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Comparison of the clinical efficacy of linagliptin with SGLT2 inhibitors in diabetic patients: A comparative cross-sectional study from Pakistan

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Abstract: This study compares linagliptin and SGLT-2 inhibitors to optimize diabetes management by evaluating their glycemic and non-glycemic effects. A cross-sectional study was conducted at the Aga Khan University Hospital, Karachi, from May to October 2023. Patients using linagliptin were assigned to group 1, while those on SGLT-2 inhibitors comprised group 2. Frequencies and percentages were used for categorical variables, and mean with standard deviation (SD) for continuous variables. An independent t-test assessed clinical outcomes before and after six months of treatment, with a significance threshold of $p<0.05$. Of the 278 patients enrolled (mean age: 53 years, SD: 13.4; 55.2% male), 39 were in group 1, and 239 in group 2. SGLT-2 inhibitors showed a greater reduction in HbA1c (-0.66 vs. -0.46, p=0.002) and diastolic blood pressure (mean difference: 2.65 mmHg, p=0.005). Linagliptin significantly reduced BMI (mean difference: 0.65 kg/m², p=0.03), while no significant weight change was observed with SGLT-2 inhibitors. SGLT-2 inhibitors provided superior glycemic control and reduced blood pressure, while linagliptin was more effective in lowering BMI. Further studies are needed to explore linagliptin's potential benefits.

Keywords: Diabetes; glycemic control; HbA1c; linagliptin; SGLT-2 inhibitors

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INTRODUCTION

Pakistan ranks as the third-largest nation globally in terms of diabetes prevalence, with approximately 33 million individuals affected by type 2 diabetes, alongside an additional 11 million adults experiencing impaired glucose tolerance. (Bhutta *et al*, 2022) Moreover, an estimated 8.9 million people in Pakistan have undiagnosed diabetes. (Bhutta *et al*, 2022) Anti-diabetic medications play a crucial role in lowering blood sugar levels and partially alleviating insulin resistance and are a cornerstone for management of type 2 diabetes. (Lin *et al*, 2023)

For over almost a century now, newer therapeutic options for the management of diabetes have been emerging, and are in fact a lot more promising due to their glycemic control in addition to their incredible weight loss properties.(Mingrone *et al*, 2022) Dipeptidyl peptidase-4 (DPP-4) inhibitors such as linagliptin is an anti-diabetic drug that function by inhibiting the enzyme DPP-4, thereby prolonging the activity of glucagon-like peptide-1 (GLP-1) and promoting glucose reduction.(Aljohani *et al*, 2024) It effectively reduces HbA1c levels but also had a unique pharmacokinetic profile, featuring non-renal excretion, eliminates the need for dose adjustment in patients with kidney disease.(Daza-Arnedo *et al*, 2021)

Sodium-glucose transport protein-2 (SGLT-2) inhibitors represent another class of oral hypoglycemic that enhance glucose excretion in urine by inhibiting glucose reabsorption at the proximal convoluted tubules in the kidney.(Saisho, 2020) They typically lower HbA1c levels by 0.6–0.8%.(Saisho, 2020) Additionally, both group of medications are not only effective in glycemic control but also aids in lowering cholesterol levels, reducing systolic blood pressure and promoting weight loss.(Son *et al*, 2021) The rationale for conducting a comparative study between linagliptin and SGLT-2 inhibitors lies in the growing need to optimize diabetes management beyond glycemic control. It is important to identify their glycemic control capacity as well as their non-glycemic properties. The study could provide critical insight into which class of drug is more suitable for specific patient populations particularly those with cardiovascular and renal concerns.

MATERIALS AND METHODS

Study design

This is a comparative cross-sectional observational study conducted at the Aga Khan University Hospital, Karachi, from May to October 2023. The study aimed to compare the efficacy of linagliptin and SGLT-2 inhibitors in terms of glycemic control and non-glycemic outcomes, such as blood pressure regulation, weight loss and reduction in complications.

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Ethical consideration

The study received a waiver from informed consent from the institutional Ethical Review Committee (ERC Number: 2023-8631-24526).

Inclusion criteria

- Patient aged 18 years and above
- Patients with a confirmed diagnosis of type 2 diabetes mellitus
- Patient who had been on linagliptin or SGLT-2 inhibitors for the past six months prior to hospital admission

Exclusion criteria

- Patient receiving insulin therapy
- Patient who were using combination of linagliptin and SGLT-2 inhibitors

Grouping and data collection

Patients using linagliptin were labeled group 1 while those on SGLT-2 inhibitors were group 2. Data was obtained from the electronic medical record database and patients file. The variables pertaining to demographic information, glycemic control (i.e. HbA1c, fasting and random blood sugars), blood pressure, weight, and body mass index (BMI) before and after six months of treatment were recorded. Complications like diabetic ketoacidosis, hypoglycemia, stroke, myocardial infarction, heart failure, urogenital infections, thromboembolism and bone fractures had been evaluated during the six months of treatment with these medications.

STATISTICAL ANALYSIS

A comparative analysis of clinical outcomes in patients with diabetes was conducted using descriptive statistics in Stata version 17. Participant socio-demographic and baseline characteristics were presented as frequencies (N) and percentages (%) for categorical variables. Mean and standard deviation (SD) were reported for continuous variables. Descriptive statistics were also employed to outline comorbidities among patients enrolled in the study. An independent sample t-test was conducted to assess the comparison of clinical outcomes among T2DM patients before and after 6 months of treatment with linagliptin and SGLT-2 inhibitors. The resulting p-values (level of significance <0.05) were reported.

RESULTS

General Socio-demographic characteristics of the study participants

We enrolled a total of 278 patients in our study. The mean age of the patients was 53 years (S.D: 13.4), with 55.2% being males. Of the 278 patients, 39 patients were in group 1 (linagliptin users) and 239 patients were in group 2 (SGLT-2 inhibitors users). The most prevalent co-morbidity among these individuals was chronic kidney disease, affecting 272 patients (98.1%). Table 1 provide a summary of socio-demographic characteristics of the study participants.

Comparison of outcomes for linagliptin versus SGLT-2 inhibitor before and after 6 months of treatment

SGLT-2 inhibitors demonstrated a significantly greater reduction in mean HbA1c levels (-0.66) compared to linagliptin (-0.46) (p=0.002). Fig. 1 illustrates the graphical representation of glycemic control between the two treatment groups. Furthermore, SGLT-2 inhibitors led to a significant decrease in diastolic blood pressure (mean difference: 2.65 mmHg, p=0.005), whereas linagliptin showed no significant change in this parameter. Additionally, linagliptin exhibited a significant decrease in BMI (mean difference: 0.65 kg/m^2, p=0.03), while SGLT-2 inhibitors did not show a significant change. Table 2 shows a detail comparison of the outcomes between the two treatment groups.

Complications among diabetic patients using Linagliptin and SGLT-2 inhibitors

Hypoglycemia rates were notably higher with linagliptin (8.1%) compared to SGLT2 inhibitors (0.5%). Myocardial infarction prevalence tended to be higher with SGLT2 inhibitors (7.1%) versus linagliptin (0.0%), though statistical significance was not reached (p-value >0.05). Prevalence of heart failure, urogenital infections, thromboembolism, and bone fractures showed no significant differences between groups. In Table 3, we showed variations in complications among patients with type 2 diabetes mellitus based on their treatment with linagliptin or SGLT2 inhibitors.

DISCUSSION

Our study identified a significant reduction in HbA1c levels after six month of treatment with SGLT-2 inhibitors, indicating effective glycemic control. In addition to lowering blood glucose, SGLT-2 inhibitors were also associated with a significant reduction in blood pressure; however, no notable impact on weight and BMI was observed. Conversely, in the smaller group of patients using linagliptin, there was a slight reduction in HbA1c, but this change was not statistically significant. Interestingly, linagliptin was associated with a significant reduction in BMI, suggesting potential benefits in weight management for this group.

In a double-blind phase 3 randomized controlled trial (RCT) on a younger population (age < 50 years) with type 2 diabetes, it was noted that after 26 weeks of treatment, the mean change in HbA1c for linagliptin compared to placebo was –0.34% from baseline, while the SGLT-2 versus placebo group showed a change of –0.84%.(Laffel *et al*, 2023) Furthermore, several other studies found that add-on therapy with DPP-4 or SGLT-2 inhibitors did reduction in HbA1c levels among patients with type 2

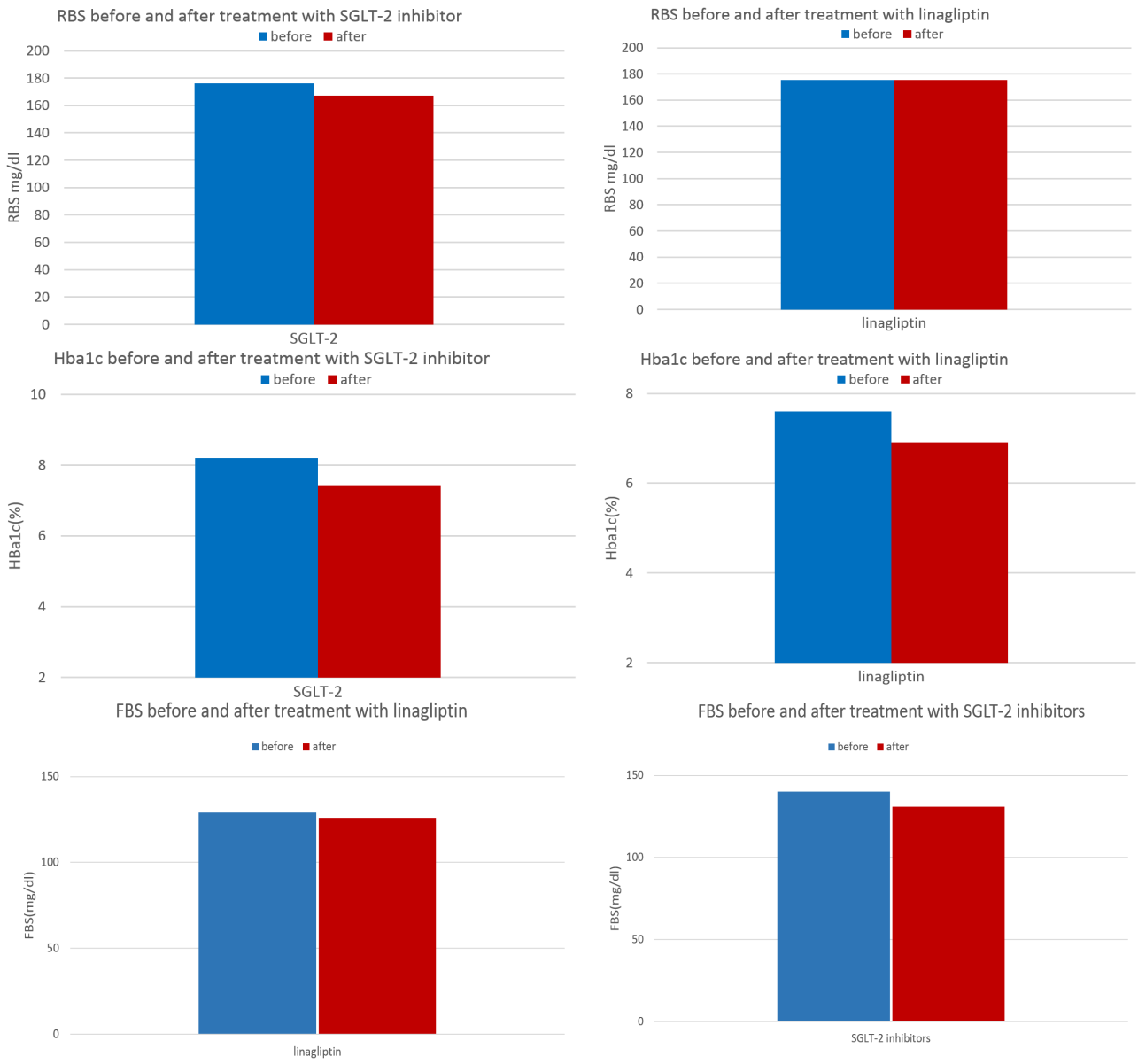

Fig. 1: Graphical representation of glycemic control between two groups

diabetes mellitus.(Scheen, 2020) The effectiveness of the combined therapy of SGLT-2 and DPP-4 was linked to a more significant reduction in HbA1c, with a mean difference after 24 weeks of treatment showed HbA1c of 7.1% compare to pre-treatment: 7.7% (P<0.001). (Nagayama *et al*, 2024) Additionally, since these studies were conducted in high-income countries, their results may not be applicable to low- and middle-income countries, particularly in South Asian regions, where eating habits, BMI thresholds, and lifestyles can differ significantly. (Caleyachetty *et al*, 2021) We found similar results in our study. After 6 months (24 weeks) of treatment, the mean change in HbA1c levels from baseline was -0.46% in the linagliptin group (p-value: 0.15) and -0.66% in the SGLT-2 inhibitor group (p-value: 0.002).

A retrospective study showed a significant reduction in blood pressure for patients treated with SGLT2 inhibitors compared to those on DPP-4 inhibitors, with mean decreases of 69.6 mmHg and 71.6 mmHg, respectively ($p < 0.05$). (Lee *et al*, 2019) Similarly, the LUNA study, a multicenter, prospective, randomized, open-label trial conducted in Japan, found a significant reduction in diastolic blood pressure (DBP) in patients treated with SGLT-2 inhibitors (mean DBP of 78 mm Hg) compared to those receiving DPP-4 inhibitors after 8 months of treatment ($p < 0.05$). (Hashimoto-Kameda *et al*, 2021) We also observed a greater reduction in blood pressure in the SGLT-2 inhibitor group compared to the linagliptin group, with mean decreases of 2.60 mmHg in systolic blood pressure and 2.65 mmHg in diastolic blood pressure.

Table 1: Socio-demographic characteristics of the study participants

Characteristics	N(%)
Age - mean (S.D.)	53.8(13.4)
Gender	
Male	153(55.2)
Female	124(44.7)
Groups	
1: Linagliptin users	39(13.7)
2: SGLT-2 inhibitor users	239(86.3)
Other concomitant oral hypoglycemic use	214(77.2)
Co-morbidity	
Chronic Kidney Disease	272(98.1)
Hypertension	158(57.1)
Ischemic Heart Disease	56(20.2)
Stroke	7(2.6)
Thyroid Disease	10(3.7)

Table 2: Comparison of outcomes before and after 6 months of treatment

Outcomes	*Linagliptin*				*SGLT-2 inhibitors*			
	Before tx	*After tx*	**MD(95% CI)*	***p-value*	*Before tx*	*After tx*	**MD(95% CI)*	***p-value*
HbA1c (%)	7.48	7.01	0.46 (-1.79-1.11)	0.15	8.10	7.44	0.66 (7.16-7.71)	0.002
FBS (mg/dl)	129.31	126.31	3 (-21-27.43)	0.79	140.79	131.68	9.11 (-1.07-19.3)	0.07
RBS (mg/dl)	177.6	176.4	1.2 (-49-52)	0.95	179.61	166.77	12.83 (-5.2-30.9)	0.16
UMA (mg/24h)	48	56.4	-516(3)	-	32.5	32.5	0 (-11.6-1.69)	1.00
SBP (mmHg)	135.44	136.66	-1.22 (-12.0-9.51)	0.81	132.02	129.91	2.60 (-0.19-5.91)	0.06
DBP (mmHg)	73.33	74.72	-1.38 (-8.11-5.33)	0.66	77.05	74.40	2.65 (0.77-4.52)	0.005
Weight (kg)	76.92	79.15	2.23	0.55	77.70	77.24	0.46 (-0.43-0.63)	0.71
BMI (kg/m^2)	29.79	29.14	0.65 (0.06-1.23)	0.03	29.06	28.96	.09 (-0.43-0.63)	0.71

*MD=Mean Difference,

** t-test was applied with level of significance (p-value) <0.05

Abbreviation: tx=treatment; FBS: fasting blood sugar; RBS: random blood sugar; UMA: urine micro-albumin; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index

Table 3: Complications among diabetic patients using Linagliptin and SGLT-2 inhibitors

Complications	Linagliptin *N= 39 (%)*	SGLT2 inhibitors *N= 239 (%)*
Hypoglycemia	3(8.1)	1(0.5)
Stroke	1(2.7)	4(1.6)
Myocardial Infarction	0(0.0)	17(7.1)
Heart Failure	0(0.0)	8(3.3)
Urogenital infection	0(0.0)	5(2.1)
Thromboembolism	0(0.0)	2(0.9)
Bone Fracture	0(0.0)	3(1.3)
Other	2(5.2)	15(6.3)

It is important to maintain a healthy weight and achieving an optimal BMI are crucial in enhancing treatment effectiveness and glycemic control for patients with diabetes mellitus. A recent study showed that different groups of anti-diabetic drugs had impact in reducing bodyweight and helps in improving glycemic control.(Lazzaroni *et al*, 2021) SGLT-2 inhibitors have been identified as significant contributors to weight loss. However, since linagliptin is a newly introduced drug in our context and has been tested on a limited number of patients, there is limited literature available to assess its effectiveness for weight loss.(Suzuki *et al*, 2024) In our study, we found a significant reduction in BMI in a small sample of patients receiving linagliptin, with a mean difference of 0.65 from baseline after 6 months of treatment (p-value: 0.03). This could have a substantial positive effect on diabetes management in our population, as obesity is a significant challenge in the South Asian region. A medication that effectively controls both blood sugar and weight could be particularly beneficial.

This study presents several strengths and limitations. Firstly, it represents pioneering research in our region, being the first study of its kind to undertake a cross-sectional comparison of pre- and post-diabetes-related clinical parameters and laboratory findings among patients treated with linagliptin versus SGLT-2 inhibitors. Secondly, our findings offer valuable insights for clinicians, aiding in the assessment of the short- and long-term efficacy of these drugs and assisting in the identification of key clinical parameters to monitor over a 6-month period to gauge clinical benefits. Moreover, conducting the study within a hospital setting ensured standardized data collection procedures and facilitated access to comprehensive medical records, thereby bolstering the reliability and accuracy of our results. Additionally, the inclusion of a diverse patient population enhances the generalizability of our findings, rendering them applicable across a broader spectrum of clinical practice.

However, our study is not devoid of limitations. Firstly, the relatively recent introduction of linagliptin in our country resulted in a smaller sample size in the linagliptin group compared to the SGLT-2 inhibitors group. Second, the study's focus on a narrow timeframe of six months overlooks the long-term effects of these medications, warranting further investigation. Third, the study does not evaluate or compare dosing regimens for these medications, which could potentially influence treatment outcomes. Lastly, our study encountered missing variables, likely stemming from financial constraints, loss to follow-up, and inadequate documentation of medical records, which may have impacted the comprehensiveness of our analysis.

The study illuminates the efficacy and possible adverse reactions associated with linagliptin and SGLT-2 inhibitors within the South Asian population. While showcasing promising effectiveness, the research emphasizes the necessity for larger-scale investigations to deepen our comprehension of the relationship between glycemic control and these medications. Significantly, the potential synergistic effects of combining linagliptin with SGLT-2 inhibitors emerge as a compelling area for future exploration in forthcoming studies.

CONCLUSION

In conclusion, our study demonstrated that SGLT-2 inhibitors, when used alone, achieved superior glycemic control compared to baseline after 6 months of treatment. Additionally, they were effective in reducing blood pressure. Conversely, linagliptin showed promising results in decreasing weight and BMI; however, further studies are necessary to fully explore its efficacy.

Conflict of interest

There is no conflict of interest between authors to declare.

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