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Effect of Dapagliflozin on Renal Function in Non-Diabetic Chronic Kidney Disease: A Randomized Controlled Study.

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Abstract

Background: Chronic kidney disease is a progressive disorder associated with increased morbidity and mortality. While SGLT2 (Sodium-Glucose Cotransporter-2) inhibitors have demonstrated renoprotective effects in diabetic CKD (Chronic Kidney Disease), evidence regarding their efficacy in non-diabetic CKD remains limited. This study evaluated the effect of dapagliflozin on renal function in patients with non-diabetic stage 3 and stage 4 CKD.***Methods:***Over the course of a year, a single-blind, randomised controlled study was carried out at Tagore Medical College and Hospital's Nephrology Outpatient Department in Chennai. Ninety persons with stage 3 or stage 4 CKD who were not diabetics were divided into two groups at random: Group A (n = 45) received standard medication plus 10 mg of dapagliflozin once daily, whereas Group B (n = 45) received standard therapy plus a placebo. At 1, 3, 6, 9, and 12 months, patients were monitored. Changes in serum creatinine, serum urea, RBS (Random Blood Sugar), and eGFR (estimated Glomerular Filtration Rate) were the main results. SPSS version 22 was used to analyse the data at a significance level of $p<0.05$.***Results:***Baseline demographic and clinical characteristics were comparable between the groups. Both groups demonstrated an initial decline in eGFR during the first three months; however, from 6 months onward, renal function remained significantly more stable in the dapagliflozin group. At 12 months, the mean eGFR decline was 2.79 mL/min/1.73 m^2 in Group A compared with 5.18 mL/min/1.73 m^2 in Group B ($p<0.001$). The reduction in RBS was significantly greater with dapagliflozin from 3 months onward (15.06 vs. 3.41 mg/dL at 12 months; $p<0.001$). Serum urea increased significantly less in the intervention group (2.32 vs. 7.12 mg/dL; $p<0.001$), while serum creatinine remained relatively stable without significant between-group differences. Mortality and adverse events were low in both groups. ***Conclusion:*** Dapagliflozin significantly slowed the progression of renal dysfunction in non-diabetic stage 3 and stage 4 CKD by preserving eGFR and limiting the rise in serum urea, while also improving glycemic parameters without major safety concerns. These findings support dapagliflozin as an effective adjunct to standard therapy for delaying CKD progression in non-diabetic patients.

Keywords: Chronic Kidney Disease, Dapagliflozin, SGLT2 Inhibitor, Non-Diabetic CKD, Estimated Glomerular Filtration Rate, Renal Function, Randomized Controlled Trial.

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INTRODUCTION

It is estimated that 700 million people worldwide suffer from CKD (Chronic Kidney Disease).[1] CKD is a serious public health issue that has a substantial impact on morbidity, mortality, lower quality of life, and shorter life expectancy. Compared to other prevalent medical disorders, kidney diseases have been the subject of fewer clinical trials, despite the availability of straightforward laboratory tests that can identify decreased kidney function.[2].

Until recently, ACE (Angiotensin-Converting Enzyme) inhibitors and ARBs (Angiotensin II Receptor Blockers)[3] were the only pharmaceuticals that had been shown to prevent the deterioration of renal function. However, research involving patients with type 2 diabetes mellitus has provided the majority of the evidence for their renoprotective properties.

In numerous extensive clinical trials including patients with type 2 diabetes, sodium-glucose cotransporter-2 (SGLT2) inhibitors have shown significant improvements in renal and cardiovascular outcomes. These medications have

demonstrated notable nephroprotective effects in addition to enhancing glycaemic management by lowering glycated haemoglobin (HbA1c) levels.[4] Long-term canagliflozin treatment dramatically decreased the risk of kidney disease progression and cardiovascular events in patients with type 2 diabetes and chronic kidney disease, according to the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial.[5].

Growing evidence indicates that the renoprotective effects of SGLT2 inhibitors go beyond glucose reduction, even if the precise mechanisms behind these advantages are yet unclear. Natriuresis and glucose-induced osmotic diuresis, which lower intraglomerular pressure and enhance renal haemodynamics, are thought to be the causes of these advantages.[5] Therefore, even in patients with non-diabetic chronic kidney disease, these beneficial haemodynamic effects may help maintain kidney function, indicating that SGLT2 inhibitors may have therapeutic promise beyond the treatment of diabetes.

AIMS AND OBJECTIVES

The aim of this study was to evaluate the effectiveness and safety of SGLT2 inhibitors in improving renal function among patients with non-diabetic stage 3 and stage 4 chronic kidney disease. The objective was to assess the effect of SGLT2 inhibitor therapy on renal function over an extended follow-up period and determine its potential role in slowing the progression of chronic kidney disease in this patient population.

MATERIALS AND METHODS

Study Design

The present study was a randomized controlled study conducted in the Department of Nephrology, Tagore Medical College and Hospital, Chennai, over a period of 12 months, from June 2024 to June 2025, after obtaining approval from the Institutional Ethics Committee.

Inclusion and Exclusion Criteria

Patients aged between 18 and 70 years with a diagnosis of non-diabetic stage 3 or stage 4 CKD were included in the study. Patients with diabetic kidney disease, a history of CAD (Coronary Artery Disease) or stroke, hepatic dysfunction, bleeding diathesis, recurrent urinary tract infections, or previous episodes of pyelonephritis were excluded from the study.

Sample Size Calculation

N = (Z 1-α/2 + Z 1-β) 2 * 2 * σ 2 / (μ 1 - μ 2) 2 Z 1-α/2 - two tailed probability for 95% confidence interval = 1.96
Z1-β - two tailed probability for 80% power = 0.84
N = (1.96 + 0.84) ^2 * 2 *23^2 / (3) ^2
N = 40.07 + 4 (considering 10% dropout)
Thus, the sample size required for each group is 45 and the total sample size is 90.[6]

Data Collection Procedure

Following Institutional Ethics Committee (IEC) approval, consecutive patients with eGFR-based stage 3 and stage 4 CKD were screened in accordance with the inclusion and exclusion criteria. Serum urea, serum creatinine, FBS (Fasting Blood Sugar), PPBS (Post-Prandial Blood Sugar), RBS (Random Blood Sugar), and eGFR were among the baseline tests that were documented, along with a thorough clinical history and physical examination. Age, gender, BMI (Body Mass Index), smoking status, alcohol intake, blood pressure (SBP and DBP), prior treatment, and stage of CKD were among the clinical and demographic characteristics that were recorded. Eligible participants were randomly allocated by the lottery method into Group A (case group), which received dapagliflozin 10 mg once daily in the morning along with standard therapy (ACE inhibitors and sodium bicarbonate), and Group B (control group), which received a placebo along with standard therapy. Written informed consent was obtained from all participants after explaining the study objectives, possible benefits, adverse effects, and follow-up schedule. Patients were followed up at 1, 3, 6, 9, and 12 months. At each follow-up visit, clinical examination and renal function assessment, including serum urea, serum creatinine, and eGFR, were performed, and participants were monitored for adverse events such as UTI (Urinary Tract Infection), pyelonephritis, recurrent or complicated UTI, hypoglycemia, fractures, amputation, renal-related adverse events, volume depletion, and mortality. Patients developing recurrent or complicated UTI, pyelonephritis, or a rapid decline in eGFR to <15 mL/min/1.73 m^2 had the study drug discontinued. The progression of renal function was assessed by comparing changes in eGFR and other renal parameters between the dapagliflozin and placebo groups over the 12-month study period.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 22.0 was used to analyse the data after it was imported into Microsoft Excel. Frequency, percentage, mean, and standard deviation were used to express descriptive statistics. When comparing categorical variables, the chi-square test or Fisher's exact test was used. The independent t-test for two groups and one-way Analysis of Variance (ANOVA) for more than two groups were used to compare continuous variables. Statistical significance was defined as a p-value of less than 0.05.

RESULTS

Table 1 illustrates the baseline demographic and lifestyle profile of the two groups. The mean age was 61.64 years in Group A and 61.89 years in Group B, with no significant difference (P=0.914). Males predominated in both groups, while the socioeconomic, smoking and alcohol distributions were also comparable.

Table 1. Baseline Demographic and Lifestyle Characteristics

Variable	Category/Measure	Group A	Group B	Total/P value
Age (years)	Mean ± SD	61.64 ± 5.8	61.89 ± 7.4	P=0.914
Age (years)	Range	35–70	34–70	—
Gender	Female, n (%)	12 (26.7%)	14 (31.1%)	26 (28.9%); P=0.432
Gender	Male, n (%)	33 (73.3%)	31 (68.9%)	64 (71.1%)
Socioeconomic status	Upper, n (%)	2 (4.4%)	3 (6.7%)	5 (5.6%); P=0.983
	Upper-middle, n (%)	7 (15.6%)	7 (15.6%)	14 (15.6%)
	Lower-middle, n (%)	19 (42.2%)	18 (40.0%)	37 (41.1%)
	Upper-lower, n (%)	11 (24.4%)	10 (22.2%)	21 (23.3%)
	Lower, n (%)	6 (13.3%)	7 (15.6%)	13 (14.4%)
Smoking	No, n (%)	25 (55.6%)	30 (66.7%)	55 (61.1%); P=0.194
	Yes, n (%)	20 (44.4%)	15 (33.3%)	35 (38.9%)
Alcohol use	No, n (%)	34 (75.6%)	30 (66.7%)	64 (71.1%); P=0.486
	Yes, n (%)	11 (24.4%)	15 (33.3%)	26 (28.9%)

Table 2 observes that previous treatment patterns and CKD stage distribution were similar between groups. CKD stage 3 constituted the majority in both groups. Baseline systolic and diastolic blood pressure, BMI, FBS and PPBS were also comparable, with all reported P values being non-significant.

Table 2. Baseline Treatment History, CKD Stage and Clinical Characteristics

Variable	Measure / Category	Group A	Group B	P value
Previous treatment	ACE inhibitor, n (%)	18 (40.0%)	18 (40.0%)	0.585
	ARB, n (%)	27 (60.0%)	25 (55.6%)	0.206
	Diuretics, n (%)	32 (71.1%)	30 (66.6%)	0.592
	Statin, n (%)	19 (42.2%)	17 (37.8%)	0.415
CKD stage	Stage 3, n (%)	30 (66.7%)	28 (62.2%)	58 (64.4%); 0.413
	Stage 4, n (%)	15 (33.3%)	17 (37.8%)	32 (35.6%)
CKD 3 substage	3a / 3b, n	13 / 17	14 / 14	—
SBP (mmHg)	Mean ± SD	144.62 ± 7.845	147.40 ± 8.20033	0.104
	Range; Min–Max	30.00; 130–160	30.00; 132–162	—
DBP (mmHg)	Mean ± SD	76.88 ± 5.283	75.44 ± 5.15	0.193
	Range; Min–Max	22.00; 68–90	22.00; 68–90	—
BMI (kg/m²)	Mean ± SD	28.3311 ± 1.46595	27.8889 ± 1.58591	0.173
	Range; Min–Max	5.90; 25.40–31.30	6.00; 25.30–31.30	—
FBS (mg/dl)	Mean ± SD	83.1333 ± 7.27574	83.9111 ± 7.73957	0.625
	Range; Min–Max	30.00; 67–97	30.00; 67–97	—
PPBS (mg/dl)	Mean ± SD	134.31 ± 13.06	135.1 ± 13.3	0.773
	Range; Min–Max	49.00; 116–165	49.00; 116–165	—

Table 3 illustrates participant retention from 1 to 12 months. Both groups started with 45 participants at the one-month assessment. The source reports discontinuation, loss to follow-up and deaths during subsequent visits, with 41 participants remaining in each group at 12 months.

Table 3. Participant Distribution During Follow-Up

Follow-up	Group A	Group B	Source-reported event
1 month	45	45	—
3 months	43	44	Group A: 1 discontinued, 1 lost to follow-up; Group B: 1 lost to follow-up
6 months	43	43	Group B: 1 death
9 months	42	42	Group A: 1 death; Group B: 1 lost to follow-up
12 months	41	41	Group A: 1 lost to follow-up; Group B: 1 death

Table 4 demonstrates the longitudinal RBS pattern. Group A showed a progressive fall in mean RBS from 123.92 mg/dl at baseline to 108.34 mg/dl at 12 months. The mean reduction was significantly greater in Group A at 3, 6, 9 and 12 months.

Table 4. Random Blood Sugar (RBS) During Follow-Up and Mean Reduction from Baseline

Time	Group A Mean ± SD	Group B Mean ± SD	Mean reduction A	Mean reduction B	P value for change
Baseline	123.92 ± 8.73	124.66 ± 9.89	—	—	—
1 month	121.05 ± 9.674	123.13 ± 9.22	2.01 ± 1.1	1.44 ± 1.23	0.082
3 months	120.05 ± 9.873	122.14 ± 9.578	3.41 ± 1.48	2.50 ± 0.224	0.001
6 months	113.258 ± 9.771	121.44 ± 9.712	7.53 ± 0.860	3.281 ± 0.82	0.001
9 months	111.62 ± 9.932	121.01 ± 10.270	12.40 ± 0.929	3.212 ± 2.07	0.001
12 months	108.34 ± 10.284	120.1 ± 11.282	15.06 ± 1.521	3.41 ± 2.078	0.001

Table 5 observes the renal function trajectory. Baseline eGFR was 32.7 ml/min/1.73 m² in Group A and 34.15 ml/min/1.73 m² in Group B (P=0.075). At 9 and 12 months, the source reports a higher eGFR decline in Group B, with stabilization of the decline in the intervention group.

Table 5. eGFR at Baseline, During Follow-Up and Mean Decline from Baseline

Time	Group A eGFR Mean ± SD	Group B eGFR Mean ± SD	Mean decline A	Mean decline B	P value
Baseline	32.7 ± 8.05	34.15 ± 9.98	—	—	0.075
1 month	30.00 ± 8.047	32.56 ± 9.938	2.7 ± 0.405	1.59 ± 0.289	0.100
3 months	29.46 ± 8.340	32.86 ± 10.031	3.1 ± 0.634	1.99 ± 0.386	0.707
6 months	29.416 ± 8.152	31.59 ± 9.976	3.1 ± 0.577	2.56 ± 0.455	0.001
9 months	29.86 ± 8.249	29.649 ± 10.05	2.81 ± 0.960	4.5 ± 0.636	0.001
12 months	29.89 ± 7.980	28.98 ± 9.954	2.79 ± 0.355	5.18 ± 0.755	0.001
Baseline range	18.9–51.6	20.3–51.1	—	—	—

Table 6 illustrates the serum creatinine pattern over 12 months. Creatinine increased in both groups, and the comparison of mean change was non-significant at all follow-up points, suggesting similar effects on this parameter according to the source.

Table 6. Serum Creatinine at Follow-Up and Mean Increase from Baseline

Time	Group A Mean ± SD	Group B Mean ± SD	Mean increase A	Mean increase B	P value
Baseline	1.82 ± 0.403	1.92 ± 0.303	—	—	—
1 month	1.8400 ± 0.406	1.960 ± 0.370	0.148 ± 0.251	0.189 ± 0.108	0.146
3 months	2.037 ± 0.410	2.04 ± 0.373	0.25 ± 0.198	0.19 ± 0.52	0.458
6 months	2.13 ± 0.415	2.073 ± 0.370	0.34 ± 0.059	0.35 ± 0.828	0.492
9 months	2.19 ± 0.422	2.19 ± 0.377	0.37 ± 0.085	0.41 ± 1.274	0.220
12 months	2.20 ± 0.418	2.27 ± 0.360	0.382 ± 0.45	0.41 ± 0.431	0.213
Baseline range	1.29–2.47	1.35–2.55	—	—	—

Table 7 observes a progressive rise in serum urea in both groups, but the increase was greater in the placebo group from 3 months onward. The reported p-values were 0.001 at 3, 9 and 12 months and 0.013 at 6 months.

Table 7. Serum Urea at Follow-Up and Mean Rise from Baseline

Time	Group A Mean ± SD	Group B Mean ± SD	Mean rise A	Mean rise B	P value
Baseline	52.68 ± 12.48	51.62 ± 11.066	—	—	—
1 month	53.85 ± 12.564	54.49 ± 11.067	1.53 ± 0.610	1.83 ± 0.096	0.063
3 months	54.86 ± 12.615	55.34 ± 11.179	1.63 ± 0.630	2.33 ± 0.096	0.001
6 months	54.94 ± 12.644	57.19 ± 11.22	2.23 ± 0.237	4.32 ± 0.461	0.013
9 months	55.02 ± 12.351	58.201 ± 11.364	2.31 ± 0.664	6.14 ± 0.375	0.001
12 months	55.053 ± 12.29341	58.6108 ± 11.27033	2.32 ± 1.284	7.12 ± 0.372	0.001
Baseline range	36.00–79.00	40.00–78.00	—	—	—

Table 8 summarizes the reported safety outcomes. Mortality was 1 (0.022%) in Group A and 2 (0.044%) in Group B, with P>0.05. The source reports one cardiovascular death in each group and one respiratory-system death in Group B. In Group A, one fracture, one renal-related adverse effect and one hypoglycemia event were reported; amputation was NIL.

Table 8. Mortality, Cause of Death and Complications

Outcome	Group A	Group B	P value / note
Mortality, n (%)	1 (0.022%)	2 (0.044%)	P>0.05
Cause of death: CVS, n (%)	1 (0.022%)	1 (0.022%)	—
Cause of death: RS, n (%)	—	1 (0.022%)	—
Fracture, n (%)	1 (0.022%)	Not reported	—
Renal-related adverse effect, n (%)	1 (0.022%)	Not reported	—
Hypoglycemia, n (%)	1 (0.022%)	Not reported	—
Amputation	NIL	Not reported	—

DISCUSSION

Demographic Characteristics

Group A (Dapagliflozin) and Group B in the current study had mean ages of 61.64 and 61.89 years, respectively, with no significant difference (P=0.914). In both groups, the majority of participants were men (73.3% in Group A and 68.9% in Group B). The majority belonged to the lower-middle socioeconomic class, and the mean BMI was 28.3311 kg/m² in Group A and 27.8889 kg/m² in Group B.

CKD commonly affects older individuals, with the average age of diagnosis between 60 and 70 years. The US National Health and Nutrition Examination Survey (NHANES) reported an average age of approximately 60.3 years, while a multinational cross-sectional study reported a worldwide average age of 63 years among CKD patients.[7,8] The male predominance in the present study is also comparable with previous observations, as men have been reported to have a 1.3–1.5 times greater risk of progression to ESRD despite a slightly higher overall CKD incidence among women.[9,10]
Effect on Egfr.

In the present study, the mean reduction in eGFR was similar in both groups up to 3 months. However, at 9 and 12 months, the decline was greater in Group B compared with Group A. At 12 months, the mean reduction in eGFR was 2.79 ml/min/1.73 m² in Group A and 5.18 ml/min/1.73 m² in Group B, with stabilization of eGFR decline in the dapagliflozin group.
Similar findings were observed in the DAPA-CKD trial, where dapagliflozin produced an initial eGFR fall of approximately −3.9 mL/min/1.73 m², followed by stabilization. At 12 months, the average eGFR change was −2.86 mL/min/1.73 m² with dapagliflozin compared with −4.62 mL/min/1.73 m² with placebo (P<0.001), representing a 38% slower decline with dapagliflozin.103 In comparison, the RENAAL trial reported an eGFR decline of approximately −4.0 mL/min/1.73 m² per year with losartan, while the IDNT trial showed a similar decline with irbesartan.[11,12] Thus, the present study supports the renal protective effect of dapagliflozin reported in previous studies.[13]

Effect on Blood Sugar

In the present study, the reduction in RBS was significantly greater in Group A at 3, 6, 9 and 12 months compared with Group B. At 12 months, the mean reduction was 15.06 mg/dl in Group A compared with 3.41 mg/dl in Group B.
The DAPA-CKD trial similarly reported a mean RBS reduction of approximately 15–20 mg/dL at 6–12 months with dapagliflozin, particularly among patients with type 2 diabetes.[6] Studies by Wanner et al. and Dekkers et al. also showed improvement in glucose handling and reduction in proximal tubular glucose reabsorption with dapagliflozin.[10,14] Thus, the present study demonstrates the additional glycemic benefit of dapagliflozin in CKD patients.

Effect on Serum Urea and Creatinine

In the present study, the rise in serum urea was significantly higher in Group B from 3 to 12 months. At 12 months, the mean rise was 7.12 mg/dl in Group B compared with 2.32 mg/dl in Group A, indicating better stabilization of renal function with dapagliflozin. Serum creatinine increased in both groups, but the difference was not statistically significant.

In the DAPA-CKD trial, dapagliflozin was associated with a slower increase in serum creatinine and delayed doubling of creatinine, with a hazard ratio of 0.61 (95% CI, 0.51–0.72) compared with placebo[6] Cherney et al. also reported a slower rise in serum urea with dapagliflozin, attributed to improved glycemic control, reduced intraglomerular pressure and reduced tubular workload.[1] In contrast, the RENAAL and IDNT studies demonstrated a more progressive rise in creatinine and urea despite ACE inhibitor or ARB therapy.[11,12] The present findings therefore support the renoprotective effect of dapagliflozin.

Mortality

In the present study, mortality was 0.022% in Group A and 0.044% in Group B, with no statistically significant difference. The DAPA-CKD trial (2020) reported mortality of 4.7% in the dapagliflozin group and 6.8% in the standard-treatment group, with a 31% relative risk reduction.[6] The lower mortality observed in the present study may be related to the smaller

sample size. The present study shows that dapagliflozin 10 mg was associated with slower eGFR decline, greater reduction in RBS and a significantly lower rise in serum urea compared with placebo.

Limitations

The study's primary drawbacks are its limited sample size and single-center methodology.

CONCLUSION

Dapagliflozin demonstrated significant renal and metabolic benefits in patients with chronic kidney disease, with better preservation of eGFR, improved glycemic control, and more stable blood urea and creatinine levels compared with standard treatment. Despite an initial transient decline in renal function, continued treatment was associated with renal preservation and delayed CKD progression. Overall, dapagliflozin was well tolerated and appears to be a safe and effective therapeutic option for CKD with additional metabolic and potential cardiorenal benefits.

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