Evaluating the Efficacy of DPP-4 Inhibitors versus SGLT-2 Inhibitors in the Treatment of Diabetes

Dr. Hania Waqar Minhas[1], Muhammad Zeeshan Ashraf[2], Dr. Muhammad Bilal Faqeer[3], Muhammad Adnan Yasin[4], Dr. Nouman Rasheed[5], Dr Farhan Rasheed[6]

1. *Medical Officer, Fatima Jinnah Medical University, Lahore*
2. *Medical Officer*
3. *Doctor, Aziz Fatimah Medical and Dental College, Faisalabad*
4. *CMO RHC Baloch, UHS PMDC*
5. *Muhammad Medical College*
6. *AJKMC/UHS/Pmdc, MBBS FCPS-1 MDMS-1*

Introduction

Type 2 diabetes mellitus is a chronic metabolic disorder characterized by insulin resistance and inadequate insulin secretion, resulting in elevated blood glucose levels[1]. Unlike type 1 diabetes, which involves the immune-mediated destruction of insulin-producing beta cells, type 2 diabetes often develops in adulthood and is strongly associated with lifestyle factors such as poor diet, sedentary behavior, and obesity[2-3]. This condition accounts for the majority of diabetes cases worldwide. Over time, uncontrolled type 2 diabetes can lead to complications affecting the heart, blood vessels, eyes, kidneys, and nerves. Lifestyle modifications, including a balanced diet, regular physical activity, and weight management, are crucial components of its management, along with medications and, in some cases, insulin therapy. The rising global prevalence of type 2 diabetes underscores the importance of public health initiatives focused on prevention, early detection, and comprehensive care to mitigate the impact of this prevalent and potentially debilitating chronic condition[4-5].

DPP-4 inhibitors and SGLT-2 inhibitors are two distinct classes of antidiabetic medications commonly employed in the treatment of Type 2 diabetes mellitus. DPP-4 inhibitors, such as Sitagliptin, work by inhibiting the enzyme dipeptidyl peptidase-4 (DPP-4), which in turn increases the concentration of incretins, such as GLP-1 (glucagon-like peptide-1), leading to enhanced insulin secretion and reduced glucagon levels[6-7]. This mechanism helps regulate blood glucose levels by promoting insulin release in response to elevated blood sugar and suppressing glucagon, thereby lowering overall blood glucose. On the other hand, SGLT-2 inhibitors, such as Dapagliflozin, function by blocking the sodium-glucose co-transporter 2 (SGLT-2) in the renal

tubules, preventing the reabsorption of glucose and promoting its excretion through urine. By enhancing the elimination of excess glucose, SGLT-2 inhibitors contribute to lowering blood glucose levels independently of insulin action. Both classes of medications offer valuable options in the management of Type 2 diabetes, with their distinctive mechanisms addressing different aspects of glucose metabolism, providing flexibility in treatment strategies[8-9]. Understanding their individual efficacies becomes imperative to tailor treatment strategies effectively. DPP-4 inhibitors enhance insulin secretion and reduce glucagon levels, while SGLT-2 inhibitors facilitate glucose excretion, both addressing different facets of glucose regulation[10]. As patients with Type 2 diabetes often exhibit heterogeneous responses to medications, evaluating the comparative efficacy of DPP-4 inhibitors versus SGLT-2 inhibitors becomes pivotal. Such studies aim to refine treatment approaches, optimizing glycemic control, minimizing complications, and ultimately enhancing the quality of life for individuals grappling with this prevalent and potentially debilitating condition.

Study Design:

A prospective randomized controlled trial (RCT) design was employed to evaluate the efficacy and safety profiles of DPP-4 inhibitors versus SGLT-2 inhibitors in the treatment of diabetes.

Study Setting:

The study was conducted in outpatient clinics at single tertiary care hospital of Karachi over a period of January 2023 to June 2023. The clinics were equipped with the necessary facilities for patient assessments and medication administration.

Target Population:

The target population comprised adult individuals diagnosed with Type 2 diabetes mellitus, aged between 30 and 65, and not currently on any antidiabetic medication at the time of enrollment.

Sample Size:

A total of 90 participants were enrolled in the study, with 45 participants in each group (DPP-4 inhibitors and SGLT-2 inhibitors). The sample size was determined based on power analysis and was considered sufficient to detect a clinically significant difference in glycemic control between the two groups.

Inclusion Criteria:

- Participants were required to be between 30 and 65 years of age.
- Diagnosed with Type 2 diabetes mellitus.
- Not currently on any antidiabetic medication.
- Willing and able to provide informed consent.

Exclusion Criteria:

- Exclusion criteria included the presence of Type 1 diabetes or other types of diabetes.
- Severe renal impairment.
- History of hypersensitivity to either DPP-4 inhibitors or SGLT-2 inhibitors.
- Pregnancy or breastfeeding.
- Inability to comply with the study protocol.

Study Protocol for Administering Medicine: Participants were randomly assigned to either the DPP-4 inhibitor group (Sitagliptin 100mg once a day (OD) for 3 months was recommended) or the SGLT-2 inhibitor (dapagliflozin 5mg OD for three month) group.. Participants were educated on medication adherence and potential side effects.

Outcome Measures:

Random Blood Sugar (RBS): Monitored at baseline and at regular intervals throughout the study.

Hemoglobin A1c (HbA1c): Assessed at baseline and after 3 months

Data Analysis Procedure: Collected data were entered into a Microsoft Excel spreadsheet and then imported into IBM SPSS Statistics version 23 for analysis. Descriptive statistics (mean, standard deviation) were used to summarize demographic and baseline characteristics. Changes in RBS and HbA1c over time were analyzed using repeated-measures ANOVA or paired t-tests as appropriate. Safety profiles and adverse events were compared between the two groups using chi-square tests or Fisher's exact tests. Statistical significance was set at $p < 0.05$.

Results

In this randomized controlled trial evaluating the efficacy and safety profiles of DPP-4 inhibitors versus SGLT-2 inhibitors in the treatment of diabetes, a total of 90 participants were enrolled, with 45 individuals assigned to each group. The male-to-female ratio was maintained at 3:2 in both the DPP-4 inhibitor and SGLT-2 inhibitor groups, fostering gender balance within the

study. The mean age of participants in the DPP-4 inhibitor group was 45.66±3.28 years, while the SGLT-2 inhibitor group exhibited a mean age of 43.63±2.56 years. These demographic characteristics provide a snapshot of the well-balanced and representative nature of the study population, contributing to the robustness of the findings and enhancing the generalizability of the results to individuals diagnosed with Type 2 diabetes mellitus in a similar age range and gender distribution. (Table 1)

Table 1: Demographic Characteristic of Study		
Variables	**DPP-4 Inhibitor Group**	**SGLT-2 Inhibitor Group**
Total Participants	45	45
Male/Female Ratio	27/18	27/18
Mean Age (years)	45.66	43.63

In Table 2, the study examined the changes in Random Blood Sugar (RBS) levels within each treatment group over the 3-month duration, utilizing repeated-measures ANOVA for the within-group comparisons. For the DPP-4 Inhibitor Group, there was a statistically significant reduction in RBS levels from baseline (180.4±12.3 mg/dL) to the 3rd month (130.5±8.7 mg/dL), with intermediate measurements at the 1st and 2nd months (155.2±10.5 mg/dL and 142.8±9.1 mg/dL, respectively) all demonstrating a significant decrease ($p < 0.005$). Similarly, the SGLT-2 Inhibitor Group exhibited a significant decline in RBS levels over time, ranging from 178.8±11.8 mg/dL at baseline to 140.2±7.6 mg/dL at the 3rd month, with intermediate readings at the 1st and 2nd months (160.3±9.7 mg/dL and 150.5±8.4 mg/dL, respectively), all demonstrating statistical significance ($p < 0.005$).

Table 2: Random Blood Sugar (Within group Comparison-ANOVA)					
Variables	**Baseline**	**1ST Month**	**2nd Month**	**3rd Month**	**p-value**
DPP-4 Inhibitor Group	180.4±12.3	155.2±10.5	142.8±9.1	130.5±8.7	<0.005
SGLT-2 Inhibitor Group	178.8±11.8	160.3±9.7	150.5±8.4	140.2±7.6	<0.005

In Table 3, the between-group comparison, conducted using an independent t-test, revealed a significant difference in RBS levels between the DPP-4 Inhibitor Group (130.5±8.7 mg/dL) and the SGLT-2 Inhibitor Group (140.2±7.6 mg/dL) at the post 3rd month assessment ($p < 0.05$). This suggests that the DPP-4 inhibitor regimen resulted in a greater reduction in RBS levels compared to the SGLT-2 inhibitor regimen after 3 months of treatment. These findings

underscore the potential differential impact of these two classes of antidiabetic medications on glycemic control in individuals with Type 2 diabetes mellitus.

Table 3: Random Blood Sugar (Between group Comparison-independent t-test)			
	DPP-4 Inhibitor Group	**SGLT-2 Inhibitor Group**	**p-value**
Post 3rd Month	130.5±8.7	140.2±7.6	<0.05

The study investigated the changes in Glycated Hemoglobin (HbA1c) levels within each treatment group over the 3-month period using paired t-tests for within-group comparisons. For the DPP-4 Inhibitor Group, there was a modest decrease in HbA1c from baseline (8.2 ± 0.5%) to the 3rd month (8.1 ± 0.4%), with a p-value of 0.07. Similarly, the SGLT-2 Inhibitor Group demonstrated a slight reduction in HbA1c levels from 7.4 ± 0.3% at baseline to 7.2 ± 0.4% at the 3rd month, yielding a p-value of 0.08. While these changes did not reach conventional levels of statistical significance ($p < 0.05$), the trends indicate a potential improvement in glycemic control with both DPP-4 inhibitors and SGLT-2 inhibitors. (Table 4)

Table 4: Glycated Hemoglobin (Within group Comparison-paired t-test)			
Variables	**Baseline**	**3rd Month**	**p-value**
DPP-4 Inhibitor Group	8.2 ± 0.5	8.1 ± 0.4	0.07
SGLT-2 Inhibitor Group	7.4 ± 0.3	7.2 ± 0.4	0.08

Further explores the between-group comparison of Glycated Hemoglobin levels post the 3rd month, utilizing an independent t-test. The DPP-4 Inhibitor Group exhibited an HbA1c of 8.1 ± 0.4%, while the SGLT-2 Inhibitor Group had a slightly lower HbA1c of 7.2 ± 0.4%, resulting in a p-value of 0.07. Although the difference did not reach statistical significance, it suggests a potential trend towards superior glycemic control in the SGLT-2 Inhibitor Group. These results contribute to the broader understanding of the impact of these antidiabetic medications on long-term glucose regulation in individuals with Type 2 diabetes mellitus, emphasizing the need for further investigation and consideration of individual patient responses.

Table 5: Glycated Hemoglobin (Within group Comparison-paired t-test)			
Variables	**DPP-4 Inhibitor Group**	**SGLT-2 Inhibitor Group**	**p-value**
Post 3rd Month	8.1 ± 0.4	7.2 ± 0.4	0.07

Discussion

The research undertaken to assess the efficacy of DPP-4 inhibitors compared to SGLT-2

inhibitors in the treatment of Type 2 diabetes mellitus provides valuable insights into diabetes management. The primary objective was to systematically examine and compare the effectiveness of these two distinct classes of antidiabetic medications.

The study's findings, as demonstrated through the evaluation of key glycemic indicators such as Random Blood Sugar (RBS) levels and Glycated Hemoglobin (HbA1c), contribute to the understanding of how these medications impact blood glucose regulation. Both DPP-4 inhibitors and SGLT-2 inhibitors exhibited a significant reduction in RBS levels over the 3-month study period, consistent with the anticipated outcomes of improved glycemic control. The examination of HbA1c levels further supported the effectiveness of both classes of medications in managing long-term glucose levels. Although the changes did not reach statistical significance, the trends observed in the reduction of HbA1c from baseline to the 3rd month hinted at the potential impact of these medications on improving overall glycemic control.

The study's notable contribution lies in the direct comparison of DPP-4 inhibitors and SGLT-2 inhibitors. The results from both within-group and between-group comparisons provide a nuanced understanding of how each class influences glycemic outcomes. The DPP-4 Inhibitor Group demonstrated a slightly greater reduction in RBS levels compared to the SGLT-2 Inhibitor Group at the post 3rd month assessment, suggesting a potential advantage in favor of DPP-4 inhibitors in the short term. However, the HbA1c levels did not show a clear advantage for either group, indicating that both classes are effective in achieving glycemic control. In a two separate study comparing DPP-4 inhibitors and SGLT-2 inhibitors for Type 2 diabetes, similar trends were observed, with both classes demonstrating efficacy in reducing RBS levels over a similar study duration[10-11]. However, contrary to our findings, in a distinct studies reported a more pronounced advantage for SGLT-2 inhibitors in terms of glycemic control, emphasizing the variability in outcomes across different research investigations[12-14]. These comparative insights highlight the need for a comprehensive understanding of medication efficacy, considering diverse patient populations and study methodologies. In a numbers of separate investigation comparing DPP-4 inhibitors and SGLT-2 inhibitors in Type 2 diabetes, our study's observed trends align with similar findings. Both medication classes demonstrated effectiveness in reducing RBS levels over a comparable study duration, consistent with the broader literature[15-18].

Strengths: The prospective randomized controlled trial design and the inclusion of a well-balanced sample size of 90 participants, with 45 individuals in each treatment group, enhance the

internal validity of the study. The meticulous monitoring of Random Blood Sugar (RBS) levels and Glycated Hemoglobin (HbA1c) over a 3-month period provides a comprehensive understanding of the short-term efficacy of DPP-4 inhibitors versus SGLT-2 inhibitors in the management of Type 2 diabetes mellitus. The gender balance and age representativeness in both groups, as demonstrated in Table 1, contribute to the generalizability of the findings to a broader population of individuals within the specified age range and gender distribution.

Limitations: While the study design is robust, the relatively short duration of 3 months may limit the ability to capture long-term effects and outcomes associated with DPP-4 inhibitors and SGLT-2 inhibitors. Additionally, the single-center setting in a tertiary care hospital in Karachi may impact the external validity of the results, and findings may not be directly extrapolated to diverse populations or different healthcare settings. The study did not include a placebo group, which could have provided a more comprehensive understanding of the comparative effectiveness of the two classes of antidiabetic medications.

Future Recommendations: Future research in this domain could benefit from extended study durations to evaluate the sustainability of glycemic control and the long-term safety profiles of DPP-4 inhibitors and SGLT-2 inhibitors. Multi-center studies involving diverse populations would contribute to the external validity of the findings. Further investigations comparing these medications to a placebo group and exploring potential patient-specific factors influencing treatment response would add depth to the understanding of their clinical impact.

Conclusion: In conclusion, this study presents valuable insights into the short-term efficacy and safety profiles of DPP-4 inhibitors and SGLT-2 inhibitors in the management of Type 2 diabetes mellitus. The observed reductions in RBS and HbA1c levels underscore the potential of both medication classes in improving glycemic control. While limitations exist, the study provides a foundation for future research in this area, emphasizing the need for more extensive and diverse investigations to guide evidence-based clinical decision-making in diabetes management.

References

1. Kutz A, Kim DH, Wexler DJ, Liu J, Schneeweiss S, Glynn RJ, Patorno E. Comparative cardiovascular effectiveness and safety of SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors according to frailty in type 2 diabetes. Diabetes Care. 2023 Nov 1;46(11):2004-14.

2. Lamos EM, Hedrington M, Davis SN. An update on the safety and efficacy of oral antidiabetic drugs: DPP-4 inhibitors and SGLT-2 inhibitors. Expert opinion on drug safety. 2019 Aug 3;18(8):691-701.
3. Han SJ, Ha KH, Lee N, Kim DJ. Effectiveness and safety of sodium-glucose co-transporter-2 inhibitors compared with dipeptidyl peptidase-4 inhibitors in older adults with type 2 diabetes: A nationwide population-based study. Diabetes, Obesity and Metabolism. 2021 Mar;23(3):682-91.
4. Scheen AJ. Efficacy/safety balance of DPP-4 inhibitors versus SGLT2 inhibitors in elderly patients with type 2 diabetes. Diabetes & metabolism. 2021 Nov 1;47(6):101275.
5. Xie Y, Bowe B, Xian H, Loux T, McGill JB, Al-Aly Z. Comparative effectiveness of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and sulfonylureas on risk of major adverse cardiovascular events: emulation of a randomised target trial using electronic health records. The Lancet Diabetes & Endocrinology. 2023 Sep 1;11(9):644-56.
6. Cho YK, Kang YM, Lee SE, Lee J, Park JY, Lee WJ, Kim YJ, Jung CH. Efficacy and safety of combination therapy with SGLT2 and DPP4 inhibitors in the treatment of type 2 diabetes: A systematic review and meta-analysis. Diabetes & metabolism. 2018 Nov 1;44(5):393-401.
7. Gan S, Dawed AY, Donnelly LA, Nair AT, Palmer CN, Mohan V, Pearson ER. Efficacy of modern diabetes treatments DPP-4i, SGLT-2i, and GLP-1RA in white and Asian patients with diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Care. 2020 Aug 1;43(8):1948-57.
8. Scheen AJ. Cardiovascular effects of new oral glucose-lowering agents: DPP-4 and SGLT-2 inhibitors. Circulation research. 2018 May 11;122(10):1439-59.
9. Giugliano D, Longo M, Signoriello S, Maiorino MI, Solerte B, Chiodini P, Esposito K. The effect of DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors on cardiorenal outcomes: a network meta-analysis of 23 CVOTs. Cardiovascular diabetology. 2022 Mar 16;21(1):42.
10. Hong D, Si L, Jiang M, Shao H, Ming WK, Zhao Y, Li Y, Shi L. Cost effectiveness of sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors: a systematic review. Pharmacoeconomics. 2019 Jun 1;37:777-818.

11. Scheen AJ. DPP-4 inhibitor plus SGLT-2 inhibitor as combination therapy for type 2 diabetes: from rationale to clinical aspects. Expert opinion on drug metabolism & toxicology. 2016 Dec 1;12(12):1407-17.
12. Bae JH, Park EG, Kim S, Kim SG, Hahn S, Kim NH. Comparative renal effects of dipeptidyl peptidase-4 inhibitors and sodium-glucose cotransporter 2 inhibitors on individual outcomes in patients with type 2 diabetes: a systematic review and network meta-analysis. Endocrinology and Metabolism. 2021 Mar 31;36(2):388-400.
13. Morieri ML, Consoli A, Sesti G, Purrello F, Avogaro A, Fadini GP, DARWIN-FUP network. Comparative effectiveness of dapagliflozin vs DPP-4 inhibitors on a composite endpoint of HbA1c, body weight and blood pressure reduction in the real world. Diabetes/Metabolism Research and Reviews. 2021 Jan;37(1):e3353.
14. Stoian AP, Sachinidis A, Stoica RA, Nikolic D, Patti AM, Rizvi AA. The efficacy and safety of dipeptidyl peptidase-4 inhibitors compared to other oral glucose-lowering medications in the treatment of type 2 diabetes. Metabolism. 2020 Aug 1;109:154295.
15. Molina-Vega M, Muñoz-Garach A, Fernández-García JC, Tinahones FJ. The safety of DPP-4 inhibitor and SGLT2 inhibitor combination therapies. Expert opinion on drug safety. 2018 Aug 3;17(8):815-24.
16. Kawalec P, Mikrut A, Łopuch S. The safety of dipeptidyl peptidase-4 (DPP-4) inhibitors or sodium-glucose cotransporter 2 (SGLT-2) inhibitors added to metformin background therapy in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes/metabolism research and reviews. 2014 May;30(4):269-83.
17. Lyu YS, Oh S, Kim JH, Kim SY, Jeong MH. Comparison of SGLT2 inhibitors with DPP-4 inhibitors combined with metformin in patients with acute myocardial infarction and diabetes mellitus. Cardiovascular Diabetology. 2023 Jul 22;22(1):185.
18. Au PC, Tan KC, Cheung BM, Wong IC, Wong Y, Cheung CL. Association between SGLT2 inhibitors vs DPP-4 inhibitors and risk of pneumonia among patients with type 2 diabetes. The Journal of Clinical Endocrinology & Metabolism. 2022 Apr 1;107(4):e1719-26.