International Journal of Advances in Medicine
Srivastava S et al. Int J Adv Med. 2025 Nov;12(6):553-557
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20253347

Original Research Article

Determining the role of SGLT2 inhibitors (dapagliflozin) on progression of proteinuria among non-diabetic adult patients with chronic kidney disease: a randomized controlled trial

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Received: 14 May 2025
Revised: 06 September 2025
Accepted: 15 September 2025

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ABSTRACT

Background: In patients with type 2 diabetes, SGLT2 inhibition lowers albuminuria and the risk of renal disease progression. Improvement in glycemic control is unlikely to be the only factor mediating these advantages. The goal of this study was to determine any possible benefit of the SGLT2 inhibitor among subjects with non-diabetic kidney disease. To determine the effect of SGLT2 inhibitor (Dapagliflozin) on proteinuria among subjects with non-diabetic kidney disease.
Methods: A randomized control trial was conducted at K.P.S PG institute of medicine in association with Department of Nephrology, GSVSPGI, GSVM medical college, Kanpur. Eligible subjects were adult patients with non-diabetic CKD with eGFR between 25-90 ml/min/1.73m^2 and having proteinuria with urinary albumin creatinine ratio (ACR)>30 mg/g for more than 3 months. Subjects were randomized to receive either dapagliflozin (10 mg) or placebo.
Results: A total of 228 subjects were screened between June 2022 to May 2023. Sixty-seven subjects met the inclusion criteria and only 46 subjects consented to participate in the study. The subjects were randomized in 1:1 ratio to receive either intervention or placebo for duration of 6 months. At the end of 6 months study period the intervention group demonstrated a median (IQR) reduction of-9.99(-63.17 -(-4.78)) mg/g (p value<0.01) in ACR along with a median (IQR) increase in eGFR of 19.23 (3.85-23.81) ml/min/1.73m^2 from baseline. The placebo group continued to show a constant decline in eGFR with a median reduction of -32.43 (-59.8- (-23.04)) ml/min/1.73m^2 from baseline with no significant change in ACR.
Conclusions: Use of SGLT2i among subjects with non-diabetic kidney disease resulted in reduction of proteinuria and an improvement in the real function. Therefore, SGLT2i may also be used among patients with non-diabetic kidney disease to check its progression.

Keywords: Albumin creatinine ratio, Chronic kidney disease, Dapagliflozin, Glomerular filtration rate, Non-diabetic, Randomized control trial

INTRODUCTION

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function for a minimum of 3 months.[1] Worldwide prevalence of CKD is 13.4%.[2] whereas India has a higher prevalence (17.4%) of CKD. Among these patients of CKD diabetic kidney disease has emerged as the leading cause of CKD, accounting for 66.4% of cases. However, non-diabetic kidney disease also resulted in a significant proportion of CKD, accounting for 33.6% cases.[3]

Albuminuria is a powerful diagnostic and prognostic marker not only for patients suffering from kidney disease but also for heart failure. Therapies such as use of ACE inhibitors/ARBs that reduce proteinuria may have nephro protective as well as cardio protective effects. Thus, monitoring of proteinuria is an important way of assessing the response to treatment in patients of CKD.[4] SGLT2i use is associated with reduction in blood sugar levels among diabetic subjects due to increased urinary loss of glucose.[5]

The use of this drug has been found to be safe and is not associated with hypoglycemia. Enhanced sodium excretion and diuresis resulting in reduction of systolic as well as intra-glomerular pressure are the underlying mechanisms leading to reduction in proteinuria.[6] The mechanism is different from that of ACEi/ARBs. Effectiveness of SGLT2i in reducing progression of CKD among diabetic patients has already been well established by many previous trials with CREDENCE trial reporting a 32% relative risk reduction of ESRD (p value=0.002).[7,14] Similarly, few recent trials have shown the effectiveness of SGLT2i among subjects with non-diabetic kidney disease.

DAPA CKD trial demonstrated a significant reduction in primary outcome (50% reduction in eGFR or onset of ESKD or death) among subjects receiving SGLT2i.[8,13] However, DIAMOND trial in 6 weeks treatment with dapagliflozin did not show any significant change in proteinuria among non-diabetic subjects with chronic kidney disease. They reported a reversible decline in mGFR and a reduction in body weight.[9]

Therefore, there is a need to confirm the effectiveness of SGLT2i on proteinuria and progression of chronic kidney disease among non-diabetic subjects.

METHODS

This single centre randomized controlled trial was conducted at K.P.S PG Institute of Medicine and Nephrology Department, GSVSPGI, GSVM medical college, Kanpur, Study period was February 2023 to April 2024.

A total of 102 subjects with non-diabetic kidney disease were screened, 56 subjects met exclusion criteria and 46 subjects were randomized to receive SGLT2i (Dapagliflozin 10 mg) or matching placebo. The trial was approved by ethics committee, GSVM Medical College Kanpur, India.

Inclusion criteria

Subjects having an age of 18 year or more and belonging to either sex were included. Subjects must have eGFR 30-90 ml/min/1.73m^2 or having urinary albumin to creatinine ratio (ACR) >30 mg/g for more than 3 months. The subject must also be on stable dose of ACEi / ARB for last 03 months.

Exclusion criteria

Subjects suffering from active UTI or a history of UTI in last 04 weeks, untreated genital mycosis, HIV, hepatitis B and C, tuberculosis were not considered for enrollment. Subjects with history of coronary artery disease (recent myocardial infarction, unstable angina), heart failure, stroke, transient ischemic attack (TIA) within 12 weeks were also not included. Pregnant and lactating females and subjects with malignancy were also ineligible.

Procedure

After randomization the subjects were followed for a period of six months. Routine urine examination, urine albumin creatinine ratio (ACR) and eGFR were calculated in both the groups at the end of 1st, 3rd and 6th month. A window period of ±7 days was allowed for each of these visits. On each visit subjects were evaluated for adverse events / serious adverse events such as UTI, genital fungal infection, hypoglycemia, volume depletion leading to hypotension, amputation or fracture. Vital of the subjects were recorded on each visit.

Statistical analysis

The distribution of different parameters between intervention arm and placebo arm were compared. Normality of the data was checked using the Shapiro wilk test. Parameters are written as median (Q1, Q3), Any significant difference between the data is checked by Mann Whitney U test with the p value taken as 0.05.

RESULTS

Total of 46 subjects with chronic kidney disease without diabetes mellitus were included in the study. Following randomized 23 subjects were allocated to the intervention arm and 23 subjects to the placebo arm. 52.2% subjects in the intervention arm and 56.5% subjects in the placebo arm were males. In this study it was observed that Progression of urinary ACR ratio shows a significant decrease in median values in intervention arm while placebo show a significant increase in median urinary albumin to creatinine ratio from baseline to 6 months of follow up, the difference is statistically significant (p value <0.01). In this study, it was observed that change in estimated glomerular filtration rate shows a significant increase in median values in intervention arm while placebo show a significant decrease in median estimated glomerular filtration rate from baseline to 6 months of follow up, the difference is statistically significant (p value <0.01).

Table 1: Change in parameters after treatment with Dapagliflozin treatment.

	Baseline		V1 (01 month±7 days) Median (Q1-Q3)		V2 (03 month±10 days) Median (Q1-Q3)		V3 (06 month±10 days) Median (Q1-Q3)	
	Intervention arm	Placebo arm	Intervention arm	Placebo arm	Interventional arm	Placeboarm	Interventional arm	Placebo arm
Systolic BP (mmHg)	131.65	143.91	- 4.88 (-7.02 - 5.66)	3.8 (-1.3-5.13)	-3.44 (-6.02 - 1.05)	-3.08 (-7.14-6.76)	-4.41 (-10.77 - 2.74)	2.9 (-0.55-13.51)
Diastolic BP (mmHg)	75.57	88.52	-2.86 (-7.32 - 6.06)	4.26 (-7.5-8.89)	3.51 (-6.4 - 11.27)	-4.26 (-7.89-12.2)	2.7 (-9.76 - 11.43)	2.63 (-1.28-14.31)
Body weight (Kg)	62.13	66.57	-1.54 (-2.78 - 0)	1.39 (0.66-2.94)	-1.8 (-2.94 - -0.34)	2.5 (1.39-4.41)	-3.51 (-5.41 - 0)	5 (2.67-5.29)
ACR (mg/g)	943	984.1	-6.4 (-27.34 - 4.74)	20.06 (2.67-36.83)	-8.15 (-43.73 - 7.39)	28.26 (6.79-85.69)	-9.99 (-63.17 - -4.78)	51.92 (21.76-112.1)
EGFR (ml/min/1.73 $m^{2)}$	28	32	0 (-9.38 - 3.85)	-17.91 (-30.95-(-4.35))	3.45 (-3.96 - 11.29)	-25 (-52.94-(-20))	19.23 (3.85 - 23.81)	-32.43 (-59.8-(-23.04))
HbA1c (%)	5.02	4.95	0 (0 - 0)	0 (0-2)	-2.06 (-3.77 - -1.82)	2.44 (1.96-4.08)	-4.08 (-7.55 - -1.82)	5.88 (2.9-6.32)
Total cholesterol (mg/dl)	190.70	227.29	-3.73 (-9.58 - 6.9)	5.39 (-3.55-15.22)	-0.9 (-4.87 - 8.99)	4.55 (-3.73-16.51)	2.17 (-10.99 - 7.32)	9.05 (-4.5-20.54)
Total triglycerides (mg/dl)	144.65	177.57	2.03 (-7.83 - 8.33)	4.45 (-5.67-18.63)	-2.98 (-9.34 - 12.27)	10.55 (-5.13-29.69)	-1.59 (-8.79 - 8.67)	5.7 (-0.26-13.07)

Table 2: Comparison of median urinary ACR values between intervention and placebo arm.

ACR	Intervention arm (Median)	Placebo (Median)
Baseline	943	984.1
1st month	710.74	1516.2
3rd months	575.555	1813.2
6th months	396.1	2124.8

Table 3: Comparison of median GFR between Intervention and placebo arm.

GFR	Interventional arm (Median)	Placebo arm (Median)
Baseline	28	32
1st month	32	29
3rd months	42	24
6th months	47	18

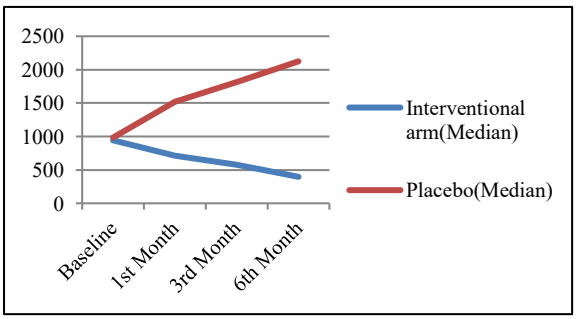

Figure 1: Comparison of median urinary ACR values between Intervention and placebo arm.

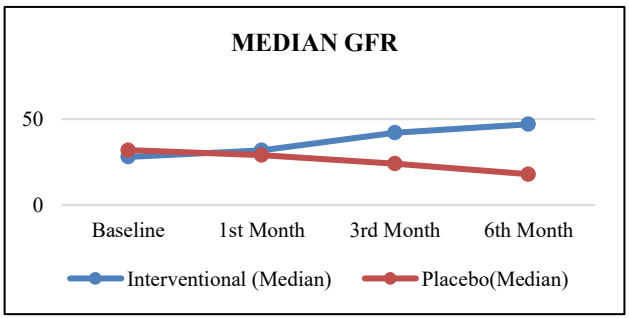

Figure 2: Comparison of mean GFR between Intervention and placebo arm.

DISCUSSION

In this randomized control trial of non-diabetic CKD patients with proteinuria it was observed that proteinuria did decrease over a period of follow up with treatment of dapagliflozin as compared to placebo, the beneficial effects of SGLT2 inhibitors on renal function are potentially mediated through non-glycemic pathways, indicating that these drugs may be helpful in non-diabetic CKD through hemodynamic effects in patients with normoglycemia.[15]

Previous studies have shown -17 % (-33.2 to 3.4; p=0.095) as percentage change mean value of ACR ratio between interventional arm as compared to placebo arm10, in our study urine albumin creatinine median values at baseline was 943 mg/g in intervention group and 984.1 mg/g in placebo group with Median change in ACR ratio from baseline to 6 months of follow up was -9.99 (-63.17-(-4.78)) in dapagliflozin group and 51.92 (21.76-112.1) change from baseline to 6 month in mean ACR values in placebo group with a statistically significant difference (p value<0.01) after dapagliflozin treatment

In a previous study, the mean (±SD) estimated GFR from baseline to 30 months in SGLT2i group as compared to placebo groups were -2.86±0.11 and -3.79±0.11 ml per minute per 1.73 m^2 per year (95% CI, 0.61 to 1.25) was observed.[11] similarity in the median change in eGFR from baseline upto 6 months was 19.23(3.85-23.81) ml per min 1.73 m^2 in dapagliflozin group and -32.43 (-59.8-(-23.04)) ml per min per 1.73 m^2 in placebo group with significant difference (p value<0.01) representing that rate of fall of eGFR is less in patients treated with intervention arm as compared to placebo in this study.

In our study median body weight at baseline was 68 kg in dapagliflozin group and 72 kg in placebo group with a median (IQR) change in body weight from baseline to 6 months was -3.51 (-5.41-0) in intervention arm group and 5 (2.67-5.29) in placebo group which was statistically significant (p<0.01) agreeing to the significant -1.5 kg of mean body weight change (95% CI -3.0 to -0.03; p=0.046) observed in a previous study.[12]

In our study there was no statistically significant change observed in systolic and diastolic blood pressure contrary to the role of SGLT2 inhibitors in decreasing systolic and diastolic blood pressure by 3 to 5 mmHg and 1 to 2 mmHg, but similar magnitude of change was observed in blood pressure values in sub groups clearly establishing the effect of SGLT2 inhibitors on blood pressure by osmotic diuresis, natriuresis and sympathetic system modifications.[16]

Limitations

However, this study had certain limitations like small sample size of 46 patients and follow up of patients could have been for longer duration, in this study urine albumin to creatinine ratio has been used as a marker for proteinuria progression which is spot test and less cumbersome but not as reliable as 24 hour urine proteinuria which could have been used for further establishing the role of dapagliflozin, more patients should have been guided and counseled to undergo renal biopsy to determine the major causes of chronic kidney disease, side effect profile of dapagliflozin like UTI, genital infections, diabetic ketoacidosis, hypotension, fractures should have been studied which was not done in this study.

CONCLUSION

In our study we found that patients with non-diabetic chronic renal diseases having significant proteinuria at baseline had a significant decline in urine albumin to creatinine ratio from baseline to follow ups in dapagliflozin group as compared to placebo, which can indicate role of dapagliflozin in providing benefits in non-diabetic renal disease also other than the already established role in diabetic kidney disease, previous studies have shown that in patients of non-insulin dependent diabetic kidney disease the urine albumin decreased by at least one third to half of baseline by SGLT2 inhibitors, in this study non diabetic kidney diseases showed significant decline in proteinuria, hence, establishing SGLT2 inhibitors role in non-diabetic renal diseases which needs to be studied further with more patients and longer follow up period.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Stevens PE, Ahmed SB, Carrero JJ, Foster B, Francis A, Hall RK, et al. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024;105(4):117–314.
2. Lv JC, Zhang LX. Prevalence and disease burden of chronic kidney disease. Renal fibrosis: mechanisms and therapies. 2019:3-15.
3. Basu M, Pulai S, Neogi S, Banerjee M, Bhattacharyya NP, Sengupta S, et al. Prevalence of non-diabetic kidney disease and inability of clinical predictors to differentiate it from diabetic kidney disease: results from a prospectively performed renal biopsy study. BMJ Open Diabetes Res Care. 2022;10(6):3058.
4. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, et al. The definition, classification and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011;80(1):17–28.
5. Sarzani R, Giulietti F, Di Pentima C, Spannella F. Sodium-glucose co-transporter-2 inhibitors: peculiar “hybrid” diuretics that protect from target organ

damage and cardiovascular events. Nutrition, Metabol Cardiovas Dis. 2020;30(10):1622-32.
6. Koh ES, Kim GH, Chung S. Intrarenal Mechanisms of Sodium-Glucose Cotransporter-2 Inhibitors on Tubuloglomerular Feedback and Natriuresis. Endocrinol Metab. 2023;38(4):359–72.
7. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. New England J Med. 2019;380(24):2295-306.
8. Heerspink HJ, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JF, McMurray JJ, Lindberg M, Rossing P, Sjöström CD. Dapagliflozin in patients with chronic kidney disease. New England J Med. 2020;383(15):1436-46.
9. Cherney DZI, Dekkers CCJ, Barbour SJ, Cattran D, Abdul Gafor AH, Greasley PJ, et al. Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial. Lancet Diabetes Endocrinol. 2020;8(7):582–93.
10. Canney M, Barbour SJ, Zheng Y, Coppo R, Zhang H, Liu ZH, et al. Quantifying Duration of Proteinuria Remission and Association with Clinical Outcome in IgA Nephropathy. J Am Soc Nephrol JASN. 2021;32(2):436–47.
11. Correction to Lancet Diabetes Endocrinol 2021; 9: 743–54. Lancet Diabetes Endocrinol. 2022;10(1):10.
12. Cherney DZ, Dekkers CC, Barbour SJ, Cattran D, Gafor AH, Greasley PJ, et al. Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial. Lancet Diab Endocrinol. 2020;8(7):582-93.
13. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020;383(15):1436–46.
14. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019;380(24):2295–306.
15. Wheeler DC, Stefansson BV, Batiushin M, Bilchenko O, Cherney DZI, Chertow GM, et al. The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial: baseline characteristics. Nephrol Dial Transplant. 2020;35(10):1700–11.
16. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393(10166):31–9.

Cite this article as: Srivastava S, Agarwal S, Gulati Y, Singh AK, Aggarwal P. Determining the role of SGLT2 inhibitors (dapagliflozin) on progression of proteinuria among non-diabetic adult patients with chronic kidney disease: a randomized controlled trial. Int J Adv Med 2025;12:553-7.