Section: Pharmacology

Original Research Article

TO EXAMINE THE EFFECTS OF FURTHER THERAPY WITH SGLT 2 INHIBITORS ON MEASURES OF BLOOD SUGAR CONTROL

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Abstract

Background: SGLT2 inhibitors are a recently developed group of oral medications that have been authorized for the management of diabetes mellitus. The aim to examine the effects of further therapy with SGLT 2 inhibitors on measures of blood sugar control. **Materials and Methods:** We chose a total of 60 patients, of either gender, aged between 18 and 70 years, who have been diagnosed with type 2 diabetes mellitus and have $HbA_{1}c$ values more than 7.0% despite therapy with metformin ± sulphonyl urea, to participate in our study. Subsequently, these individuals were started on either Empa or Dapa, both of which are gliflozins, as an adjunctive therapy. All subjects voluntarily consented to participate in the research. The study excluded pregnant individuals, people with systemic illnesses unrelated to diabetes, and those with a S. creatinine clearance below 60ml/min. **Result:** The average HbA1c level reduced from 8.85% at the beginning of the study to 7.54% after 3 months, and further decreased to 7.12% after 6 months. The decreases seen at both time periods compared to baseline were statistically significant, with p-values of <0.001. Similarly, the average fasting blood sugar (FBS) levels declined from 161.91 mg/dL at the beginning to 141.20 mg/dL after 3 months, and further reduced to 121.37 mg/dL after 6 months. The p-values for both comparisons were less than 0.001. The levels of blood sugar after a meal, known as postprandial blood sugar (PPBS), decreased significantly from 242.06 mg/dL at the start of the study to 201.44 mg/dL after 3 months, and further to 181.21 mg/dL after 6 months. The statistical analysis demonstrated p-values of less than 0.001 for both comparisons. The correlation analysis revealed statistically significant negative connections between the initial HbA1c levels and the subsequent decreases in glycemic indices. The decrease in HbA1c showed a correlation coefficient of -0.70 with a p-value of <0.001, suggesting that higher initial HbA1c levels were linked to more significant decreases in HbA1c. Similarly, the correlation coefficients for decreases in FBS and PPBS were -0.54 and -0.61, respectively, both with p-values less than 0.001. **Conclusion:** SGLT 2 inhibitors are a promising new category of medications for diabetes that provide enhanced control of fasting blood sugar (FBS), postprandial blood sugar (PPBS), and glycated hemoglobin (HbA1c).

INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as a promising class of oral antidiabetic drugs that not only improve glycemic control but also confer cardiovascular and renal benefits. These agents work by inhibiting the reabsorption of glucose in the proximal renal tubules, leading to increased glucose excretion in the urine and subsequently lowering blood glucose levels. Recent studies have demonstrated the efficacy of SGLT2 inhibitors in improving glycemic indices, making them a crucial component in the management of type 2 diabetes mellitus (T2DM).[1] The clinical benefits of SGLT2 inhibitors in glycemic control are well-documented. SGLT2 inhibitors significantly reduce HbA1c levels, fasting plasma glucose, and

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body weight in patients with T2DM. Furthermore, the EMPA-REG OUTCOME trial demonstrated that empagliflozin, an SGLT2 inhibitor, not only improved glycemic control but also reduced the risk of cardiovascular death in patients with T2DM and established cardiovascular disease.[2] In addition to their glycemic benefits, SGLT2 inhibitors have shown potential in protecting against the progression of renal disease in diabetic patients. The CREDENCE trial reported that canagliflozin reduced the risk of kidney failure and other renal outcomes in patients with T2DM and chronic kidney disease, highlighting the dual benefit of these agents in glycemic and renal health.[3]

Despite these promising results, the impact of further treatment with SGLT2 inhibitors on various glycemic indices remains an area of active research. Recent studies have sought to evaluate the long-term efficacy and safety of SGLT2 inhibitors in different populations and clinical settings. For example, the DAPA-HF trial explored the effects of dapagliflozin on heart failure outcomes in patients with and without diabetes, demonstrating significant improvements in glycemic control among diabetic participants.[4,5] Moreover, the mechanisms underlying the glycemic effects of SGLT2 inhibitors continue to be elucidated. Emerging evidence suggests that these agents may improve insulin sensitivity and beta-cell function, thereby providing a more comprehensive approach to diabetes management. Understanding these mechanisms is critical for optimizing the use of SGLT2 inhibitors in clinical practice and tailoring treatment strategies to individual patient needs.[6] Sodium-glucose cotransporter-2 (SGLT2) inhibition is a novel approach that efficiently reduces elevated blood glucose levels without depending on the secretion or action of insulin. Moreover, this inhibitory impact might lead to a little increase in urine output as a consequence of osmotic diuresis, leading to the elimination of glucose via urine and contributing to weight loss through a mild decrease in caloric intake. Dapagliflozin, a medicine for type 2 diabetes that blocks SGLT2, has shown effectiveness in controlling blood glucose levels whether taken alone or in combination with metformin, sulfonylurea, or insulin. Nevertheless, the efficacy of its combination with thiazolidinedione remains unestablished.[7]

The objective of this research was to evaluate the influence of gliflozins (SGLT2 inhibitors) on HbA1c levels when administered as an adjunctive therapy in patients with type 2 diabetes mellitus who were inadequately controlling their condition with metformin alone or with sulfonylurea.

The main goal was to ascertain the mean reduction in HbA1c levels after 3 and 6 months of therapy. The secondary goals were to investigate the impact of gliflozins on the mean reduction in fasting blood sugar (FBS) and postprandial blood sugar (PPBS) levels after 3 and 6 months, and to evaluate any adverse medication responses over the 6-month period.

MATERIALS AND METHODS

This study was a prospective observational investigation conducted at the Department of Pharmacology. We chose a total of 60 patients, independent of gender, aged between 18 and 70 years, who have been diagnosed with type 2 diabetes mellitus and have HbA_1c values more than 7.0% despite therapy with metformin ± sulphonyl urea, to participate in our study. Subsequently, these individuals were started on either Empa or Dapa, both of which are gliflozins, as an adjunctive therapy. All subjects voluntarily consented to participate in the research. The study excluded pregnant individuals, those with systemic disorders other than diabetes, and those with a S. creatinine clearance below 60ml/min.

Methodology

The study guaranteed the maintenance of patient information confidentiality and anonymity during and after the research. The study was conducted in accordance with the standards of the International Conference on Harmonization-Good Clinical Practice (ICH-GCP). The trial cohort included of people who had been diagnosed with type 2 diabetes mellitus and had HbA1c values over 7%. These participants were not effectively managing their condition with metformin alone or in combination with sulfonylurea. Subsequently, these individuals were administered one of the gliflozins as an adjunctive therapy. The patients in this study adhered to the specified inclusion and exclusion criteria. Each patient had a series of three consultations, which included an initial session followed by two further follow-up appointments at the third and sixth month. During the first consultation, we gathered crucial data including the patient's demographic characteristics, clinical diagnosis, comorbidities, treatment history, current medicines and doses, as well as their test results for HbA1c, FBS, and PPBS. Follow-up undertaken at the third and sixth months. The ADR profile was also seen throughout the future visits. The study did not include any invasive investigation. The act of rechallenging was not carried out.

Statistical analysis

The imported data was analyzed using SPSS 25.0 in Microsoft Excel. Qualitative characteristics were characterized using percentage distribution. The quantitative variables were described using statistical metrics such as the mean, standard deviation, minimum, and maximum. A paired t-test was used to analyze the comparison of quantitative variables between the pre-test and post-test. A significant criterion was established at a p-value below 0.05.

RESULTS

The demographic profile of the participants indicated a higher percentage of males (63.33%) compared to females (36.67%). The age distribution revealed that the largest group of patients (38.34%) was aged between 40-50 years, followed by 23.33% in the 50-

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60 age range, 18.33% in the 30-40 age range, 16.67% above 60 years, and 13.33% in the 18-30 age range. Regarding the duration of diabetes, the majority of patients had been living with the condition for 5-10 years (43.33%), followed by those with less than 5 years (36.67%), and those with more than 10 years (20%). Additionally, a significant portion of the patients had comorbid conditions, with 63.33% having hypertension, 23.33% having dyslipidemia, and 13.34% 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. The mean HbA1c decreased from 8.85% at baseline to 7.54% at 3 months, and further to 7.12% 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 161.91 mg/dL at baseline to 141.20 mg/dL at 3 months, and to 121.37 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 242.06 mg/dL at baseline to 201.44 mg/dL at 3 months, and to 181.21 mg/dL at 6 months, again with p-values <0.001 for both comparisons.

The adverse drug reaction (ADR) profile revealed that 23.33% of the patients encountered genital mycotic infections, 18.33% suffered from urinary tract infections, 11.67% reported dehydration, and 6.67% had hypoglycemia. Nevertheless, a significant proportion of 40% of the patients did not have any negative side effects from the additional SGLT2 inhibitor medication, suggesting that its safety profile is very easy to handle.

When evaluating the impact of empagliflozin and dapagliflozin on glycemic indicators, no notable differences were found between the two medications. The average HbA1c level for patients treated with empagliflozin was 7.07%, but for those treated with dapagliflozin, it was 7.18%. The statistical analysis yielded a p-value of 0.12. The average fasting blood sugar (FBS) levels were 119.23 mg/dL for empagliflozin and 122.04 mg/dL for dapagliflozin, with a p-value of 0.20. Similarly, the average postprandial blood sugar (PPBS) levels were 179.11 mg/dL for empagliflozin and 182.32 mg/dL for dapagliflozin, with a p-value of 0.12. These findings indicate that both medications have the same level of effectiveness in improving glycemic control.

The correlation study showed strong negative connections between the initial HbA1c levels and the decreases in glycemic indices. The decrease in HbA1c showed a correlation coefficient of -0.70 with a p-value of <0.001, suggesting that higher initial HbA1c levels were linked to more significant decreases in HbA1c. Similarly, the correlation coefficients between decreases in FBS and PPBS were -0.54 and -0.61, respectively, both with p-values less than 0.001.

Table 1: Demographic Profile of Study Subjects.

Characteristic	N =60	%
Gender		
Male	38	63.33
Female	22	36.67
Age Group (years)		
18-30	8	13.33
30-40	11	18.33
40-50	17	28.34
50-60	14	23.33
Above 60	10	16.67
Duration of Diabetes		
<5 years	22	36.67
5-10 years	26	43.33
>10 years	12	20
Comorbid Conditions		
Hypertension	38	63.33
Dyslipidemia	14	23.33
Both Hypertension & Dyslipidemia	8	13.34

Table 2: Comparison of Glycemic Parameters

Child Pugh Turcotte grade	Increased TSH (hypothyroidism)	Decreased T3	Decreased T4
A	0	2 (14.28)	1 (5.5)
B	2 (10.52)	0	2 (11.11)
C	17 (89.47)	12 (85.71)	15 (83.22)
Total	19 (100)	14 (100)	18 (100)

Table 3: Adverse Drug Reactions (ADRs) Profile

ADR Type	N =60	%
Genital Mycotic Infections	14	23.33
Urinary Tract Infections	11	18.33
Dehydration	7	11.67
Hypoglycemia	4	6.67
None	24	40

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Table 4: Effect of Gliflozin Type on Glycemic Parameters

Parameter	Empagliflozin (Mean ± SD)	Dapagliflozin (Mean ± SD)	P-value
HbA1c (%)	7.07 ± 0.80	7.18 ± 1.08	0.12
FBS (mg/dL)	119.23 ± 5.31	122.04 ± 2.22	0.20
PPBS (mg/dL)	179.11 ± 4.15	182.32 ± 3.08	0.12

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

Parameter	Correlation Coefficient (r)	P-value
Reduction in HbA1c (%)	-0.70	<0.001
Reduction in FBS (mg/dL)	-0.54	<0.001
Reduction in PPBS (mg/dL)	-0.61	<0.001

DISCUSSION

Type 2 diabetes mellitus (T2DM) is a progressive chronic illness. Insulin resistance and a progressive decline in insulin production are the defining characteristics of this condition. Type 2 diabetes mellitus (T2DM) is associated with significant repercussions that impact both microvascular and macrovascular systems. It has undergone thorough examination in the medical profession for several years.[8] Multiple rigorous randomized control trials have shown a significant reduction in microvascular occurrences among persons who were administered hypoglycemic medicines, leading to a drop in HbA1c levels.[9] Given the progressive nature of the illness, patients are need to take a combination of several kinds of antidiabetic medications. Considering this issue, the American Diabetes Association (ADA) advises that persons with type 2 diabetes mellitus (T2DM) should strive for HbA1c treatment goals below 7% to reduce the likelihood of sickness and complications.[10]

Fortunately, there have been notable advancements in medicine in this field, such as the discovery of SGLT2 inhibitors. Sodium glucose co-transporter type 2 inhibitors are becoming a practical option for treating type 2 diabetic mellitus (T2DM). These drugs lower elevated blood sugar levels by blocking the reabsorption of glucose in the proximal tubule of the kidney. This leads to glycosuria, causing a fall in blood glucose levels, as well as an increase in urine output. The development of this pharmaceutical category has brought fresh hope for persons with diabetes and medical professionals treating this condition, due to the significant improvements in blood sugar regulation and other health-related benefits.[11] The research respondents' demographic profile indicated a greater percentage of male (63.33%) in comparison to females (36.67%). These results align with the findings of previous research, such as the one conducted by Pantalone et al,[12] which also observed a greater occurrence of type 2 diabetes in male as compared to female. The age distribution revealed that the majority of patients fell within the 40-50 age range, which corresponds to the typical age at which type 2 diabetes often develops, as found in previous studies, such as those conducted by Wild et al,[13] who identified the highest occurrence of type 2 diabetes in individuals of middle age. In terms of the length of diabetes, the majority of patients had been living with the illness for a period of 5-10 years (43.33%), followed by those with fewer than 5 years (36.67%), and those with more than 10 years (20%). The distribution of patients in this research is comparable to the results of the UKPDS study,[14] which similarly identified a substantial number of individuals who had been living with diabetes for 5-10 years at the time of diagnosis. The occurrence of other medical disorders such as hypertension (63.33%) and dyslipidemia (23.33%) is indicative of the metabolic syndrome often linked to type 2 diabetes, as stated by Grundy et al.[14] Significant improvements were seen in glycemic markers when comparing baseline measurements to follow-up visits at 3 and 6 months. The average HbA1c level reduced from 8.85% at the beginning of the study to 7.54% after 3 months, and further decreased to 7.12% after 6 months. These decreases align with results from previous trials examining the effectiveness of SGLT2 inhibitors. For example, a research conducted by Bailey et al,[15] found that the combination of dapagliflozin and metformin resulted in comparable decreases in HbA1c levels. In the same way, the DECLARE-TIMI 58 study showed significant decreases in HbA1c levels while using dapagliflozin treatment for a duration of 24 weeks.[16,17]

Significant decreases were seen in both the mean fasting blood sugar (FBS) levels and postprandial blood sugar (PPBS) levels. The fasting blood sugar (FBS) levels reduced from 161.91 mg/dL at the beginning to 141.20 mg/dL after 3 months and further decreased to 121.37 mg/dL after 6 months. Similarly, the postprandial blood sugar (PPBS) levels declined from 242.06 mg/dL at the beginning to 201.44 mg/dL after 3 months and further decreased to 181.21 mg/dL after 6 months. These findings are consistent with the results of the EMPA-REG OUTCOME study, which demonstrated substantial decreases in both fasting blood sugar (FBS) and postprandial blood sugar (PPBS) levels with empagliflozin treatment.[18]

The ADR profile indicated that 23.33% of patients experienced genital mycotic infections, 18.33% had urinary tract infections, 11.67% reported dehydration, and 6.67% 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

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reported in previous clinical trials and observational studies. The relatively high proportion of patients without any ADRs (48%) suggests a favorable 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 Zelniker et al., 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 randomized controlled trials (RCTs).[18] 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 program, which reported that patients with higher baseline HbA1c levels showed greater reductions in HbA1c with canagliflozin therapy.[19]

CONCLUSION

SGLT 2 inhibitors are a promising new category of medications for diabetes that provide enhanced control of fasting blood sugar (FBS), postprandial blood sugar (PPBS), and glycated hemoglobin (HbA1c).

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