

Short-term comparative effects of semaglutide, either alone or in conjunction with canagliflozin, on early diabetic kidney disease

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Abstract: Background: Diabetic kidney disease (DKD) is a common complication of type 2 diabetes mellitus and an important cause of end-stage renal disease. Metabolic dysfunction, albuminuria, and chronic low-grade inflammation characterize early DKD, leading to progressive renal impairment. To date, SGLT2 inhibitors and GLP-1 receptor agonists are known to provide renoprotective and metabolic benefits; however, there is limited evidence available regarding the combined use of these treatments in early DKD. **Objectives:** This study evaluated the short-term effects of canagliflozin and semaglutide, administered alone or in combination, on renal function, metabolic parameters, and systemic inflammatory markers in patients with early-stage DKD. **Methods:** In this randomized controlled trial, 120 patients with early-stage diabetic kidney disease were randomly allocated (1:1:1:1) to four groups (n = 30 each): canagliflozin (100 mg orally once daily), semaglutide (0.25 mg once weekly with escalation to 1.0 mg after 4 weeks), combination treatment, or placebo/control. **Participants:** All participants were provided standard background care. Treatment continued for 24 weeks. The main renal outcomes were urinary albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR). Glycemic control, insulin resistance, lipid parameters, and inflammatory biomarkers (HbA1c, fasting glucose, HOMA-IR, TNF- α , IL-6, CRP) were considered as secondary outcomes. Safety assessment was conducted using binary safety assessment. **Results:** At 24 weeks, combination therapy achieved significantly greater reductions in UACR compared with monotherapy and placebo ($P < 0.05$). Across treatment groups, a small reduction in eGFR was observed without significant between-group differences. Measurements of HbA1c, fasting glucose, HOMA-IR, lipid parameters, and inflammatory markers showed better results in the combination therapy group compared to single-agent therapy ($P < 0.05$). Rates of adverse events were similar between the groups. **Conclusion:** Combined canagliflozin and semaglutide therapy demonstrated superior short-term benefits in reducing albuminuria, improving metabolic control, and attenuating systemic inflammation in early DKD, supporting further long-term evaluation of renal and cardiovascular outcomes.

Keywords: Canagliflozin; Combination therapy; Early diabetic kidney disease; Inflammatory biomarkers; Metabolic parameters; Renal outcomes; Semaglutide

Submitted on 30-01-2026 – Revised on 08-02-2026 – Accepted on 09-02-2026

INTRODUCTION

Diabetic kidney disease (DKD) is a major and alarming complication of type-2 diabetes that contributes significantly to end-stage renal diseases worldwide as its major root cause (Ebadi, 2025). As the burden of diabetes progressively increases worldwide, DKD has emerged as possibly the most pressing concern for public health care, causing increased diseases, increased severity of disease, increased expenditure and decreased quality of life (Gullaksen *et al.*, 2023). During its initial phase, DKD presents as a mild increase in the rate of albuminuria in the urine, indicating initial damage to the glomeruli and as such, its early identification and management assume major importance to slow down the progression of the disease and cause a delay in ESRD (Bae, 2025). Although the blockers of RAS—ACE inhibitors and ARBs—are emergently used to treat the disease, their efficacy has been variable and inadequate in slowing down or even holding back the progress of the disease (Vernstrom *et al.*, 2024a).

Recent studies suggest that diabetic nephropathy (DN) is essentially a complex progression involving a combination of metabolic diseases, including elevated blood sugar, insulin resistance and lipid abnormalities, along with low-grade, systemic inflammation. This interplay is referred to as the Metabolic-Inflammation Axis, illustrated in fig. 1. In this model, metabolic disorders appear to trigger inflammatory responses, leaving behind distinct markers indicative of kidney damage. However, current understanding of DKD leans more toward association rather than causation. Consequently, researchers are redirecting their focus toward therapies that simultaneously target both metabolic disorders and inflammation as a potential solution for diabetes mellitus (DM) patients experiencing DKD (Vernstrom *et al.*, 2024b).

SGLT2 inhibitors, which include drugs such as canagliflozin, are beneficial for type 2 diabetics as they improve blood sugar and urinary albumin levels in the blood, assist with weight reduction and increase insulin sensitivity (Gullaksen *et al.*, 2023). They also have the potential to improve blood flow to the kidneys and decrease inflammation in the body. Although it is still

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uncertain to what extent SGLT2 inhibitors will improve or protect the kidneys, the signs so far have been positive. With regard to GLP-1 receptor agonists, drugs such as semaglutide have cardiovascular and metabolic advantages and potential benefits for the kidneys, especially in the early stages of the disease (Gullaksen *et al.*, 2024).

While these classes are effective on their own, there is a clear need for randomized, open-label, head-to-head studies to specifically evaluate the effects of combining these two classes in the early stages of DKD. More data is necessary, particularly regarding how this combination influences kidney function, glucose metabolism, systemic inflammation and other factors in the initial stages of the disease. This need is further highlighted by the gaps in our current understanding, especially in light of the research that explores similar concepts and interventions but involves different groups, dosing regimens and outcomes (Fu *et al.*, 2024).

This research has aimed to investigate the performance, on a short-term basis, when used separately or in combination, of canagliflozin and semaglutide in the management of patients with early-stage DKD. The parameters that have been considered in relation to kidney function are UACR and eGFR, as well as several aspects of metabolic health, such as levels of HbA1c, insulin resistance via calculation of HOMA-IR and systemic inflammation as indicated by TNF-alpha, IL-6 and CRP levels (Alicic *et al.*, 2025).

This study zooms in on individuals with early-stage DKD and examines short-term outcomes to provide a slice of clinical evidence regarding the impact of combination therapy on metabolic responses and markers. The present work does not attempt to delineate the mechanisms or clearly demonstrate long-term protection for the kidneys. As such, the outcomes will direct further study (Zhang *et al.*, 2025; Economos and MacIsaac, 2025). By reviewing the potential advantages and disadvantages of dual therapy for individuals with early-stage DKD, we will refine treatment strategies and inform the design of long-term studies to adequately evaluate these phenomena.

MATERIALS AND METHODS

Study participants and protocol

This randomized, controlled trial involved 120 subjects with early-stage DKD who were inpatients at the Endocrinology and Nephrology departments of Xi'an Gem Flower Changqing Hospital from January 2022 to June 2023. Participants were randomly allocated in a 1:1:1:1 ratio to four groups, with each group consisting of 30 subjects. The groups included canagliflozin, semaglutide, combination therapy and control subjects receiving a placebo. An investigator, who did not influence patient inclusion or outcomes, prepared a randomization sequence using a computer. To maintain the integrity of the allocation process, opaque envelopes were used to conceal

group assignments. Although the medications differed in shape, size and method of administration, blinding regarding their formulations was not possible; however, the staff conducting tests remained unaware of which treatment each patient was receiving.

The Ethics Committee of Xi'an Gem Flower Changqing Hospital approved the research protocol for the proposed study and informed consent was obtained from each participant prior to data collection. The sample size was calculated based on a 95% confidence level and the anticipated variability of urinary albumin to creatinine ratios, resulting in a minimum requirement of 96 participants. To accommodate a potential dropout rate of 10%–20% or more, the expected number of participants has been increased to 120. It is important to note that the proposed research is not intended to detect small differences between groups or to explore exploratory variables. A schematic outlining the proposed research and patient participation is illustrated in fig. 1 (Alharbi, 2024).

Inclusion and exclusion criteria

The eligible participants were adults aged 18 to 75 years with type 2 diabetes, as defined by the WHO 2019 criteria, who also had early diabetic kidney disease characterized by a UACR between 30 and 300 mg/g and an eGFR of at least 60 mL/min/1.73 m². Participants needed to have an HbA1c level ranging from 6.0% to 10.0% and must have been able to provide informed consent and comply with the study procedures. Subjects were excluded if they had primary kidney diseases, such as lupus nephritis; significant secondary nephropathies, such as those associated with advanced sickle cell disease; an eGFR below 60; liver enzyme levels exceeding twice the upper limit of normal; NYHA class IV heart failure; known allergic reactions to any of the study drugs; were pregnant or lactating; had recently used (within 3 months) medications that could significantly alter metabolic or inflammatory parameters; or had major active comorbidities, including infections or cancer (Ebadi and Alp Arici, 2022).

Treatment protocol

The same level of initial care was provided to all participants, which included diabetes-focused dietary advice and a customized program of moderate-intensity aerobic exercise, conducted five times a week for a minimum duration of 30 minutes per session (Ebadi, 2025). Other glucose-lowering medications, excluding SGLT2 inhibitors and GLP-1 receptor agonists, as well as blood pressure medications, excluding ACE inhibitors and ARBs, were adjusted to the desired levels without influencing the interventions being studied as follows:

Canagliflozin group: Participants received 100 mg of canagliflozin orally once daily in the morning for a duration of 24 weeks. We monitored adherence to the treatment and any adverse effects experienced by the

subjects during this period. Subjects could be withdrawn from the study if they experienced adverse effects or due to loss of consent (Rroji and Spasovski, 2024).

Semaglutide group: Individuals were administered 0.25 mg of semaglutide as a once-weekly subcutaneous injection. This dosage was then escalated to 1.0 mg per week after four weeks, continuing for a total of 24 weeks. We paid careful attention to gastrointestinal and other potential adverse effects.

Combination therapy group: Subjects received canagliflozin, 100 mg orally once daily, in combination with semaglutide, starting at 0.25 mg once a week and gradually increasing to 1.0 mg after four weeks, for a total duration of 24 weeks. Dose adjustments were made only if safety concerns arose, at which point the medication was withdrawn. Blood glucose, blood pressure and renal function were monitored at regular intervals (Alharbi, 2024).

Placebo group: Participants in this group received placebo pills administered in the same manner as those in the previous groups.

Outcome measures and detection methods

The study participants' baseline demographic and clinical information, such as their age, sex, BMI, blood pressure and how long they had had diabetes, was recorded when they first entered the study. The main renal endpoints were the estimated glomerular filtration rate (eGFR) and the urinary albumin to creatinine ratio (UACR). We looked at these at the beginning, at week 12 and at week 24. The CKD-EPI equation, which takes into account serum creatinine levels, was used to figure out the eGFR. Fasting blood glucose and glycated hemoglobin were two other secondary metabolic measurements. At the start of the study and after 24 weeks of treatment, both variables were measured. We figured out the homeostatic model of insulin resistance by multiplying the levels of fasting insulin by the levels of fasting glucose and then dividing by 22.5.

As part of the secondary endpoints, other lipid parameters were also looked at. We used standard ELISA kits to measure systemic inflammatory markers like TNF- α , IL-6 and CRP at the start of the study and again at week 24. These markers were used as associative rather than causative/explanatory. Throughout the study, safety monitoring included looking into serious events like hypoglycemia, hypotension, hyperkalemia and genitourinary infections. Every four weeks, tests were done on the liver, kidneys and electrolytes.

Statistical analysis

Statistical analysis was performed using SPSS version 26.0 and GraphPad Prism version 9.0 software. Continuous variables are expressed as the mean \pm standard deviation

(SD). The paired t-test was used to compare paired samples within the same group. The ANOVA test was used to compare different groups and the Least Significant Difference (LSD) test was used for post-hoc analysis of continuous data that was normally distributed. The chi-square test was utilized for the analysis of categorical (non-continuously distributed) data, whereas the Kruskal–Wallis H test was employed for non-normally distributed continuous data. For all tests done in this study, p values of less than 0.05 were considered statistically significant.

RESULTS

Comparison of baseline characteristics

All four groups began the study roughly equal. These groups had remarkably few contrastive elements regarding the various baseline characteristics, clinical features, kidney function, metabolic status and levels of inflammation. While such variables as age, gender distribution, duration of diabetes, BMI, blood pressure (both systolic and diastolic), HbA1c, UACR, eGFR and the metabolic and inflammatory profiles had few, if any, significant differences ($P > 0.05$ for each), the groups are presumably equally balanced for further assessment (Table 1).

Changes in the parameters of renal function

Changes in the UACR

By weeks 12 and 24, all active treatment groups showed a drop in UACR from the baseline. Comparisons between groups showed that the combination therapy group had bigger drops in UACR than the monotherapy and placebo groups at these times (ANOVA $P < 0.05$). These results indicate positive short-term trends in albuminuria, rather than offering statistically conclusive within-group effects or proof of prolonged renoprotective efficacy (Table 2). In this context, at week 24, a greater proportion of participants in the combination therapy group achieved a UACR ≤ 30 mg/g compared to those in the canagliflozin and semaglutide monotherapy groups (62.5% vs. 35.0% and 37.5%; χ^2 test, $P < 0.05$).

Change in eGFR

At week 24, eGFR showed a minimal numeric decrease across all groups, as illustrated in the figure above. While there was an overall difference among the groups, no significant intergroup variations indicating the preservation of renal function were observed. The minimal numeric change occurred outside the combination group, with the most substantial decrease noted in the combination group. This outcome aligns with the anticipated short-term effects of SGLT2 inhibitors on hemodynamics and should not be interpreted as evidence of either preservation or deterioration of kidney function (Table 3).

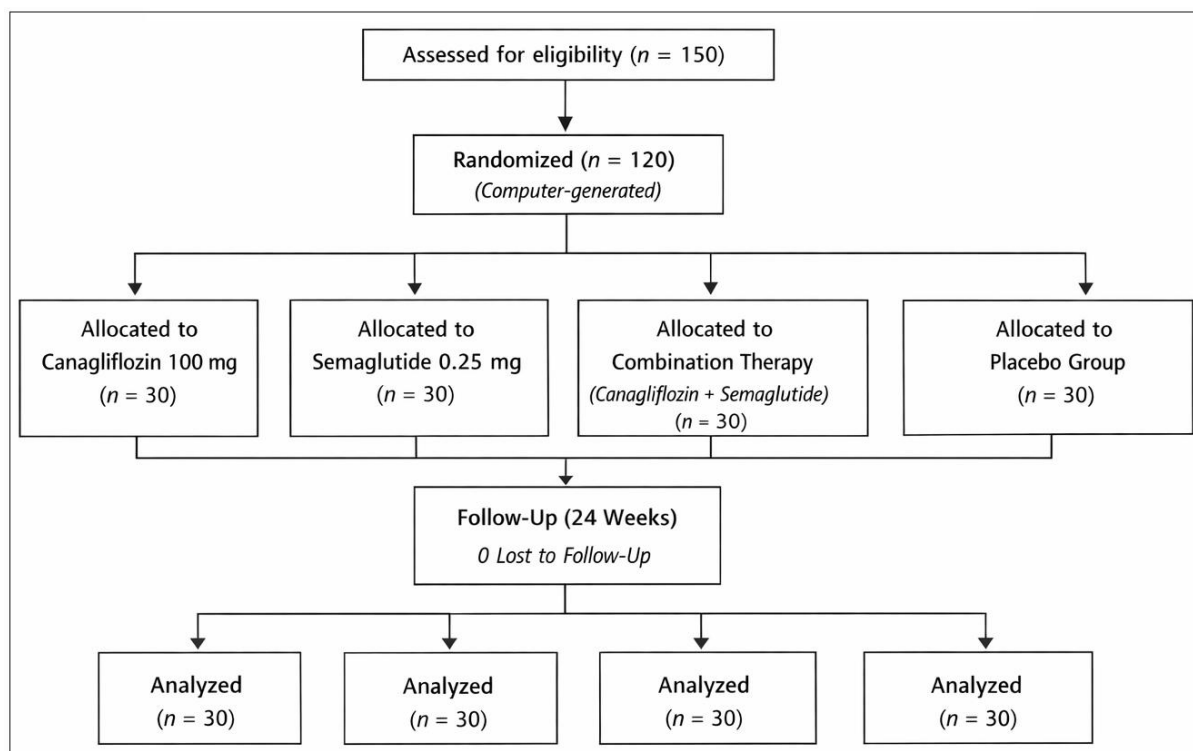


Fig. 1: Flow diagram illustrating patient enrollment, randomization, treatment allocation, and follow-up in the study

Table 1: Comparison of baseline characteristics among the four groups

Indicator	Canagliflozin (n=30)	Semaglutide (n=30)	Combination (n=30)	Placebo (n=30)	F/ χ^2	P value
Gender (male/female)	16/14	17/13	18/12	15/15	0.451	0.924
Age (years)	55.89 ± 7.98	57.32 ± 8.13	56.78 ± 7.65	57.10 ± 7.83	0.348	0.789
Diabetes duration (years)	7.65 ± 3.21	7.82 ± 3.11	7.55 ± 3.03	7.99 ± 3.25	0.231	0.884
BMI (kg/m ²)	25.98 ± 3.02	25.78 ± 2.92	26.12 ± 2.89	26.10 ± 2.95	0.345	0.785
SBP (mmHg)	134.45 ± 12.15	135.23 ± 11.92	134.89 ± 12.05	135.65 ± 12.31	0.186	0.948
DBP (mmHg)	82.12 ± 9.02	82.79 ± 8.96	81.76 ± 9.14	82.45 ± 9.21	0.056	0.991
HbA1c (%)	7.86 ± 1.01	7.92 ± 0.99	7.84 ± 1.02	7.88 ± 1.03	0.115	0.985
UACR (mg/g)	132.45 ± 35.67	131.12 ± 33.82	130.45 ± 34.25	131.86 ± 34.98	0.089	0.996
eGFR (mL/min/1.73 m ²)	85.45 ± 12.17	84.65 ± 11.85	85.11 ± 12.03	84.98 ± 11.92	0.142	0.933

Note: Data are presented as mean ± SD or as count and percentage

Table 2: UACR Changes before and after Treatment (mg/g)

Time point	Canagliflozin	Semaglutide	Combination	Placebo	F value	P value
Baseline	132.45 ± 35.67	131.12 ± 33.82	130.45 ± 34.25	131.86 ± 34.98	0.115	0.892
12 weeks	98.64 ± 28.35	97.22 ± 27.12	67.45 ± 22.13	101.23 ± 30.42	16.358	<0.001
24 weeks	89.64 ± 25.73	85.32 ± 24.18	45.27 ± 18.36	95.45 ± 28.76	45.351	<0.001

Note: Data are presented as mean ± SD

Table 3: eGFR before and after Treatment (mL/min/1.73 m²)

Time point	Canagliflozin	Semaglutide	Combination	Placebo	F value	P value
Baseline	85.45 ± 12.17	84.65 ± 11.85	85.11 ± 12.03	84.98 ± 11.92	0.142	0.933
24 weeks	81.35 ± 11.67	80.78 ± 10.98	75.56 ± 11.34	79.45 ± 11.60	3.171	0.046

Note: Data are given as mean ± SD

Table 4: Alterations in glycemic parameters pre- and post-treatment

Parameter	Group	Baseline	24 weeks	t value	P value
FBG (mmol/L)	Canagliflozin	8.76 ± 1.35	7.23 ± 1.02	5.719	<0.001
	Semaglutide	8.83 ± 1.29	7.35 ± 1.14	5.437	<0.001
	Combination	8.79 ± 1.32	6.54 ± 0.98*#	8.656	<0.001
HbA1c (%)	Canagliflozin	7.85 ± 1.02	7.02 ± 0.85	3.954	<0.001
	Semaglutide	7.93 ± 0.98 → 7.05 ± 0.88	7.05 ± 0.88	4.121	<0.001
	Combination	7.84 ± 1.02	6.41 ± 0.79*#	6.982	<0.001

Note: Values are expressed as mean ± SD; P < 0.05 vs. baseline within the same group; P < 0.05 vs. monotherapy groups

Changes in metabolic parameters

After 24 weeks, there was a significant improvement in fasting blood glucose (FBG) and HbA1c levels in all active treatment groups when compared to baseline (P < 0.05). The comparison of glycemic changes indicated that the level of glycemic control was greater with combination therapy than with either monotherapy (P < 0.05) (Table 4). Insulin resistance, assessed through the homeostasis model assessment of insulin resistance (HOMA-IR), along with lipid parameters, was considered as a secondary exploratory endpoint. HOMA-IR values and lipid parameters showed numerical changes compared to baseline across all active treatment groups, with a more pronounced effect in the combination treatment group. Due to the exploratory nature of these endpoints, no between-group significance was evaluated.

Inflammatory biomarkers

Systemic inflammatory markers, including tumor necrosis factor-alpha (TNF-alpha), interleukin 6 (IL-6) and C-reactive protein (CRP), were investigated as secondary exploratory outcomes. At 24 weeks, all active treatment groups exhibited numerically lower systemic inflammatory markers compared to baseline, with more significant reductions observed in the combination group. This finding represents a short-term associative relationship and does not imply causality regarding the primary renal outcomes. No mediation, interaction, or causal analysis was conducted.

Safety outcomes

Adverse events, such as hypoglycemia, hypotension, electrolyte imbalance and genitourinary infections, were infrequent and similar across the four groups (all P > 0.05). No serious adverse events related to treatment were reported during the 24-week study period.

DISCUSSION

DKD is a complicated and ongoing problem that comes from type 2 diabetes (Ebadi, 2025). It happens when the body's metabolism goes out of control and there is a low-level, long-term state of inflammation (Rabbani et al., 2025). Some people talk about the metabolic-inflammatory axis to explain why both of these factors seem to be pulling

on each other all the time. But the idea behind this is more about making connections than following a set of steps. When blood sugar levels rise, insulin resistance occurs and lipid metabolism becomes dysregulated; these factors appear to signal a concurrent escalation in systemic inflammation (Rroji and Spasovski, 2024). These, in turn, seem to cause problems with how blood vessels work, damage to the kidney's filtering structures and, finally, albuminuria, which is when albumin is found in urine. There is a growing interest in treatments, especially for early-stage DKD, that have both anti-inflammatory and metabolic effects (Młynarska et al., 2024).

The current randomized controlled trial examined the effects of canagliflozin and semaglutide, either individually or in combination, on early-stage diabetic kidney disease (DKD). Notably, the combination of canagliflozin and semaglutide resulted in greater positive changes in metabolism and more significant albuminuria reduction in the short term compared to either drug used alone (Granata et al., 2022). It is important to clarify that we are not claiming that the combination is necessarily synergistic or that it will always halt the progression of DKD. Our focus was specifically on early-stage disease, which differentiates current study from others in the field (McFarlin et al., 2024).

The combination therapy demonstrated a greater reduction in the urinary albumin-creatinine ratio (UACR); however, it is important to remember that this reduction is still an indirect measure (Alharbi, 2024). Additionally, 24 weeks is insufficient to determine the true and lasting effects of protecting the kidneys and nephrons, as well as slowing the progression of DKD. While it is true that a higher number of individuals in the combination group showed a decline in UACR levels to less than 30 mg/g, this reduction serves merely as an indirect indicator. It is crucial to keep in mind that 24 weeks is a relatively short duration (Mazzieri et al., 2024; Mazzeo et al., 2025). There was a small numerical loss in the estimated GFR in all groups, but only in the combination therapy group was this change statistically significant. This is in keeping with the short-term hemodynamic effects associated with SGLT2 inhibitors and should not be regarded as evidence of damage to the kidneys/kidney protection. It is clear that there were no

clear differences between the groups, confirming the need to interpret renal outcome data in short-duration trials (Gullaksen *et al.*, 2023; Rroji and Spasovski, 2024; Alharbi, 2024).

The combination group had better glycemic control than the monotherapy groups. The combination group had lower levels of fasting blood glucose and HbA1c. In these active treatments, insulin resistance (measured by HOMA-IR) and lipid levels also got better. The combination treatment was the best overall, according to the numbers. Nevertheless, given that this is a secondary endpoint, we should anticipate these results based on our understanding of the pharmacology of SGLT2 and GLP1R antagonists. Furthermore, the lack of adjustments for glycemic control, weights, or interaction tests precludes definitive conclusions regarding the benefits in the renal and metabolic systems arising from either additive or synergistic pharmacological mechanisms (Fu *et al.*, 2024; Alicic *et al.*, 2025; Zhang *et al.*, 2025; Economos and MacIsaac, 2025).

After treatment, systemic inflammation factors such as tumor necrosis factor- α , interleukin-6 and C-reactive protein decreased in all active treatment groups. However, the combination treatment demonstrated a more significant effect. As previously noted, none of the data provided specified factors related to kidney inflammation, fibrosis, or cellular damage. Additionally, no research has been conducted on interactions and mediation to support these inferences. Therefore, we cannot conclude that the changes in these factors are directly due to inflammation; rather, they seem to be associated with improved metabolic parameters (Huang *et al.*, 2022; Shokravi *et al.*, 2025).

The 24-week clinical study showed that the combined therapy was safe for patients. There were very few side effects and none of them were considered serious. This is in line with what we know about the safety of both canagliflozin and semaglutide. Nonetheless, apprehensions persist regarding the practicality of this therapy for patients, whether administered orally or through injection, as well as its acceptability among patients, despite these factors not being evaluated in the study (Gajjar *et al.*, 2025). There are a few things to keep in mind. One problem is that the study didn't last long enough to see how it would affect the heart and kidneys in the long run. Another limitation is the small sample size, which can make the statistical results less reliable, especially for secondary endpoints. Furthermore, the trial participants were in the initial phases of DKD with well-preserved renal function, which may not accurately reflect individuals with more advanced DKD or those in inferior overall health. Finally, the cost of dual therapy, especially with semaglutide, may be a problem in places where resources are limited (Gullaksen *et al.*, 2023; Wang and Zhang, 2024).

In summary, the significance of the current study is to contribute to an expanding body of knowledge regarding the clinical profile of the combined effect of canagliflozin and semaglutide on individuals with early-stage DKD, at least in the short term. The results showed that the drug combo provided much better short-term metabolic control and a positive trend in albuminuria compared with using either medication alone. However, it has still to be shown whether or not the supposed synergistic action has been proven and whether it offers long-term kidney safety and mechanisms by larger studies with the required power and with specific examination of kidney-related biomarkers and clinical outcomes (Agarwal *et al.*, 2025).

CONCLUSION

Patients with early diabetic kidney disease were given a combination of both types of medication. This led to better metabolic control and a slight improvement in albuminuria when taken together, but not when taken alone. There were no extra side effects. The caveat here, of course, is that these results only show a comparison and an association and they don't prove that the condition can be preserved in the long term in terms of kidney function. It is even clearer when we think about how small the change in eGFR was. Overall, the information adds to what we know about how the combined therapy might help a small group of people with early diabetic kidney disease. It also shows how important it is to do bigger and longer-term studies that look at kidney function-related markers and clinical outcomes.

Acknowledgements

None.

Authors' contributions

Wang Long: Contributed to study design, data collection and analysis; Li Ningning: Oversaw the study concept, data interpretation and manuscript writing; Huang Weijun: Assisted with statistical analysis and manuscript revisions. All authors approved the final manuscript.

Funding

There was no funding.

Data availability statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval

This study was approved by the Ethics Committee of Xi'an Gem Flower Changqing Hospital of Xi'an (approval number: DX-123-978). All participants provided written informed consent prior to inclusion in the study. This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

Conflict of interest

The authors declare no conflicts of interest related to this study.

Supplementary data

<https://www.pjps.pk/uploads/2026/05/SUP1778785418.pdf>

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