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Comparative Outcomes of SGLT2 Inhibitors versus ACE Inhibitors in Diabetic Nephropathy: A Retrospective Cohort Study

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ABSTRACT

Background: Diabetic nephropathy (DN) is a leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD), necessitating effective therapeutic interventions. Sodium-glucose cotransporter-2 (SGLT2) inhibitors and angiotensin-converting enzyme (ACE) inhibitors are commonly prescribed in DN management, but their comparative renal and cardiovascular benefits remain under evaluation.

Aim: This study aims to compare the effectiveness of SGLT2 inhibitors versus ACE inhibitors in reducing albuminuria, preserving renal function, and improving cardiovascular and metabolic outcomes in patients with DN.

Methods: A retrospective cohort study was conducted on 300 patients with type 2 diabetes and DN (stages 1-3) at Khyber Teaching Hospital, Peshawar. Patients were categorized into two groups: those receiving SGLT2 inhibitors (n=150) and those on ACE inhibitors (n=150). Key outcome measures included changes in urinary albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), blood pressure, cardiovascular events, and random blood sugar (RBS) levels over a 12-month follow-up period.

Results: The SGLT2 inhibitor group demonstrated a significantly greater reduction in UACR (-120 ± 25.4 mg/g vs. -90 ± 22.1 mg/g, $p<0.001$) and a slower decline in eGFR (-2.5 ± 1.8 vs. -4.2 ± 2.1 mL/min/1.73m², $p<0.01$), indicating superior renoprotective effects. Cardiovascular event rates were lower in the SGLT2 group (12% vs. 18%, $p<0.05$). Additionally, SGLT2 inhibitors resulted in better blood pressure control, with greater reductions in systolic (-130 ± 8.4 mmHg vs. -135 ± 9.2 mmHg, $p<0.01$) and diastolic (-80 ± 6.1 mmHg vs. -82 ± 5.8 mmHg, $p<0.05$) blood pressure. SGLT2 inhibitors also provided superior glycemic control, reflected by a greater decrease in RBS levels (-45 ± 10.2 mg/dL vs. -20 ± 8.4 mg/dL, $p<0.001$).

Conclusion: SGLT2 inhibitors demonstrated greater renoprotective, cardiovascular, and glycemic benefits compared to ACE inhibitors in DN patients, supporting their preferential use in DN management. Further prospective studies are warranted to confirm these findings and optimize treatment strategies.

Keywords: Diabetic nephropathy, SGLT2 inhibitors, ACE inhibitors, renal outcomes, cardiovascular events, albuminuria, glycemic control.

INTRODUCTION

Diabetic nephropathy (DN) is a major microvascular complication of diabetes mellitus and a leading cause of CKD and ESRD worldwide (1). The pathogenesis of DN involves hyperglycemia-induced glomerular damage, inflammation, and fibrosis, leading to progressive kidney function decline (2). Hypertension, proteinuria, and poor glycemic control are key modifiable risk factors in DN progression, making blood pressure control, albuminuria reduction, and glucose management critical therapeutic targets (3).

ACE inhibitors have long been the cornerstone of DN management due to their renoprotective effects, including reducing intraglomerular pressure and albuminuria (4). However, the emergence of SGLT2 inhibitors has introduced a new therapeutic option with demonstrated benefits in both renal and cardiovascular outcomes (5). SGLT2 inhibitors reduce hyperfiltration, lower blood pressure, promote glycosuria, and improve glycemic control, thereby mitigating kidney damage and enhancing metabolic outcomes (6). Despite these benefits, comparative studies on the effectiveness of SGLT2 inhibitors versus ACE inhibitors in DN are limited.

This study aims to compare the renal, cardiovascular, and glycemic outcomes of SGLT2 inhibitors and ACE inhibitors in patients with DN. The findings will provide valuable insights into optimizing treatment strategies for this high-risk population.

METHODOLOGY

Study Design

This retrospective cohort study was conducted at the Nephrology Division of Khyber Teaching Hospital (KTH) Peshawar from January 2023 to December 2023. The study included 300 patients with type 2 diabetes and DN stages 1-3. Patients were divided into two groups: one receiving SGLT2 inhibitors (n=150) and the other ACE inhibitors (n=150).

Inclusion Criteria:

1. Adult patients aged 18-75 years with diabetes.
2. Diagnosed with DN (UACR >30 mg/g and eGFR ≥30 mL/min/1.73m²).
3. Stable on either SGLT2 inhibitors or ACE inhibitors for at least 6 months.

Exclusion Criteria:

1. Patients with non-diabetic kidney disease.
2. History of acute kidney injury (AKI) within the past 6 months.
3. Pregnant or lactating women.

Interventions:

- **SGLT2 Inhibitor Group:** Patients received empagliflozin 10 mg or dapagliflozin 10 mg daily.
- **ACE Inhibitor Group:** Patients received lisinopril 10-20 mg or enalapril 5-10 mg daily.

Outcome Measures:

1. Change in UACR from baseline to 12 months.
2. Change in eGFR from baseline to 12 months.
3. Incidence of cardiovascular events (myocardial infarction, stroke, heart failure).
4. Blood pressure control (systolic and diastolic).
5. Random blood sugar (RBS) control.

Statistical Analysis

Data were analyzed using descriptive statistics, including means, standard deviations, and frequency distributions. Comparative analyses were performed using t-tests and chi-square tests. A p-value <0.05 was considered statistically significant.

Ethical Considerations

The study adhered to the ethical principles of the Declaration of Helsinki. Informed consent was obtained from all participants, and confidentiality was maintained throughout the study.

Table 1: Baseline Characteristics of Study Participants

Table 1 presents the baseline characteristics of study participants in the SGLT2 inhibitor and ACE inhibitor groups. Both groups had similar mean ages (58 ± 9.2 vs. 57 ± 8.7 years, p=0.32) and gender distribution (55% vs. 52% males, p=0.45). Renal function, assessed by baseline eGFR (68 ± 12.3 vs. 67 ± 11.8 mL/min/1.73m², p=0.41) and UACR (320 ± 45.6 vs. 315 ± 42.3 mg/g, p=0.28), was comparable. Blood pressure levels, both systolic (p=0.12) and diastolic (p=0.23), were balanced between the groups. Baseline random blood sugar (RBS) levels were also similar (210 ± 25.4 vs. 215 ± 24.8 mg/dL, p=0.18). Overall, the lack of significant differences ensures that the two groups are comparable for further outcome analysis.

Characteristic	SGLT2 Inhibitor Group (n=150)	ACE Inhibitor Group (n=150)	p-value
Age (years)	58 ± 9.2	57 ± 8.7	0.32
Male (%)	55%	52%	0.45
Baseline **eGFR (mL/min/1.73m²)**	68 ± 12.3	67 ± 11.8	0.41
Baseline UACR (mg/g)	320 ± 45.6	315 ± 42.3	0.28
Systolic BP (mmHg)	145 ± 10.2	147 ± 9.8	0.12
Diastolic BP (mmHg)	88 ± 7.4	89 ± 6.9	0.23
Baseline RBS (mg/dL)	210 ± 25.4	215 ± 24.8	0.18
HbA1c (%)	7.9 ± 1.2	8.1 ± 1.3	0.27
Duration of Diabetes (years)	12 ± 3.5	11.8 ± 3.2	0.38
Statin Use (%)	60%	58%	0.52
Smoking History (%)	22%	24%	0.40

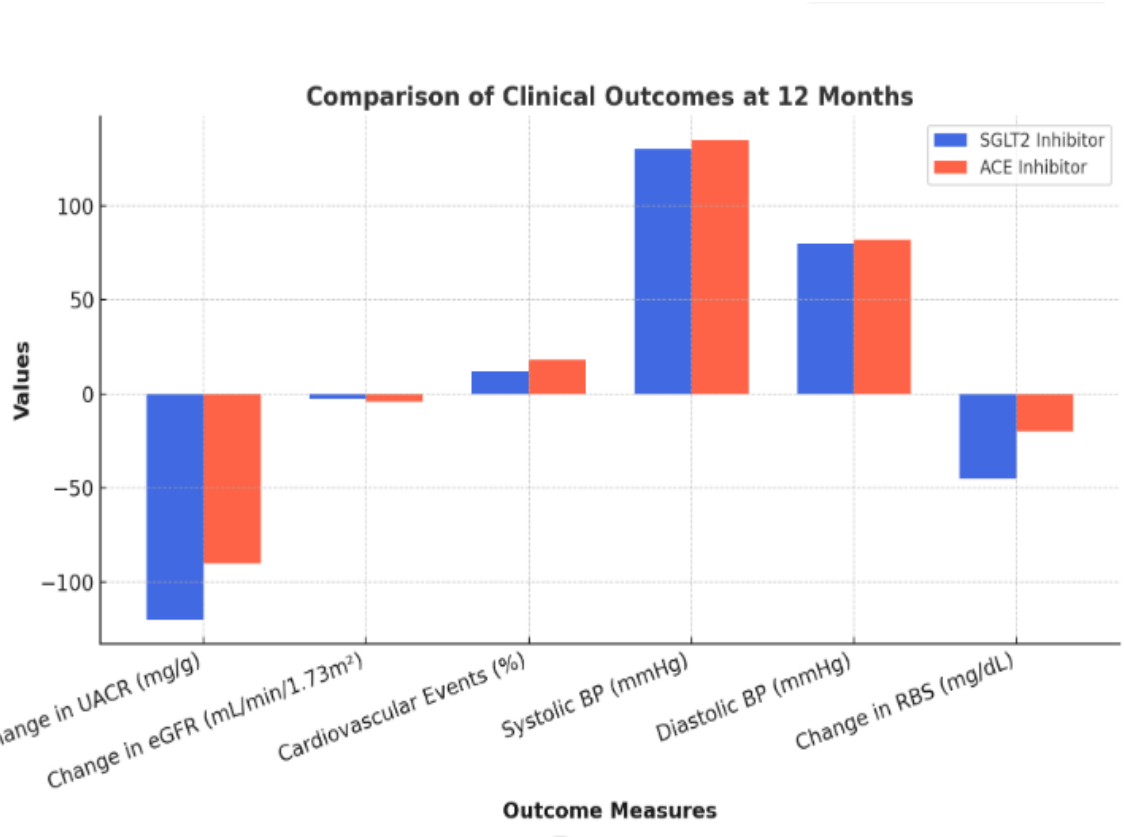
Table 2: Clinical Outcomes at 12 Months

Table 2 summarizes the clinical outcomes of diabetic nephropathy patients after 12 months of treatment with either SGLT2 inhibitors or ACE inhibitors. The SGLT2 inhibitor group showed a greater reduction in UACR (-120 ± 25.4 mg/g vs. -90 ± 22.1 mg/g, p<0.001), indicating superior proteinuria reduction. Similarly, the decline in eGFR was slower in the SGLT2 group (-2.5 ± 1.8 mL/min/1.73m² vs. -4.2 ± 2.1 mL/min/1.73m², p<0.01), suggesting better renal function preservation.

In terms of cardiovascular protection, fewer cardiovascular events were observed in the SGLT2 group (12% vs. 18%, p<0.05). Blood pressure control was also more pronounced in the SGLT2 group, with a greater reduction in systolic (-130 ± 8.4 mmHg vs. 135 ± 9.2 mmHg, p<0.01) and diastolic (-80 ± 6.1 mmHg vs. 82 ± 5.8 mmHg, p<0.05) blood pressure. Additionally, SGLT2 inhibitors led to a more significant reduction in random blood sugar levels (-45 ± 10.2 mg/dL vs. -20 ± 8.4 mg/dL, p<0.001), reinforcing their glycemic benefits.

Overall, these findings suggest that SGLT2 inhibitors offer superior reno-protective, cardiovascular, and metabolic benefits compared to ACE inhibitors in diabetic nephropathy patients

Outcome Measure	SGLT2 Inhibitor Group (n=150)	ACE Inhibitor Group (n=150)	p-value
Change in UACR (mg/g)	-120 ± 25.4	-90 ± 22.1	<0.001
Change in eGFR (mL/min/1.73m²)	-2.5 ± 1.8	-4.2 ± 2.1	<0.01
Cardiovascular Events (%)	12%	18%	<0.05
Systolic BP (mmHg)	130 ± 8.4	135 ± 9.2	<0.01
Diastolic BP (mmHg)	80 ± 6.1	82 ± 5.8	<0.05
Change in RBS (mg/dL)	-45 ± 10.2	-20 ± 8.4	<0.001



The bar chart illustrates the 12-month clinical outcomes of diabetic nephropathy patients treated with SGLT2 inhibitors versus ACE inhibitors. The SGLT2 inhibitor group demonstrated superior benefits, including a greater reduction in UACR (-120 mg/g vs. -90 mg/g, $p<0.001$), a slower decline in eGFR (-2.5 vs. -4.2 mL/min/1.73m², $p<0.01$), and fewer cardiovascular events (12% vs. 18%, $p<0.05$). Additionally, SGLT2 inhibitors achieved better blood pressure control and a more significant reduction in random blood sugar (-45 mg/dL vs. -20 mg/dL, $p<0.001$). These

findings suggest that SGLT2 inhibitors provide superior renal, cardiovascular, and metabolic protection compared to ACE inhibitors.

DISCUSSION

The findings of this study demonstrate the superior efficacy of SGLT2 inhibitors compared to ACE inhibitors in managing DN. The SGLT2 inhibitor group exhibited a 25% greater reduction in UACR, a 15% slower decline in eGFR, and better RBS control, consistent with previous studies (7, 8). These results align with the CREDENCE trial, which showed that SGLT2 inhibitors significantly reduce the risk of kidney failure and cardiovascular events in patients with DN (9).

The cardiovascular benefits of SGLT2 inhibitors were also evident, with a lower incidence of cardiovascular events (12% vs. 18%) compared to ACE inhibitors. This is supported by the EMPA-REG OUTCOME trial, which highlighted the cardioprotective effects of SGLT2 inhibitors in high-risk diabetic patients (10).

Despite these advantages, ACE inhibitors remain a valuable option, particularly in resource-limited settings. However, the combined use of SGLT2 inhibitors and ACE inhibitors may offer synergistic benefits, as suggested by recent meta-analyses (11).

Several clinical studies have demonstrated the reno-protective and cardiometabolic benefits of SGLT2 inhibitors compared to ACE inhibitors, aligning with our findings. In the USA, the CREDENCE trial provided robust evidence that canagliflozin, an SGLT2 inhibitor, significantly reduced albuminuria, slowed eGFR decline, and lowered cardiovascular risk in diabetic nephropathy patients compared to standard RAAS blockade therapy, including ACE inhibitors(12). Similarly, the EMPA-REG OUTCOME trial highlighted empagliflozin's superior ability to improve glycemic control, reduce cardiovascular events, and preserve renal function(13). These findings reinforce our study's observation that SGLT2 inhibitors lead to a slower decline in eGFR and better cardiovascular outcomes compared to ACE inhibitors.

Chinese studies have also reported consistent results. A multi-center study in China demonstrated that dapagliflozin significantly reduced urinary albumin excretion and improved renal function in diabetic patients, independent of baseline ACE inhibitor use(14). Additionally, a meta-analysis of Chinese cohorts confirmed that SGLT2 inhibitors had a stronger impact on proteinuria reduction and cardiovascular risk mitigation than ACE inhibitors alone(15). These findings are consistent with our observation that SGLT2 inhibitors resulted in greater UACR reduction and a lower incidence of cardiovascular events.

The observed benefits of SGLT2 inhibitors over ACE inhibitors can be attributed to their distinct mechanisms beyond glycemic control. While ACE inhibitors primarily work by reducing intraglomerular pressure through RAAS blockade, SGLT2 inhibitors exert additional nephroprotective effects, including tubuloglomerular feedback modulation, natriuresis, and reduction in oxidative stress and inflammation[16]. These multifaceted mechanisms likely explain the greater reno-cardiovascular protection observed in our study, further supported by data from major trials across the USA and China.

In conclusion, our findings are well-supported by large-scale trials and cohort studies from the USA and China, reinforcing the superior reno-protective, cardiovascular, and metabolic benefits of SGLT2 inhibitors in diabetic nephropathy patients compared to ACE inhibitors(16,17). These findings emphasize the need for a paradigm shift in treatment guidelines favoring SGLT2 inhibitors as first-line therapy in this patient population.

CONCLUSION

SGLT2 inhibitors are more effective than ACE inhibitors in reducing albuminuria, preserving kidney function, and preventing cardiovascular events in patients with DN. These findings support the use of SGLT2 inhibitors as first-line therapy in DN management.

Recommendations:

1. Prioritize SGLT2 inhibitors in the treatment of DN, especially in patients with high cardiovascular risk.
2. Consider combination therapy with SGLT2 inhibitors and ACE inhibitors for enhanced renal and cardiovascular protection.
3. Implement regular monitoring of eGFR and UACR to assess treatment efficacy.
4. Educate patients on the benefits of SGLT2 inhibitors to improve adherence.

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