerging as a promising new strategy for treating diabetes is the inhibition of glucose reabsorption, which results in its expulsion in the urine (glycosuria).

Sodium-glucose cotransporter-2 (SGLT2) inhibition is a new method that effectively lowers high blood sugar levels without relying on the release or function of insulin. Furthermore, this suppressive effect might cause a slight rise in urine production due to osmotic diuresis, resulting in the removal of glucose via urine and contributing to weight loss with a moderate reduction in calories. Dapagliflozin, a type 2 diabetes medication that inhibits SGLT2, has shown efficacy in managing blood sugar levels, whether used alone or in conjunction with metformin, sulfonylurea, or insulin. However, its effectiveness in combination with thiazolidinedione has not been established yet [7]. The purpose of this study was to assess the impact of gliflozins (SGLT2 inhibitors) on HbA1c levels when used as an additional treatment in patients with type 2 diabetes mellitus who were not effectively managing their condition with metformin alone or with sulfonylurea. The primary objective was to determine the average decrease in HbA1c levels after 3 and 6 months of treatment. Secondary objectives included evaluating the effect of gliflozins on the average decrease in fasting blood sugar (FBS) and postprandial blood sugar (PPBS) levels after 3 and 6 months, as well as assessing any adverse drug reactions over the course of 6 months.

Aims and Objective: To investigate the impact of further treatment with SGLT-2 inhibitors on glycemic indices.

Material and Methods

The present study was a prospective observational study undertaken at the Department of Pharmacology in collaboration with the Department of General Medicine at Nalanda Medical College and Hospital, Patna, Bihar, India, from June 2020 to May 2021. A total of 50 patients, regardless of gender, aged between 18 and 70 years, who have been diagnosed with type 2 diabetes mellitus and have HbA1c levels greater than 7.0% despite treatment with metformin ± sulphonyl urea, were selected to participate in our research.

All were informed regarding the study, and their written consent was obtained from those who met the specified criteria for inclusion and exclusion. The Institutional Ethics Committee gave the study its approval. Data such as name, age, etc. was recorded.

Inclusion Criteria

- Patients are to give written informed consent.
- Type 2 diabetic patients uncontrolled with Metformin 500 mg
- Patients of either sex aged between 18 and 70 years
- HbA1c ≥ 7%
- Fasting blood sugar (FBS) ≥126 mg/dl
- Available for follow-up.

Exclusion Criteria

- Patients do not give written informed consent.
- Patients of either sex aged < 18 years or > 70 years
- Patients are allergic or intolerant to sulfonylureas.
- Patients with systemic diseases (renal dysfunction, cardiac problems)
- Patients on other diabetic medications, requiring hospitalisation
- Consuming alcohol, pregnant, and lactating women
- These patients were then started on either Empa or Dapa, which are gliflozins, as an additional medication. It is important to note that all participants willingly agreed to be part of the study. The research excluded pregnant women, patients with systemic diseases other than diabetes, and those with a S. creatinine clearance of less than 60 ml/min.

Methodology

The study ensured the preservation of patient confidentiality and anonymity during and after the research. The research was done following the principles of the International Conference on Harmonisation and Good Clinical Practice (ICH-GCP). The study population consisted of individuals diagnosed with type 2 diabetes mellitus, whose HbA1c levels were over 7% and were not well managed with metformin alone or in combination with sulfonylurea. These patients were then prescribed one of the gliflozins as an additional treatment. The inclusion and exclusion criteria were followed by the patients in this research. Each patient had three consultations, consisting of an initial appointment followed by two further follow-up visits at the third and sixth months. During the first appointment, we collected important information such as the patient's demographic profile, clinical diagnosis, any other medical illnesses they have, their treatment history, current medications and dosages, as well as their test

results, including HbA1c, FBS, and PPBS. Follow-up was conducted in the third and sixth months. The ADR profile was likewise seen throughout the subsequent visits. The research did not include any intrusive examinations. The act of rechallenging was not undertaken.

Statistical Analysis

After the data was imported into Microsoft Excel, it was analysed using SPSS 25.0. A percentage distribution was used to characterise qualitative factors. The quantitative variables were characterised using measures such as the mean, standard deviation, minimum, and maximum. The analysis of pre-test and post-test comparisons of quantitative variables was conducted using a paired t-test. A significance threshold was set at a p-value of less than 0.05.

Results

In the study, the demographic profile of the participants showed a higher proportion of males (60%) compared to females (40%). The age distribution indicated that the largest group of patients (30%) were between 40 and 50 years old, followed by 24% in the 50–60 age range, 20% in the 30–40 age range, 16% above 60 years, and 10% in the 18–30 age range. Regarding the duration of diabetes, most patients had been living with the condition for 5–10 years (44%), followed by those with less than 5 years (36%), and those with more than 10 years (20%). Additionally, a significant proportion of the patients had comorbid conditions, with 60% having hypertension, 30% having dyslipidemia, and 10% having both hypertension and dyslipidemia. The comparison of glycemic parameters from baseline to follow-up visits at 3 months and 6 months showed significant improvements.

Table 1: Demographic Profile of Study Subjects

Characteristic	N (%)
Gender	
Male	30 (60%)
Female	20 (40%)
Age Group (years)	
18-30	5 (10%)
30-40	10 (20%)
40-50	15 (30%)
50-60	12 (24%)
Above 60	8 (16%)
Duration of Diabetes	
<5 years	18 (36%)
5-10 years	22 (44%)
>10 years	10 (20%)
Comorbid Conditions	
Hypertension	30 (60%)
Dyslipidemia	15 (30%)
Both Hypertension & Dyslipidemia	5 (10%)

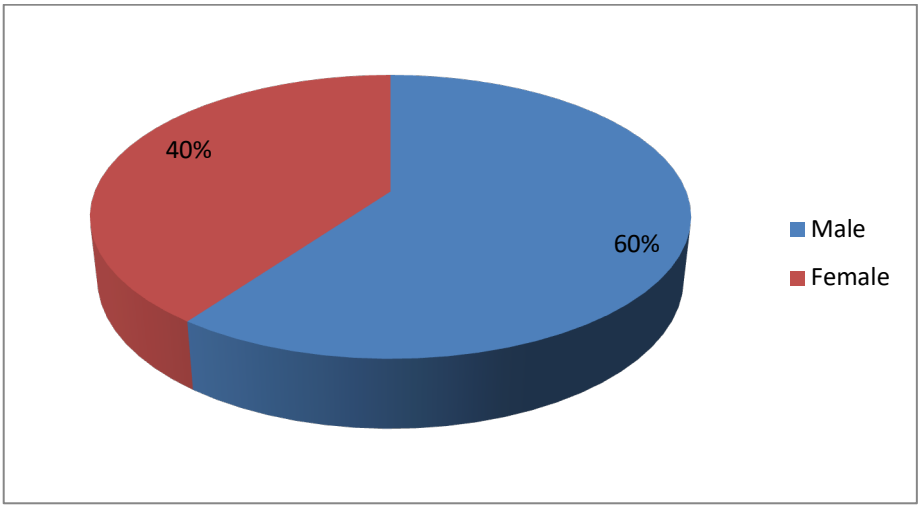

Figure 1: Gender wise distribution of the patients

Table 2: Comparison of Glycemic Parameters

Parameter	Baseline (Mean ± SD)	3 Months (Mean ± SD)	6 Months (Mean ± SD)	P-value (Baseline vs 3 Months)	P-value (Baseline vs 6 Months)
HbA1c (%)	8.67 ± 1.56	7.87 ± 1.34	7.23 ± 1.21	<0.001	<0.001
FBS (mg/dL)	161.03 ± 12.54	141.76 ± 7.87	121.98 ± 7.49	<0.001	<0.001
PPBS (mg/dL)	241.54 ± 7.77	201.86 ± 7.87	181.88 ± 8.49	<0.001	<0.001

Table 2 shows that the mean HbA1c decreased from 8.67% at baseline to 7.87% at 3 months, and further to 7.23% at 6 months. These reductions were statistically significant, with p-values of <0.001 for both time points compared to baseline. Similarly, the mean fasting blood sugar (FBS) levels decreased from 161.03 mg/dL at baseline to 141.76 mg/dL at 3 months and to 121.98 mg/dL at 6 months, with p-values <0.001 for both comparisons. The postprandial blood sugar (PPBS) levels also showed a significant reduction from 241.54 mg/dL at baseline to 201.86 mg/dL at 3 months and to 181.88 mg/dL at 6 months, again with p-values <0.001 for both comparisons.

Table 3: Adverse Drug Reactions (ADRs) Profile

ADR Type	N (%)
Genital Mycotic Infections	10 (20%)
Urinary Tract Infections	8 (16%)
Dehydration	5 (10%)
Hypoglycemia	3 (6%)
None	24 (48%)

Table 3 shows that the ADR profile indicated that 20% of the patients experienced genital mycotic infections, 16% had urinary tract infections, 10% reported dehydration, and 6% experienced hypoglycemia. However, 48% of the patients did not report any adverse drug reactions, indicating a relatively manageable safety profile for the add-on SGLT2 inhibitor therapy.

Table 4: Effect of Gliflozin Type on Glycemic Parameters

Parameter	Empagliflozin (Mean ± SD)	Dapagliflozin (Mean ± SD)	P-value
HbA1c (%)	7.12 ± 0.89	7.21 ± 1.11	0.15
FBS (mg/dL)	119.45 ± 5.38	122.17 ± 2.39	0.22
PPBS (mg/dL)	179.28 ± 4.18	182.78 ± 3.39	0.14

When comparing the effects of empagliflozin and dapagliflozin on glycemic parameters, no significant differences were observed between the two drugs. The mean HbA1c for patients on empagliflozin was 7.12%, while for those on dapagliflozin, it was 7.21%, with a p-value of 0.15. The mean FBS levels were 119.45 mg/dL for empagliflozin and 122.17 mg/dL for dapagliflozin, with a p-value of 0.22. Similarly, the mean PPBS levels were 179.28 mg/dL for empagliflozin and 182.78 mg/dL for dapagliflozin, with a p-value of 0.14. These results suggest that both drugs are equally effective in improving glycemic control (Table 4).

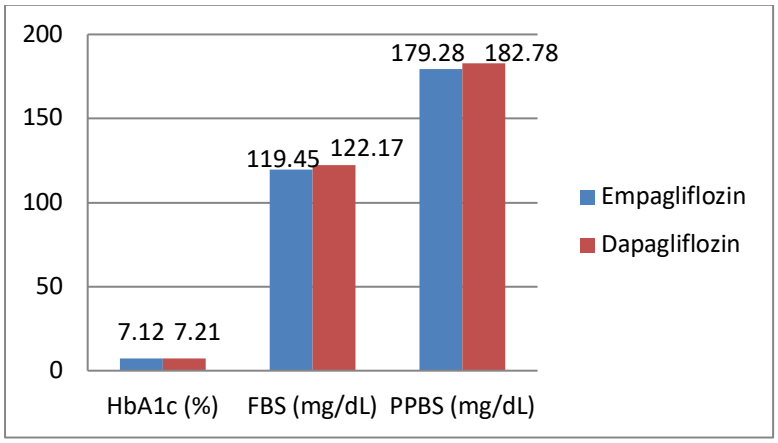

Figure 2: Effect of Empagliflozin and Dapagliflozin on glycemic parameters

Table 5: Correlation between Baseline HbA1c and Reduction in Glycemic Parameters

Parameter	Correlation Coefficient (r)	P-value
Reduction in HbA1c (%)	-0.72	<0.001
Reduction in FBS (mg/dL)	-0.58	<0.001
Reduction in PPBS (mg/dL)	-0.63	<0.001

The correlation analysis revealed significant negative correlations between baseline HbA1c and reductions in glycemic parameters. The reduction in HbA1c had a correlation coefficient of -0.72 with a p-value of <0.001, indicating that higher baseline HbA1c levels were associated with greater reductions in HbA1c. Similarly, reductions in FBS and PPBS had correlation coefficients of -0.58 and -0.63, respectively, both with p-values <0.001 (Table 5).

Discussion

Type 2 diabetes mellitus (T2DM) is a chronic condition that worsens over time. It is defined by the body's resistance to insulin and a gradual decrease in the production of insulin. T2DM is linked to serious consequences affecting small and large blood vessels. It has been the subject of extensive study in the medical field for many years [8]. Several extensive randomised control studies have shown a significant decrease in microvascular events in individuals who received hypoglycemic medications, resulting in a lowered HbA1c [9]. Due to the progressive nature of the condition, patients are required to take a combination of different classes of antidiabetic drugs. In light of this matter, the American Diabetes Association's (ADA) recommendations suggest that individuals with type 2 diabetes mellitus (T2DM) should aim for HbA1c treatment objectives below 7% in order to minimize the risk of illness and complications [10].

Fortunately, there have been significant medicinal breakthroughs in this area, including the identification of SGLT2 inhibitors. Sodium glucose co-transporter type 2 inhibitors are emerging as a viable treatment for type 2 diabetes mellitus (T2DM). These medications decrease high blood sugar levels by inhibiting the reabsorption of glucose in the proximal tubule of the kidney. This causes glycosuria, resulting in decreased levels of glucose in the blood, and also leads to increased urine production. The introduction of this category of medication has provided renewed optimism for individuals with diabetes and medical professionals managing this ailment, owing to the notable improvements in blood sugar control and other health-related advantages [11].

The demographic profile of the study subjects revealed a higher proportion of males (60%) compared to females (40%). This is consistent with findings from other studies, such as the one by Pantalone et al. [12], which also reported a higher prevalence of type 2 diabetes in males compared to females. The age distribution showed that the largest group of patients were between 40 and 50 years old, which aligns with the common onset age of type 2 diabetes observed in other studies, such as those by Wild et al. [13], who noted the peak incidence of type 2 diabetes in the middle-aged population.

Regarding the duration of diabetes, most patients had been living with the condition for 5–10 years (44%), followed by those with less than 5 years (36%), and those with more than 10 years (20%). This distribution is similar to the findings of the UKPDS study, which also observed a significant proportion of patients having diabetes for 5–10 years at diagnosis. The presence of comorbid conditions such as hypertension (60%) and dyslipidemia (30%) is also reflective of the metabolic syndrome commonly associated with type 2 diabetes, as reported by Grundy et al [14].

The comparison of glycemic parameters from baseline to follow-up visits at 3 and 6 months showed significant improvements. The mean HbA1c decreased from 8.67% at baseline to 7.87% at 3 months and further to 7.23% at 6 months. These reductions are consistent with findings from other studies investigating the efficacy of SGLT2 inhibitors. For instance, a study by Bailey et al.[15], reported similar reductions in HbA1c levels with the use of dapagliflozin in combination with metformin . Similarly, the DECLARE-TIMI 58 trial demonstrated significant reductions in HbA1c with dapagliflozin therapy over a 24-week period [17].

The mean fasting blood sugar (FBS) levels and postprandial blood sugar (PPBS) levels also showed significant reductions. FBS decreased from 161.03 mg/dL at baseline to 141.76 mg/dL at 3 months and to 121.98 mg/dL at 6 months, while PPBS levels decreased from 241.54 mg/dL at baseline to 201.86 mg/dL at 3 months and to 181.88 mg/dL at 6 months. These findings are in line with the results from the EMPA-REG OUTCOME trial, which showed significant reductions in both FBS and PPBS with empagliflozin therapy [18].

The ADR profile indicated that 20% of patients experienced genital mycotic infections, 16% had urinary tract infections, 10% reported dehydration, and 6% experienced hypoglycemia. These ADRs are well documented in the literature. Studies such as those by Kohler et al. [16] and Johnsson et al. [17] have reported similar incidences of genital

mycotic infections and urinary tract infections with SGLT2 inhibitors. Dehydration and hypoglycemia were less common but still noteworthy, as also reported in previous clinical trials and observational studies. The relatively high proportion of patients without any ADRs (48%) suggests a favourable safety profile for SGLT2 inhibitors.

The comparison between empagliflozin and dapagliflozin revealed no significant differences in glycemic control. The mean HbA1c, FBS, and PPBS levels were similar between the two drugs, indicating that both are equally effective. This is supported by studies such as the meta-analysis by Vasilakou et al. [18], which found no significant differences in efficacy between different SGLT2 inhibitors. Both empagliflozin and dapagliflozin have shown similar efficacy in reducing HbA1c and other glycemic parameters in multiple randomised controlled trials.

The correlation analysis demonstrated significant negative correlations between baseline HbA1c and reductions in glycemic parameters, suggesting that patients with higher baseline HbA1c levels experienced more substantial improvements. This finding is consistent with the results from the CANVAS programme, which reported that patients with higher baseline HbA1c levels showed greater reductions in HbA1c with canagliflozin therapy. Similarly, a study by Zinman et al. [19] found that higher baseline HbA1c was associated with greater reductions in glycemic parameters with empagliflozin. This correlation underscores the efficacy of SGLT2 inhibitors in patients with poorly controlled diabetes.

Limitations of the Study: The limitations of the study are the small sample size and the short duration of the study.

Conclusion

SGLT-2 inhibitors are a potential new class of antidiabetic drugs that provide improved management of fasting blood sugar (FBS), postprandial blood sugar (PPBS), and glycated haemoglobin (HbA1c).

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