scientific reports

Check for updates

OPEN

Triple therapy of RAS inhibitors, dapagliflozin, and finerenone in diabetic kidney disease patients with nephrotic-range proteinuria: a real-world study

Chenjie Gu[1,3], Xinwei Li[1,3], Xianan Guo[1], Jingying Zhou[1], Le Kang[2]✉ & Ming Fang[1]✉

Patients with diabetic kidney disease (DKD) and nephrotic-range proteinuria (NRP) face an extremely high cardiorenal risk. Renin-angiotensin system (RAS) inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and the non-steroidal mineralocorticoid receptor (ns-MR) antagonist finerenone are the cornerstone therapies for DKD. However, real-world data on the efficacy and safety of triple therapy with RAS inhibitors, SGLT2 inhibitors, and finerenone in DKD patients with NRP remain scarce. This retrospective study included adult DKD patients with NRP treated with triple therapy. Clinical parameters assessed included proteinuria, renal function, serum albumin, serum potassium, and adverse events during follow-up. Twenty DKD patients with NRP (mean age 61 ± 12 years; female/male 8/12) were included. Baseline characteristics were as follows: UPCR 5275.53 [3838.11, 8976.90] mg/g, UACR 4144.54 [3077.21, 6070.61] mg/g, eGFR 48.51 ± 21.31 ml/min/1.73 m², serum potassium 4.11 ± 0.53 mmol/L. Compared to baseline, UPCR decreased by 55.49% ($P < 0.001$), UACR decreased by 59.66% ($P < 0.001$), and eGFR declined by 4.03 mL/min/1.73 m² at month 12 ($P = 0.170$). Serum albumin increased from 34.5 ± 6.9 g/L to 38.6 ± 4.9 g/L ($P = 0.061$) at month 12. No serious adverse events, such as hyperkalemia (> 5.5 mmol/L), were observed. This real-world study shows the efficacy of triple therapy with RAS inhibitors, dapagliflozin, and finerenone in DKD patients with NRP, along with a favorable safety profile.

Keywords Mineralocorticoid receptor antagonist, Sodium-glucose cotransporter-2 inhibitor, Type 2 diabetes, Chronic kidney disease, Nephrotic-range proteinuria

Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease (CKD) worldwide. DKD patients face a high risk of kidney failure, cardiovascular disease, and mortality[1–3]. A higher urine albumin-to-creatinine ratio (UACR) and lower estimated glomerular filtration rate (eGFR) in DKD patients are associated with increased risk[4]. Hemodynamic, metabolic, and inflammatory factors are believed to contribute to and exacerbate albuminuria and proteinuria in diabetic populations. Proteinuria, particularly nephrotic-range proteinuria (NRP), accelerates kidney function decline and increases premature cardiovascular morbidity and mortality[5,6].

Inhibitors of the renin-angiotensin system (RAS), sodium-glucose cotransporter-2 (SGLT2) inhibitors, and non-steroidal mineralocorticoid receptor (ns-MR) antagonists have demonstrated cardiorenal benefits in diabetic patients in large clinical trials[7–10]. Despite these advancements, residual cardiorenal risk remains high in DKD patients. Therefore, new therapeutic strategies to improve cardiorenal outcomes are urgently needed.

Dual blockade of SGLT2 or the mineralocorticoid receptor, in addition to RAS inhibitors, provides additive cardiorenal protection in proteinuric kidney disease with diabetes[11,12]. However, clinical data on triple inhibition of RAS/SGLT2/MR in patients with diabetes, particularly those with NRP, remain limited, with most evidence coming from case reports or *post hoc* subgroup analyses of randomized controlled trials.

[1]Department of Nephrology, Renal Translational Medicine Center of Liaoning Province, The First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, China. [2]Medical College of Dalian University, Dalian, Liaoning, China. [3]Chenjie Gu and Xinwei Li contributed equally to this work. ✉email: klfmdd@126.com; fangming0411@126.com

To date, no real-world study has specifically investigated the triple inhibition of RAS/SGLT2/MR in DKD patients with NRP. To address this critical gap, we aim to evaluate the efficacy and safety of triple therapy with RAS inhibitors, SGLT2 inhibitors, and finerenone.

Methods

This retrospective study was conducted at the First Affiliated Hospital of Dalian Medical University between January 2023 and December 2024. DKD patients were prescribed finerenone in addition to stable, maximally tolerated RAS inhibitors and SGLT2 inhibitors. DKD patients with at least one follow-up visit were screened. The inclusion criteria were as follows: age ≥ 18 years, urine protein-to-creatinine ratio (UPCR) ≥ 3500 mg/g or UACR ≥ 2200 mg/g, and estimated glomerular filtration rate (eGFR) ≥ 25 mL/min/1.73 m^2. Exclusion criteria included: immune-mediated or inherited kidney diseases, discontinuation of any drug for more than 2 weeks during follow-up, and loss to follow-up. The study flow chart is shown in Fig. 1. The primary endpoint of the study is ≥ 30% reduction in UPCR and UACR. Key outcomes include major adverse kidney events (MAKEs, which consists of eGFR reduction ≥ 50%, end-stage kidney disease, and death). Based on our previous study findings[13], it was calculated that sample size of 11 for UPCR and 10 for UACR would achieve 80% power. Assuming dropout rate 20%, 13 patients for UPCR and 11 patients for UACR were sufficient to detect a 30% further reduction in UPCR and UACR.

Demographic data, clinical history, medications, and laboratory results (UPCR, UACR, serum potassium, albumin, and creatinine levels) were collected at baseline and follow-up visits. eGFR was calculated using the 2021 CKD-EPI equation. All patients were followed up every 1–3 months. Adverse events were also recorded. All data were collected from electronic health records.

Continuous variables with normal distribution were expressed as mean ± standard deviation (SD), while those with skewed distribution were expressed as median [interquartile range (IQR), Q1, Q3]. All data underwent through normality tests to verify their normality. UPCR and UACR were log-transformed to achieve normal distribution. The least squares mean (LSM) of UPCR and UACR was calculated based on the original data and expressed as LSM (95% confidence interval [95% CI]). Wilcoxon matched-pairs signed rank test was used to analyze between median of normally-distributed data and skewed data. Wilcoxon r value and its 95% CI were used to demonstrate the effect sizes of Wilcoxon matched-pairs signed rank test. Effect sizes were interpreted based on established guidelines, with $r \approx 0.1$ considered a small effect, $r \approx 0.3$ a medium effect, and $r \approx 0.5$ a large effect. Analysis of variance (ANOVA) with mixed effects model (restricted maximum likelihood method) was used to evaluate the significance of the data and handle the missing values. The Geisser and Greenhouse epsilon hat method were used to correct data without assuming sphericity. Eta squared and its 95% CI were used to demonstrate the effect sizes of ANOVA. Effect sizes were interpreted based on established guidelines, with eta squared ≈ 0.01 considered a small effect, eta squared ≈ 0.06 a medium effect, and eta squared ≈ 0.14 a large effect. A two-tailed P value < 0.05 was considered statistically significant. Statistical analyses and data visualizations were performed using GraphPad Prism 10.6.0 (GraphPad Software, Boston, Massachusetts, USA).

The study was approved by the Research Ethics Committee of the First Affiliated Hospital of Dalian Medical University (PJ-KS-KY-2024-84) and adhered strictly to the principles of the Declaration of Helsinki. All patients provided informed consent, and their data were anonymized to ensure privacy.

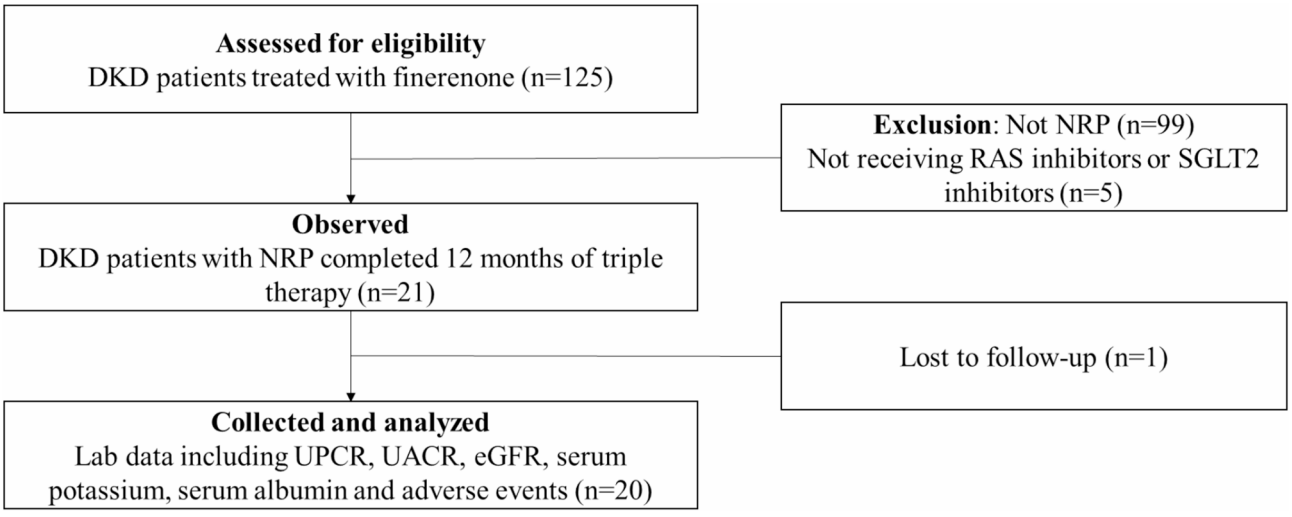

Fig. 1. CONSORT-style flow diagram of the study. Abbreviations: DKD, diabetic kidney disease; NRP, nephrotic-range proteinuria; RAS inhibitors, renin-angiotensin system inhibitors; SGLT2 inhibitors, sodium-glucose cotransporter-2 inhibitors; UPCR, urine protein-to-creatinine ratio; UACR, urine albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate.

Results

Baseline data

20 patients were included in our study. The baseline demographic and clinical data are presented in Table 1. At baseline, the mean age was 61 ± 12 years, with 40% females and 60% males. 11 (55%) had smoking history. The median UPCR was 5275.53 [3838.11, 8976.90] mg/g, and the median UACR was 4144.54 [3077.21, 6070.61] mg/g. The median BMI was 25.07 [22.59, 31.98] kg/m^2. The mean serum albumin was 34.5 ± 6.9 g/L, and the mean eGFR was 48.51 ± 21.31 mL/min/1.73 m^2. The mean serum potassium was 4.11 ± 0.53 mmol/L. The mean systolic blood pressure (SBP) is 150 ± 18 mmHg, and the mean diastolic blood pressure (DBP) is 92 ± 9 mmHg. Among the patients, 18 (90%) had hypertension, 6 (30%) had a history of ischemic heart disease, 2 (10%) had a history of heart failure with preserved ejection fraction (HFpEF), and 4 (20%) had a history of stroke. Ten (50%) patients received angiotensin II receptor blocker irbesartan, while the other ten (50%) received angiotensin receptor-neprilysin inhibitor sacubitril/valsartan. Three (15%) patients were treated with glucagon-like peptide-1 receptor (GLP-1R) agonists. All patients received maximal tolerated or labelled dose of RAS inhibitors had received at least 3-month combination therapy of RAS inhibitors and dapagliflozin before finerenone.

Effectiveness on UPCR, UACR and serum albumin level

At the point of 12 months prior to baseline, the UPCR was 5042.80 [3733.02, 7682.26] mg/g and UACR was 4000.00 [2789.72, 5978.42] mg/g. And all patients were with NRP at 12 months prior to the study. The trends of UPCR and UACR LSM ratios compared to baseline are presented in Fig. 2A and B. At the end of 12 months of treatment, the median UPCR was 2667.50 [1668.34, 3662.62] mg/g, and the median UACR was 1640.96 [1020.42, 2735.61] mg/g (Supplementary Fig. 1 and Supplementary Table 1). At month 12, there was a 55.49% reduction in the LSM of UPCR compared to baseline, from 6516.21 (95% CI 5475.56-7556.85) mg/g to 2900.38 (95% CI 1859.74-3941.03) mg/g ($P < 0.001$), and a 59.66% reduction in the LSM of UACR from 4857.65 (95% CI 4092.37-5622.93) mg/g to 1959.66 (95% CI 1209.89-2709.44) mg/g ($P < 0.001$) (Supplementary Fig. 2 and Supplementary Table 2). The effect size (eta squared) and 95% CI of the aforementioned analyses were 0.342 (0.163–0.443) and 0.390 (0.21–0.468). Serum albumin levels are shown in Fig. 2C. The mean serum albumin was 38.6 ± 4.9 g/L at month 12 ($P = 0.061$) (Supplementary Table 1). The effect size (eta squared) and 95%CI were 0.124 (0-0.213). The proportions of UPCR and UACR reduction from baseline are presented in Fig. 3A and B. The proportion of patients with a 30–50% reduction in UPCR and UACR was 30%, and the proportion of patients with a > 50% reduction in UPCR and UACR was 70% at month 12. At the end of follow-up, the mean SBP was 136 ± 14 mmHg, the mean DBP was 88 ± 8 mmHg. The mean BMI was 26.49 ± 4.75 kg/m^2. All patients (100%) achieved the primary endpoints at month 12.

Safety and adverse events

The mean eGFR, comparison of median 12-month changes of eGFR before and after the baseline, and mean serum potassium levels are presented in Fig. 4A and B, and Fig. 4C. The mean 12-month eGFR loss prior to baseline was 16.79 ml/min/1.73 m^2. A mild decline of 4.03 mL/min/1.73 m^2 in eGFR was observed from baseline to 44.48 ± 23.18 mL/min/1.73 m^2 ($P = 0.170$) at month 12. The effect size (eta squared) and 95% CI was 0.087 (0-0.164). Compared to prior 12-month change of eGFR to baseline, triple therapy had stable kidney function (median -11.40 ml/min/1.73 m^2 vs. -2.76 ml/min/1.73 m^2) ($P = 0.031$). The effect size (r value) and 95% CI was 0.468 (0.035–0.755). No MAKEs were recorded during the study period. The mean serum potassium level was 4.42 ± 0.49 mmol/L at month 12 ($P = 0.011$). The effect size (eta squared) and 95% CI was 0.182 (0.032–0.281). Throughout the follow-up visits, serum potassium remained below 5.5 mmol/L. Comparing month 12 to baseline, there was only a modest increase of 0.31 mmol/L in the mean serum potassium level. No adverse events, such as hyperkalemia (> 5.5 mmol/L), hypotension, or hyponatremia, were recorded during the study.

Discussion

To our knowledge, this is the first real-world study assessing the effects of triple therapy with RAS inhibitors, SGLT2 inhibitors, and finerenone in DKD patients with NRP.

In our analysis, we observed a significant reduction in UPCR and UACR in DKD patients with NRP under the triple therapy of RAS inhibitors, dapagliflozin, and finerenone. Notably, although these patients, who were already receiving stable RAS inhibitors and dapagliflozin, still had NRP, they exhibited further and sustained reductions in proteinuria following the addition of finerenone. In our cohort, UPCR was reduced by 55.49%, and UACR by 59.66% at month 12. Current guidelines recommend an early reduction in UACR of at least 30% within 3–6 months as a surrogate endpoint for favorable long-term cardiorenal outcomes in people with type 2 diabetes. Further analysis in our study revealed that 85% of patients experienced a ≥ 30% decrease in UACR after 3 months, and all patients showed a ≥ 30% decrease in both UACR and UPCR at month 12. Based on our previous real-world study, we again provide evidence of the anti-proteinuric effectiveness of triple therapy with RAS inhibitors, dapagliflozin, and finerenone in DKD patients, even in high-risk populations with NRP[13].

DKD patients with NRP often experience more severe clinical symptoms, such as edema, hypoalbuminemia, and thrombotic complications[14]. When compared with the baseline characteristics of the NRP subgroup in the EMPA-REG OUTCOME study, our participants were of similar age but had more severe disease, with higher UACR, more pronounced hypoalbuminemia, and varying degrees of edema[15]. In the present study, these symptoms were significantly alleviated during the follow-up period. This improvement is partly attributable to the implementation of triple therapy with RAS inhibitors, dapagliflozin, and finerenone, which led to a reduction in proteinuria and, consequently, the improvement of hypoalbuminemia.

NRP in diabetic patients is often associated with more rapid loss of kidney function. The persistent state of NRP significantly increases the risk of major adverse kidney and cardiovascular events in DKD patients[16].

Categories	All patients ($n = 20$)
Demographic data	
Age, years	61 (12)
Female/Male	8 (40%)/12 (60%)
Smoking history	11 (55%)
Laboratory data	
BMI, kg/m^2	25.07 [22.59, 31.98]
Systolic blood pressure, mmHg	150 (18)
Diastolic blood pressure, mmHg	92 (9)
UPCR, mg/g	5275.53 [3838.11, 8976.90]
UACR, mg/g	4144.54 [3077.21, 6070.61]
eGFR, mL/min/1.73 m^2	48.51 (21.31)
Serum albumin, g/L	34.5 (6.9)
Serum creatinine, μmol/L	142 (56)
Serum potassium, mmol/L	4.11 (0.53)
Serum hemoglobin, g/L	120 (24)
Serum uric acid, μmol/L	436 [364, 484]
Cystatin C, mg/L	2.34 (0.64)
TG, mmol/L	1.95 [1.54, 2.73]
LDL-C, mmol/L	2.87 (1.33)
HDL-C, mmol/L	1.21 (0.36)
TC, mmol/L	4.75 [3.70, 7.60]
HbA1c, %	7.65 [6.28, 8.78]
Clinical history	
Diabetes duration, years	16 (7)
Diabetic retinopathy	8 (40%)
Hypertension	18 (90%)
Ischemic heart disease	6 (30%)
HFpEF	2 (10%)
Stroke	4 (20%)
Medication history	
RAS inhibitors	20 (100%)
Irbesartan	10 (50%)
Sacubitril-valsartan	10 (50%)
SGLT2 inhibitor (dapagliflozin)	20 (100%)
ns-MR antagonist (finerenone)	20 (100%)
α-blockers	2 (10%)
β-blockers	9 (45%)
Calcium channel blockers	9 (45%)
Diuretics	8 (40%)
PCSK9 inhibitors	3 (15%)
Statins	14 (70%)
Antiplatelet drugs	8 (40%)
Insulin	10 (50%)
Biguanides	2 (10%)
α-glucosidase inhibitors	3 (15%)
GLP-1R agonists	3 (15%)

Table 1. The baseline clinical data of 20 DKD patients. Data were expressed as mean (standard deviation), number (percentage), or median [interquartile interval (IQR) Q1, Q3]. eGFR was calculated by using 2021 CKD-EPI equation. Abbreviations: DKD, diabetic kidney disease; UPCR, urine protein-to-creatinine ratio; UACR, urine albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; HbA1c, hemoglobin A1c; HFpEF, heart failure with preserved ejection fraction; RAS inhibitors, renin–angiotensin system inhibitors; SGLT2 inhibitor, sodium-glucose cotransporter-2 inhibitor; ns-MR antagonist, non-steroidal mineralocorticoid receptor antagonist; PCSK9 inhibitors, proprotein convertase subtilisin/kexin type-9 inhibitors; GLP-1R agonists, glucagon-like peptide-1 receptor agonists.

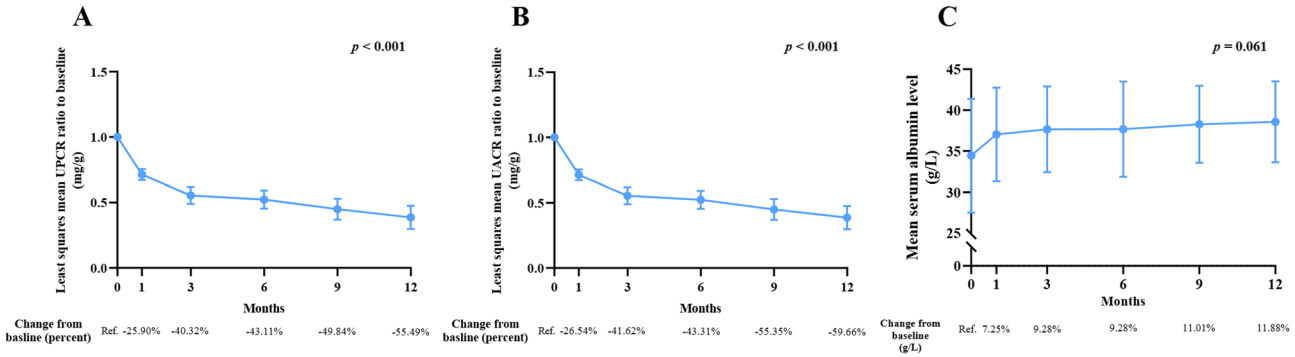

Fig. 2. Changes in UPCR, UACR, and serum albumin from baseline to month 12. (A) LSM of UPCR relative to baseline, showing a 55.49% reduction from baseline to month 12. (B) LSM of UACR relative to baseline, showing a 59.66% reduction from baseline to month 12. (C) Mean serum albumin level, which increased by 11.88% from baseline to month 12. Point: mean. Bar: 95% confidence interval for (A) and (B), standard deviation for (C). Abbreviations: LSM, least squares mean; UPCR, urine protein-to-creatinine ratio; UACR, urine albumin-to-creatinine ratio.

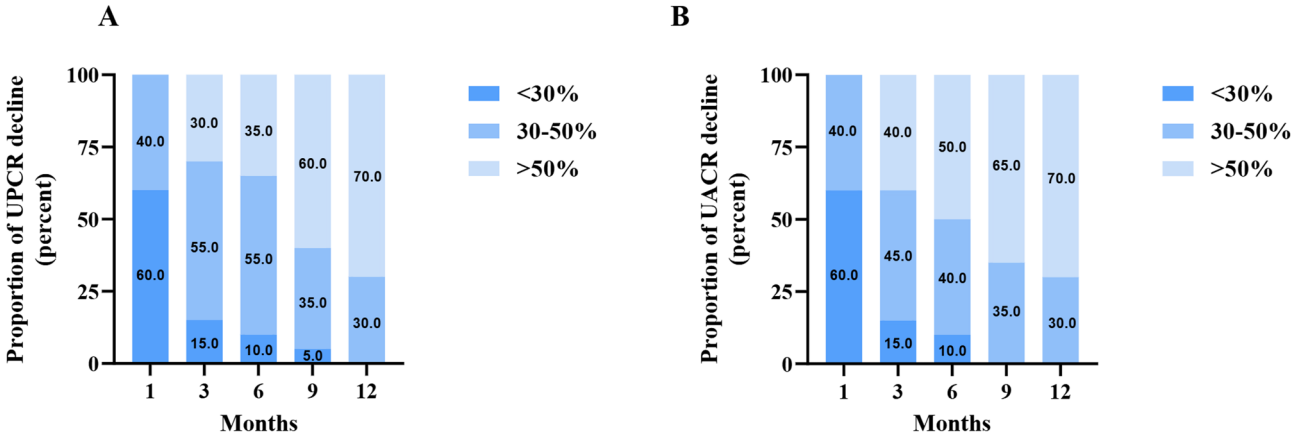

Fig. 3. Proportion of UPCR and UACR decline percentages from baseline at different visits. (A) UPCR. (B) UACR. Bar: percentage of the proportion. Abbreviations: UPCR, urine protein-to-creatinine ratio; UACR, urine albumin-to-creatinine ratio.

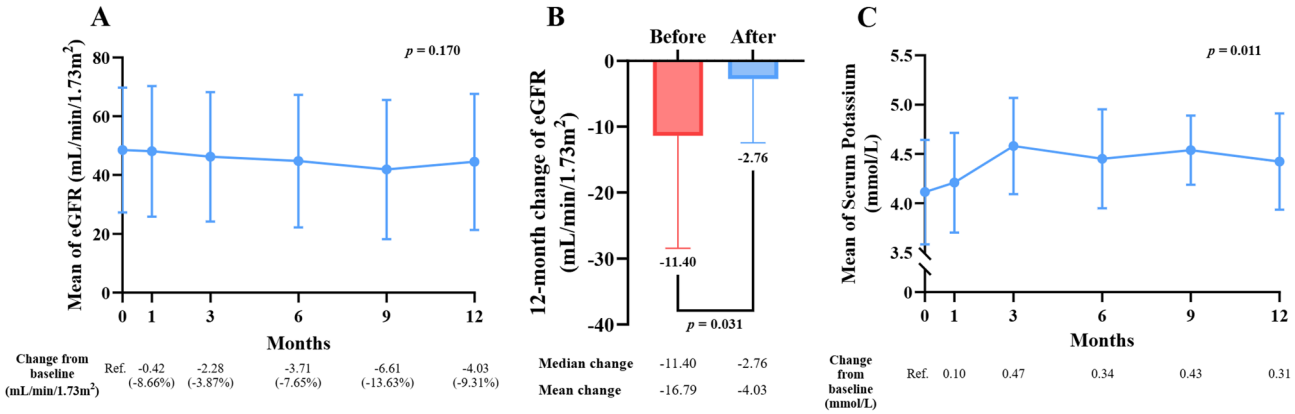

Fig. 4. Mean eGFR, comparison of median 12-month changes of eGFR before and after the baseline, and mean serum potassium levels from baseline to month 12. (A) Mean eGFR, with a change of -4.03 mL/min/1.73 m^2 from baseline to month 12. Point: mean. Error bar: standard deviation. (B) Comparison of median 12-month changes of eGFR before and after the initiation of triple therapy. Bar, median. Error bar, interquartile range. (C) Mean serum potassium level, which increased by 0.31 from baseline to month 12. Point: mean. Error bar: standard deviation. Abbreviations: eGFR, estimated glomerular filtration rate.

Among proteinuric CKD populations in landmark trials, SGLT2 inhibitors have been shown to slow long-term eGFR decline in CKD patients as well as reduce cardiorenal risk[17], while finerenone has demonstrated efficacy in CKD patients with type 2 diabetes[7,9]. Furthermore, *post hoc* analyses revealed the beneficial effects of combining SGLT2 inhibitors and MR antagonists in patients with diabetes and CKD. Despite the known adverse effects of steroid MR antagonists (spironolactone and eplerenone), SGLT2 inhibitors still reduce major adverse kidney events without increasing the risk of treatment-emergent hyperkalemia or acute kidney injury[18–20]. Recently, a prespecified pooled analysis of FIDELITY demonstrated that finerenone offers beneficial cardiorenal outcomes, regardless of whether SGLT2 inhibitors were used at baseline or initiated during the trials, and that SGLT2 inhibitors also reduced the risk of hyperkalemia[21,22]. However, proven therapies for DKD with NRP remain limited. *Post hoc* analyses of EMPA-KIDNEY and EMPA-REG OUTCOME showed that empagliflozin could be an effective and safe treatment option for slowing kidney disease progression and improving clinical outcomes in patients with type 2 diabetes and NRP or UACR greater than 2000 mg/g[15,23,24]. In our study, the 12-month loss of eGFR prior to baseline is 16.79 ml/min/1.73 m^2 while eGFR decreased by only 4.03 mL/min/1.73 m^2 (9.31%) from baseline after 12 months of triple therapy with RAS inhibitors, dapagliflozin, and finerenone in high-risk DKD patients with NRP.

The potential mechanisms of triple therapy with RAS inhibitors, dapagliflozin, and finerenone in reducing proteinuria require further investigation. First, both RAS and SGLT2 inhibitors can lower intraglomerular pressure by dilating the efferent arteriole and restoring tubuloglomerular feedback[25,26]. Second, finerenone likely protects glomerular structure by reducing inflammation and fibrosis through MR blockade[27]. Third, attenuation of oxidative stress and improvement of tubular hypoxia may also contribute to the reduction of proteinuria[28]. Fourth, finerenone also preserve the glomerular endothelial glycocalyx with reduction of metalloproteinase in plasma and urine[29]. Therefore, these complementary mechanisms justify the use of combination therapy[30].

However, our study has several limitations. Firstly, it is a single-center, retrospective cohort study. Secondly, kidney biopsy may be necessary to further confirm pathological diagnoses in DKD patients with NRP. Thirdly, future studies should evaluate the impact of full implementation of guideline-directed medical therapy, including glucagon-like peptide-1 agonists, in DKD patients with NRP.

Conclusion

Triple therapy with RAS inhibitors, dapagliflozin, and finerenone may be an effective option to reduce proteinuria and albuminuria in DKD patients with NRP, while also slowing chronic kidney disease progression. Additionally, this triple therapy shows a relatively safe profile in high-risk DKD populations.

Data availability

Our data in this study will be shared upon a reasonable request to the corresponding author.

Received: 4 April 2025; Accepted: 3 November 2025
Published online: 08 December 2025

References

1. Kovesdy, C. P. Epidemiology of chronic kidney disease: an update 2022. *Kidney Int. Suppl.* **12**, 7–11. https://doi.org/10.1016/j.kisu.2021.11.003 (2022).
2. Gupta, S., Dominguez, M. & Golestaneh, L. Diabetic kidney disease: an update. *Med. Clin. North. Am.* **107**, 689–705. https://doi.org/10.1016/j.mcna.2023.03.004 (2023).
3. Cheng, H. T., Xu, X., Lim, P. S. & Hung, K. Y. Worldwide epidemiology of Diabetes-Related End-Stage renal Disease, 2000–2015. *Diabetes Care*. **44**, 89–97. https://doi.org/10.2337/dc20-1913 (2021).
4. Sarnak, M. J. & Astor, B. C. Implications of proteinuria: CKD progression and cardiovascular outcomes. *Adv. Chronic Kidney Dis.* **18**, 258–266. https://doi.org/10.1053/j.ackd.2011.04.002 (2011).
5. Nagaram, S. et al. Prognostic impact of proteinuria at manifestation in adult nephrotic syndrome patients: insights from a prospective cohort study. *Cureus* **16**, e62143. https://doi.org/10.7759/cureus.62143 (2024).
6. Iimori, S. et al. Prognosis of chronic kidney disease with normal-range proteinuria: the CKD-ROUTE study. *PLoS One*. **13**, e0190493. https://doi.org/10.1371/journal.pone.0190493 (2018).
7. Heerspink, H. J. L. et al. Dapagliflozin in patients with chronic kidney disease. *N. Engl. J. Med.* **383**, 1436–1446. https://doi.org/10.1056/NEJMoa2024816 (2020).
8. McMurray, J. J. V. et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N. Engl. J. Med.* **381**, 1995–2008. https://doi.org/10.1056/NEJMoa1911303 (2019).
9. Bakris, G. L. et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N. Engl. J. Med.* **383**, 2219–2229. https://doi.org/10.1056/NEJMoa2025845 (2020).
10. Pitt, B. et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N. Engl. J. Med.* **385**, 2252–2263. https://doi.org/10.1056/NEJMoa2110956 (2021).
11. Neumiller, J. J., Alicic, R. Z. & Tuttle, K. R. Optimization of guideline-directed medical therapies in patients with diabetes and chronic kidney disease. *Clin. Kidney J.* **17**, sfad285. https://doi.org/10.1093/ckj/sfad285 (2024).
12. Ortiz, A. et al. Mineralocorticoid receptor antagonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. *Nephrol. Dia. Transplant. Off. Publ. Eur. Dialysis Transpl. Assoc. Eur. Ren. Assoc.*. **38**, 10–25. https://doi.org/10.1093/ndt/gfab167 (2023).
13. Zhou, J. et al. Effectiveness and safety of finerenone in diabetic kidney disease patients: a real-world observational study from China. *Ren. Fail.* **46**, 2400541. https://doi.org/10.1080/0886022X.2024.2400541 (2024).
14. Kitai, Y. et al. Nephrotic range proteinuria as a strong risk factor for rapid renal function decline during pre-dialysis phase in type 2 diabetic patients with severely impaired renal function. *Clin. Exp. Nephrol.* **19**, 1037–1043. https://doi.org/10.1007/s10157-015-1094-2 (2015).
15. Ruggenenti, P. et al. Nephrotic-range proteinuria in type 2 diabetes: effects of empagliflozin on kidney disease progression and clinical outcomes. *EClinicalMedicine* **43**, 101240. https://doi.org/10.1016/j.eclinm.2021.101240 (2022).
16. Kalay, Z. et al. SGLT-2 inhibitors in nephrotic-range proteinuria: emerging clinical evidence. *Clin. Kidney J.* **16**, 52–60. https://doi.org/10.1093/ckj/sfac189 (2023).

17. van Mil, D. et al. Early changes, and residual albuminuria: post hoc analysis of a randomized clinical trial of Dapagliflozin in chronic kidney disease. *Clin. J. Am. Soc. Nephrol.* **19**, 1574–1584. https://doi.org/10.2215/CJN.0000000000000550 (2024). Baseline.
18. Georgianos, P. I. & Agarwal, R. Mineralocorticoid receptor antagonism in chronic kidney disease. *Kidney Int. Rep.* **6**, 2281–2291. https://doi.org/10.1016/j.ekir.2021.05.027 (2021).
19. Rossing, P. et al. Finerenone in predominantly advanced CKD and type 2 diabetes with or without Sodium-Glucose Cotransporter-2 inhibitor therapy. *Kidney Int. Rep.* **7**, 36–45. https://doi.org/10.1016/j.ekir.2021.10.008 (2022).
20. Chung, M. C. et al. Sodium-Glucose transport protein 2 inhibitor use for type 2 diabetes and the incidence of acute kidney injury in Taiwan. *JAMA Netw. Open.* **6**, e230453. https://doi.org/10.1001/jamanetworkopen.2023.0453 (2023).
21. Rossing, P. et al. Finerenone in patients with chronic kidney disease and type 2 diabetes by Sodium-Glucose cotransporter 2 inhibitor treatment: the FIDELITY analysis. *Diabetes Care.* **45**, 2991–2998. https://doi.org/10.2337/dc22-0294 (2022).
22. Agarwal, R. et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *Eur. Heart J.* **43**, 474–484. https://doi.org/10.1093/eurheartj/ehab777 (2022).
23. Fernández-Fernandez, B., Sarafidis, P., Soler, M. J. & Ortiz, A. EMPA-KIDNEY: expanding the range of kidney protection by SGLT2 inhibitors. *Clin. Kidney J.* **16**, 1187–1198. https://doi.org/10.1093/ckj/sfad082 (2023).
24. Effects of empagliflozin on progression of chronic. Kidney disease: a prespecified secondary analysis from the empa-kidney trial. *Lancet Diabets Endocrionol.* **12**, 39–50. https://doi.org/10.1016/s2213-8587(23)00321-2 (2024).
25. Tonneijck, L. et al. Glomerular hyperfiltration in diabetes: mechanisms, clinical Significance, and treatment. *J. Am. Soc. Nephrol.* **28**, 1023–1039. https://doi.org/10.1681/ASN.2016060666 (2017).
26. Heerspink, H. J., Perkins, B. A., Fitchett, D. H., Husain, M. & Cherney, D. Z. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney Effects, potential Mechanisms, and clinical applications. *Circulation* **134**, 752–772. https://doi.org/10.1161/CIRCULATIONAHA.116.021887 (2016).
27. Grune, J. et al. Selective mineralocorticoid receptor cofactor modulation as molecular basis for finerenone's antifibrotic activity. *Hypertension* **71**, 599–608. https://doi.org/10.1161/HYPERTENSIONAHA.117.10360 (2018).
28. Khan, M. S. & Lea, J. P. Kidney and cardiovascular-protective benefits of combination drug therapies in chronic kidney disease associated with type 2 diabetes. *BMC Nephrol.* **25**, 248. https://doi.org/10.1186/s12882-024-03652-5 (2024).
29. Crompton, M. et al. Mineralocorticoid receptor antagonism in diabetes reduces albuminuria by preserving the glomerular endothelial glycocalyx. *JCI Insight*. **8**, 2563. https://doi.org/10.1172/jci.insight.154164 (2023).
30. Naaman, S. C. & Bakris, G. L. Diabetic nephropathy: update on pillars of therapy slowing progression. *Diabetes Care*. **46**, 1574–1586. https://doi.org/10.2337/dci23-0030 (2023).

Acknowledgements

We are very grateful to all patients who participated in this study.

Author contributions

M.F and L.K designed the study and contributed to methodology. C.G collected the data and conducted the analysis. C.G, X.G, X.L and J.Z interpreted the data and drafted manuscript. M.F and L.K revised manuscript. All authors contributed significantly to the study and approved the final version of this manuscript.

Funding

This study was supported by the Dalian Municipal Paramount Project Grant (Grant number 2023DF001) and the National Natural Science Foundation of China (Grant number 82100735).

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-27239-8.

Correspondence and requests for materials should be addressed to L.K. or M.F.