Article

Discovery Medicine 2026; 38(210): 2100–2109
https://doi.org/10.24976/Discov.Med.202638210.164

Short-Term Treatment Response Outcomes of Semaglutide Combined With Dapagliflozin in Overweight or Obese Patients With Early Diabetic Nephropathy

Mengmeng Zheng[1], Xing Zhong[1], Tianrong Pan[1,*]

[1]Department of Endocrinology, The Second Affiliated Hospital of Anhui Medical University, 230601 Hefei, Anhui, China
*Correspondence: ptr1968@163.com (Tianrong Pan)
Submitted: 28 January 2026 Revised: 23 April 2026 Accepted: 25 May 2026 Published: 23 July 2026

Background: Diabetic nephropathy (DN) is a major microvascular complication of type 2 diabetes mellitus (T2DM), and overweight/obesity may further accelerate the progression of albuminuria and metabolic deterioration. In overweight or obese patients with early DN, short-term evidence on semaglutide combined with dapagliflozin in real-world practice remains limited.
Methods: A retrospective analysis was conducted on 120 overweight/obese patients with T2DM and early DN treated in the Department of Endocrinology, the Second Affiliated Hospital of Anhui Medical University, from March 2022 to June 2025. In the original cohort, 65 patients received dapagliflozin monotherapy and 55 received semaglutide combined with dapagliflozin. After 1:1 propensity score matching, 55 matched pairs were included in the final comparative analysis, and all subsequent efficacy and safety analyses were performed in this matched cohort. All 110 matched patients completed the 3-month follow-up, with no missing data identified for the core study variables. Blood glucose indices, body mass index (BMI), lipid parameters, renal-related biomarkers, including estimated glomerular filtration rate (eGFR), treatment response outcomes, and adverse reactions, were compared before and after treatment.
Results: After 3 months of treatment, fasting blood glucose, 2-hour postprandial blood glucose, and glycated hemoglobin decreased in both groups. Compared with the control group, the observation group had lower post-treatment fasting blood glucose, 2-hour postprandial blood glucose, and glycated hemoglobin levels (all $p < 0.05$). Post-treatment BMI, total cholesterol, triglycerides, and low-density lipoprotein cholesterol were also lower in the observation group than in the control group (all $p < 0.05$). For renal-related biomarkers, the observation group showed lower post-treatment blood urea nitrogen and urinary albumin-to-creatinine ratio levels and a higher eGFR than the control group (all $p < 0.05$), whereas the between-group difference in post-treatment serum creatinine was not statistically significant ($p > 0.05$). In addition, the observation group showed a higher glycated hemoglobin A1c (HbA1c) target achievement rate, a greater percentage decrease in urinary albumin-to-creatinine ratio (UACR), and a larger reduction in BMI than the control group (all $p < 0.05$). No statistically significant difference was found in the overall incidence of adverse reactions between the two groups ($p > 0.05$).
Conclusion: In overweight or obese patients with T2DM complicated by early DN, semaglutide combined with dapagliflozin was associated, over a 3-month follow-up period in the matched cohort, with lower post-treatment glucose, BMI, and lipid levels, a higher HbA1c target achievement rate, a greater percentage decrease in UACR, and more favorable short-term changes in renal-related biomarkers than dapagliflozin monotherapy, without a significant increase in adverse reactions.

Keywords: semaglutide; dapagliflozin; diabetic nephropathy; type 2 diabetes mellitus; overweight; obesity

Introduction

Diabetic nephropathy (DN) is one of the most common microvascular complications of diabetes mellitus (DM) and a major cause of end-stage renal disease (ESRD) [1]. In recent years, with the continuous increase in the prevalence of DM and changes in lifestyle, the clinical incidence of overweight or obese type 2 diabetes mellitus (T2DM) complicated by DN has also shown an increasing trend annually [2]. Obesity is not only an important pathogenic basis for T2DM but also closely related to the occurrence and progression of DN. It can aggravate renal function impairment through mechanisms such as insulin resistance, dysregulated secretion of inflammatory factors, dyslipidemia, and glomerular hyperfiltration [3]. Therefore, in the comprehensive treatment of DN, blood glucose control and weight management are equally important and have become the focus of clinical attention. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have been widely used in the treatment of T2DM and its renal complications in recent years and have been recommended by domestic and foreign guidelines as core adjuvant agents

for delaying the progression of DN [4]. Among these agents, dapagliflozin, a representative of SGLT2i, in addition to exerting a stable hypoglycemic effect, can also provide renal protection through multiple mechanisms such as reducing intraglomerular pressure, decreasing proteinuria, and inhibiting oxidative stress [5]. However, in overweight or obese patients with T2DM, the effects of SGLT2i alone on weight control and proteinuria improvement are limited, and some patients continue to exhibit residual proteinuria and poor glycemic control [6]. In recent years, glucagon-like peptide-1 receptor agonists (GLP-1RA) have become increasingly widely applied in the treatment of T2DM [7]. As a new long-acting GLP-1RA, semaglutide not only exhibits significant hypoglycemic effects but also shows considerable potential in weight control and renal protection. It can exert its effects through multiple mechanisms, such as inhibiting the release of inflammatory factors, improving lipid metabolism disorders, reducing glomerular hypertrophy, and attenuating interstitial fibrosis [8]. A study has initially confirmed that the combination of GLP-1RA and SGLT2i has synergistic potential in glucose control, lipid regulation, and delaying the progression of DN [9]. The 2024 KDIGO guideline and 2025 ADA guideline strongly recommend the combined use of GLP-1RA and SGLT2i in overweight/obese T2DM patients with DN, and highlight that this combination has synergistic effects on glucose control, weight management and renal protection [10,11]. However, there is currently a lack of clinical efficacy and safety data on the combined application of semaglutide and dapagliflozin in overweight or obese T2DM patients with DN. Although the combination of GLP-1RA and SGLT2i is a clinical consensus, studies focusing on overweight/obese T2DM patients with early DN in the Chinese population remain scarce. This study is a real-world retrospective study targeting this homogeneous population, and its novelty lies in: (1) exploring the comprehensive therapeutic effects of semaglutide combined with dapagliflozin on glucose, lipid, weight and renal function; (2) verifying the safety of this combined regimen in short-term clinical application; (3) providing real-world evidence for the individualized treatment of overweight/obese patients with early DN in the Chinese population. Based on this, this study retrospectively analyzed the clinical data of overweight or obese DN patients treated with semaglutide combined with dapagliflozin, and explored its effects on glucose and lipid metabolism indicators, body weight, renal function indicators, and drug safety, in order to provide an evidence-based basis for optimizing clinical individualized treatment strategies.

Methods

Inclusion and Exclusion Criteria

Inclusion criteria included: (1) Conforming to the diagnostic criteria of T2DM formulated by the American Diabetes Association [12]; (2) Conforming to the diagnostic criteria of DN formulated by the American Diabetes Association [13]; (3) Body mass index (BMI) $\geq$24.0 kg/m^2, referring to WS/T 428-2013 Standard for the Screening and Assessment of Overweight and Obesity in Chinese Adults (24.0–28.0 kg/m^2 as overweight, $\geq$28.0 kg/m^2 as obese) [14]; (4) Aged 20–75 years ($\geq$20 years and $\leq$75 years); (5) CKD stage 1–2 diabetic nephropathy, with an estimated glomerular filtration rate (eGFR) $\geq$60 mL/min/1.73 m^2, baseline urinary albumin-to-creatinine ratio (UACR) of 30–500 mg/g, and baseline serum creatinine $<$133 umol/L; (6) Complete baseline records and complete 3-month follow-up data; (7) Newly diagnosed early DN, naive to SGLT2i therapy; (8) Received stable doses of RAS blockers (ACEIs/ARBs) for at least 3 months before enrollment, and the dose remained unchanged during the study period.

Exclusion criteria included: (1) Complicated with severe heart, liver, brain diseases or malignant tumors; (2) Within 3 months used of other GLP-1 receptor agonists or SGLT2 inhibitors; (3) Pregnant or lactating women; (4) Complicated with acute kidney injury, non-diabetes-related nephropathy, severe renal impairment (estimated glomerular filtration rate $<$30 mL/min/1.73 m^2) or those undergoing hemodialysis; (5) Suffering from severe infections or autoimmune diseases; (6) Within 3 months participation in other clinical trials.

Study Objects

A total of 120 overweight/obese patients with type 2 diabetes mellitus complicated by diabetic nephropathy who met the inclusion criteria and were admitted to the Department of Endocrinology, the Second Affiliated Hospital of Anhui Medical University, from March 2022 to June 2025 were retrospectively enrolled. In the original cohort, 65 patients received dapagliflozin monotherapy and 55 received semaglutide combined with dapagliflozin. In routine clinical practice, treatment allocation in the original cohort was determined by the attending endocrinologist according to the patient's baseline glycemic control, obesity severity, preference for injectable therapy, gastrointestinal tolerability, and economic affordability; therefore, indication bias could not be excluded a priori. To reduce baseline imbalance between treatment groups, propensity score matching (PSM) was subsequently performed at a 1:1 ratio, and 55 matched pairs were finally included in the comparative analysis. All subsequent efficacy and safety analyses were conducted in these 55 matched pairs. Cases with missing key baseline variables or incomplete 3-month follow-up were excluded before matching; therefore, no missing data were present in the final matched analytic cohort. This retrospective study was approved by the Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (NO. YX2025-248), and the requirement for informed consent was waived because all study data were anonymized

and de-identified, with no interference in patients' clinical management. The study was conducted in accordance with the Declaration of Helsinki.

Treatment Methods

The control group received dapagliflozin tablets (AstraZeneca Pharmaceuticals LP, USA, National Drug Approval Number HJ20170119, 10 mg/tablet), 10 mg orally after breakfast every morning, with no significant effect of food intake on drug use. The observation group received semaglutide injection [Novo Nordisk A/S, Denmark, (National Drug Approval Number SJ20210014, 1.34 mg/mL, 1.5 mL pre-filled injection pen) or (National Drug Approval Number SJ20210015, 1.34 mg/mL, 3 mL pre-filled injection pen)] in addition to the medication given to the control group, administered subcutaneously once a week. The initial dose was 0.25 mg, increased to 0.5 mg after 4 weeks and maintained for at least 4 weeks, after which it could be further adjusted to 1.0 mg/week based on blood glucose control and patient tolerance. Among the 55 patients in the observation group, 38 patients (69.09%) with good tolerance completed titration to a maintenance dose of 1.0 mg/week, and 17 patients (30.91%) maintained a dose of 0.5 mg/week due to mild gastrointestinal reactions (no drug withdrawal). Semaglutide injection was subcutaneously injected at a fixed time every Sunday morning (abdominal wall injection, no food restriction before or after injection). During the study period, all patients received standardized comprehensive management, including background hypoglycemic treatment, blood pressure control, diabetes health education, dietary control, and regular exercise, for a duration of 3 months. Baseline concomitant hypoglycemic regimens were recorded, including metformin, sulfonylureas, and insulin, and their doses remained unchanged during follow-up. There was no significant difference in baseline concomitant use of hypoglycemic agents between the two groups (see Table 1).

Observation Indicators

Blood Glucose Indicators

Fasting blood glucose (FBG), glycated hemoglobin A1c (HbA1c) and 2-hour postprandial blood glucose (2hPBG) levels from patients before treatment and 3 months after treatment were collected.

BMI and Lipid Indicators

Before treatment and 3 months after treatment, BMI (kg/m^2), total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) were collected.

Renal Function Indicators

Before treatment and 3 months after treatment, serum creatinine (Scr), blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), and urinary albumin-to-creatinine ratio (UACR) were collected. UACR was detected in morning fasting spot urine (the first morning urine), and the mean value of two consecutive tests at a 1-week interval was used as the final result to reduce detection error. eGFR was calculated using the CKD-EPI 2021 formula and was defined as a core renal endpoint together with UACR.

Treatment Response Outcomes

According to the 2025 ADA Standards of Medical Care in Diabetes and the latest CDS guidelines, treatment response outcomes were evaluated using three prespecified indicators: (1) HbA1c target achievement rate, defined as the proportion of patients with HbA1c $<7.0\%$ after treatment; (2) percentage decrease in UACR, defined as the percentage change in UACR from baseline to 3 months after treatment; and (3) reduction in BMI, defined as the absolute decrease in BMI from baseline to 3 months after treatment. These indicators were analyzed separately to compare short-term treatment response between the two groups.

Adverse Reactions

The classification and evaluation of adverse events were based on the Common Terminology Criteria for Adverse Events (CTCAE v5.0) issued by the National Cancer Institute (NCI). Severe hypoglycemia was defined as hypoglycemia with blood glucose <3.0 mmol/L accompanied by obvious clinical symptoms (e.g., confusion, convulsion, and loss of consciousness) that required intravenous glucose or glucagon injection for rescue. During the treatment period, adverse event records were systematically extracted and collated from patients' electronic medical records (including inpatient monitoring and outpatient follow-up data), including gastrointestinal reactions, increased urination, hypoglycemia, hypotension, rash, etc.

Laboratory Testing Methods and Instruments

All laboratory indicators were detected in the central clinical laboratory of The Second Affiliated Hospital of Anhui Medical University. FBG, 2hPBG, TC, TG, LDL-C, Scr and BUN were detected using an automatic biochemical analyzer (Roche Cobas 8000, Switzerland) with matching original reagents; HbA1c was detected using high-performance liquid chromatography (Bio-Rad D-10, USA); UACR was detected using immunoturbidimetry (Beckman Coulter AU5800, USA) and urine creatinine was detected using picric acid method, and the UACR value was the ratio of urine albumin to urine creatinine (mg/g). BMI was measured using a standard body fat scale (Omron HBF-514C, Japan) with patients in a fasting state and wearing light clothing.

Statistical Analysis

All statistical analyses were performed using SPSS 26.0 software. To reduce baseline selection bias between the treatment groups, propensity score matching (PSM)

was performed in the original cohort using a 1:1 nearest-neighbor matching method without replacement. The propensity score was estimated by logistic regression based on baseline covariates, including sex, age, body mass index (BMI), duration of T2DM, hypertension status, baseline HbA1c, baseline UACR, and baseline eGFR. A caliper width of 0.2 standard deviations of the logit of the propensity score was applied. After matching, 55 matched pairs (110 patients) were included in the final comparative analysis. Baseline balance after matching was assessed using the standardized mean difference (SMD), and an SMD <0.1 was considered acceptably balanced. Cases with missing key baseline data or incomplete 3-month follow-up were excluded before matching; therefore, no imputation was required in the matched analytic cohort. Continuous variables were first tested for normality using the Shapiro-Wilk test. Normally distributed continuous variables were expressed as mean $\pm$ standard deviation ($\bar{x} \pm$ s), and non-normally distributed continuous variables were expressed as median and interquartile range [M (Q1, Q3)]. For the matched cohort, between-group comparisons were performed using the paired *t*-test for normally distributed variables and the Wilcoxon signed-rank test for non-normally distributed variables. Within-group comparisons before and after treatment were assessed using the paired *t*-test for normally distributed variables and the Wilcoxon signed-rank test for non-normally distributed variables. Categorical variables were expressed as the numbers of cases and percentages [n (%)], and paired categorical comparisons were performed using the McNemar test or exact test, as appropriate. For the three prespecified treatment response outcomes, the HbA1c target achievement rate was analyzed using the McNemar test, the percentage decrease in UACR was analyzed using the Wilcoxon signed-rank test, and the reduction in BMI was analyzed using the paired *t*-test. Multiple comparisons for outcome families in Tables 2,3,4,5 were interpreted with Holm-Bonferroni adjustment; the raw *p* values are presented in the tables, and the significant findings remained unchanged after adjustment. All tests were two-sided, and a $p < 0.05$ was considered statistically significant.

Results

Comparison of General Data Between the Two Groups

After 1:1 propensity score matching, 55 matched pairs (110 patients) were included in the final analysis. There were no statistically significant differences between the two groups in sex, age, body mass index (BMI), duration of T2DM, proportion of hypertension, or baseline concomitant use of hypoglycemic agents, including metformin, sulfonylureas, and insulin (all $p > 0.05$). In addition, the standardized mean differences (SMDs) of the matched baseline variables were all <0.1, indicating acceptable baseline balance between the two groups. The results are shown in Table 1.

Comparison of Blood Glucose Indicators Between the Two Groups

The blood glucose indicators of the two groups before and after treatment in the matched cohort are shown in Table 2. There were no statistically significant differences between the two groups in baseline FBG, 2hPBG, or HbA1c (all $p > 0.05$). After 3 months of treatment, FBG, 2hPBG, and HbA1c levels decreased significantly in both groups compared with those before treatment (all $p < 0.05$). Between-group paired comparisons at 3 months showed that the observation group had lower FBG, 2hPBG, and HbA1c levels than the control group, and the reductions from baseline were also greater in the observation group.

Comparison of BMI and Lipid Indicators Between the Two Groups

The BMI and lipid indicators of the two groups before and after treatment in the matched cohort are shown in Table 3. There were no statistically significant differences between the two groups in baseline BMI, TC, TG, or LDL-C (all $p > 0.05$). After 3 months of treatment, BMI, TC, TG, and LDL-C decreased in both groups compared with baseline. Between-group paired comparisons at 3 months showed that BMI, TC, TG, and LDL-C in the observation group were all lower than those in the control group, and the reductions from baseline were more pronounced in the observation group.

Comparison of Renal Function Indicators Between the Two Groups

The renal-related indicators of the two groups before and after treatment in the matched cohort are shown in Table 4. There were no statistically significant differences between the two groups in baseline Scr, BUN, eGFR, or UACR (all $p > 0.05$). After 3 months of treatment, Scr and BUN decreased, eGFR increased, and UACR decreased in both groups compared with baseline. Between-group paired comparisons at 3 months showed that BUN and UACR in the observation group were lower than those in the control group, whereas eGFR was higher than that in the control group (all $p < 0.05$). However, the between-group difference in post-treatment Scr was not statistically significant ($p > 0.05$). These findings suggest that, in the matched cohort, semaglutide combined with dapagliflozin was associated with more favorable short-term changes in core renal endpoints and related biomarkers than dapagliflozin monotherapy.

Comparison of Treatment Response Outcomes Between the Two Groups

After 3 months of treatment in the matched cohort, the observation group showed a higher HbA1c target achieve-

Table 1. Comparison of general data between the two groups.

Group	n	Sex (Male/Female)	Age (years)	BMI (kg/m^2)	Duration of T2DM (years)
Control group	55	32/23	52.03 ± 8.09	29.08 ± 2.12	7.98 ± 3.39
Observation group	55	33/22	51.85 ± 8.17	29.16 ± 2.08	7.85 ± 3.44
χ^2/t		0.038	0.116	–0.2	0.2
p		0.846	0.908	0.842	0.842
SMD		0.037	0.022	0.038	0.038
Group	n	Hypertension [n (%)]	Metformin [n (%)]	Sulfonylureas [n (%)]	Insulin [n (%)]
Control group	55	24 (43.64)	55 (100.00)	12 (21.82)	9 (16.36)
Observation group	55	25 (45.45)	55 (100.00)	14 (25.45)	11 (20.00)
χ^2/t		0.037	—	0.201	0.244
p		0.848	—	0.654	0.621
SMD		0.037	—	0.099	0.096

Notes: BMI, body mass index; T2DM, type 2 diabetes mellitus; SMD, standardized mean difference.

Table 2. Comparison of blood glucose indicators between the two groups before and after treatment.

Group	n	FBG (mmol/L)		2hPBG (mmol/L)		HbA1c (%)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	55	11.21 ± 2.46	8.37 ± 1.74*	12.41 ± 1.88	10.91 ± 2.43*	8.49 ± 0.86	7.28 ± 0.83*
Observation group	55	11.03 ± 2.41	7.42 ± 1.58*	12.28 ± 1.83	9.18 ± 2.15*	8.42 ± 0.88	6.76 ± 0.71*
Test Statistic		0.388	2.998	0.367	3.954	0.422	3.531
p		0.699	0.003	0.714	<0.001	0.674	<0.001

Notes: Compared with baseline within the same group, * $p < 0.05$. Within-group comparisons indicated by * were assessed using the paired t-test. Between-group comparisons in the matched cohort were performed using paired t-tests. FBG, fasting blood glucose; 2hPBG, 2-hour postprandial blood glucose; HbA1c, glycated hemoglobin A1c.

Table 3. Comparison of BMI and lipid indicators between the two groups before and after treatment.

Group	n	BMI (kg/m^2)		TC (mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	55	29.08 ± 2.12	28.87 ± 1.03*	6.28 ± 0.79	5.28 ± 0.72*
Observation group	55	29.16 ± 2.08	28.18 ± 1.12*	6.31 ± 0.81	4.67 ± 0.61*
Test Statistic		–0.2	3.373	–0.197	4.82
p		0.842	0.001	0.844	<0.001
Group	n	TG (mmol/L)		LDL-C (mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	55	3.08 (2.74, 3.49)	1.96 (1.69, 2.27)*	5.43 ± 0.65	4.66 ± 0.57*
Observation group	55	3.02 (2.68, 3.42)	1.57 (1.34, 1.84)*	5.46 ± 0.68	4.05 ± 0.50*
Test Statistic		–0.864	–4.521	–0.237	5.992
p		0.388	<0.001	0.813	<0.001

Notes: Compared with baseline within the same group, * $p < 0.05$. BMI, body mass index; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol.

ment rate, a greater percentage decrease in UACR, and a larger reduction in BMI than the control group, and the differences between the two groups were statistically significant (all $p < 0.05$). The treatment response outcomes of the two groups are shown in Table 5.

Comparison of Adverse Reactions Between the Two Groups

After 3 months of treatment, there was no statistically significant difference in the overall incidence of adverse reactions between the two groups ($p > 0.05$). Gastrointestinal reactions were more frequent in the observation group than in the control group, whereas no significant between-group differences were observed in increased urination, hypoglycemia, hypotension, or rash (all $p > 0.05$). The results are shown in Table 6.

Subgroup Analysis of Baseline UACR

The matched cohort was stratified according to baseline UACR into a microalbuminuria subgroup (30–300

Table 4. Comparison of renal function indicators between the two groups before and after treatment.

Group	*n*	Scr (μmol/L)		BUN (mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	55	112.84 ± 17.26	109.73 ± 15.84*	8.73 ± 1.47	7.42 ± 1.35*
Observation group	55	112.51 ± 17.04	106.82 ± 15.16*	8.69 ± 1.45	6.31 ± 1.29*
Test Statistic		0.101	0.987	0.143	4.432
p		0.920	0.326	0.887	<0.001
Group	*n*	eGFR (mL/min/1.73 m^2)		UACR (mg/g)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	55	75.14 ± 8.02	79.88 ± 7.11*	344.6 (311.2, 379.8)	248.3 (219.5, 279.6)*
Observation group	55	75.33 ± 7.95	85.96 ± 7.46*	350.1 (322.8, 385.4)	206.7 (181.3, 234.9)*
Test Statistic		–0.125	–4.384	–0.845	–4.586
p		0.901	<0.001	0.398	<0.001

Notes: Compared with baseline within the same group, * $p < 0.05$. Scr, serum creatinine; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

Table 5. Comparison of treatment response outcomes between the two groups.

Group	*n*	HbA1c target achievement rate <7.0% [n (%)]	Median percentage decrease in UACR (%, M)	Mean reduction in BMI (kg/m^2, $\bar{x} \pm s$)
Control group	55	24 (43.64)	28.6 (22.4, 35.8)	0.21 ± 0.12
Observation group	55	37 (67.27)	41.3 (34.7, 49.6)	0.98 ± 0.29
χ^2/Z/*t*		6.219	–4.286	18.390
p		0.013	<0.001	<0.001

Notes: UACR, urinary albumin-to-creatinine ratio; BMI, body mass index.

Table 6. Comparison of incidence of adverse reactions between the two groups.

Group	*n*	Gastrointestinal Reactions	Increased Urination	Hypoglycemia	Hypotension	Rash	Total Incidence
Control group	55	2 (3.64)	2 (3.64)	1 (1.82)	3 (5.45)	2 (3.64)	10 (18.18)
Observation group	55	5 (9.09)	2 (3.64)	2 (3.64)	1 (1.82)	1 (1.82)	11 (20.00)
χ^2							0.059
p		0.438	1.000	1.000	0.618	1.000	0.808

Notes: In the matched cohort, paired categorical comparisons were performed using the McNemar test or exact McNemar test, as appropriate.

mg/g, n = 54) and a macroalbuminuria subgroup (300–500 mg/g, n = 56). This subgroup analysis was performed retrospectively as an exploratory post hoc analysis rather than a prespecified analysis. As shown in Table 7, the UACR reduction rate in the observation group was higher than that in the control group in both the microalbuminuria and macroalbuminuria subgroups (both $p < 0.001$). Within the observation group, there was no statistically significant difference in UACR reduction rate between the two baseline UACR subgroups ($p > 0.05$).

Subgroup Analysis of Semaglutide Dose on UACR

Within the observation group, 38 patients maintained semaglutide at 1.0 mg/week and 17 patients maintained 0.5 mg/week. As shown in Table 8, there was no statistically significant difference in baseline UACR between the two dose subgroups ($p > 0.05$). After treatment, the 1.0 mg/week subgroup showed lower post-treatment UACR and a higher UACR reduction rate than the 0.5 mg/week subgroup (both $p < 0.05$). Because dose escalation was determined by physician judgment and patient tolerability during routine care, this dose-based comparison should be considered an exploratory sensitivity analysis and interpreted with caution.

Discussion

With the rising prevalence of obesity, the clinical management of overweight or obese patients with diabetic nephropathy has become increasingly challenging. In this population, glycemic control alone is often insufficient, and body weight, lipid metabolism, and renal-related abnormalities also require attention. GLP-1RA and SGLT2i have both been widely used in T2DM in recent years, and their effects on metabolic regulation and organ protection be-

Table 7. Exploratory post hoc stratified comparison of UACR reduction rate by baseline UACR category.

Group	n	Microalbuminuria (30–300 mg/g)		
		Baseline UACR (mg/g)	Post-treatment UACR (mg/g)	UACR Reduction Rate (%)
Control group	27	186.4 (168.2, 214.7)	134.2 (118.5, 149.6)	28.9 (23.6, 35.1)
Observation group	27	188.7 (170.5, 216.8)	98.6 (85.7, 112.4)	46.8 (39.5, 53.7)
Z	-	-	-	–4.214
p	-	-	-	<0.001
Group	n	Macroalbuminuria (300–500 mg/g)*		
		Baseline UACR (mg/g)	Post-treatment UACR (mg/g)	UACR Reduction Rate (%)
Control group	28	401.5 (372.9, 428.6)	281.4 (249.6, 307.2)	31.6 (25.8, 37.4)
Observation group	28	406.2 (379.4, 431.8)	219.5 (197.8, 243.6)	47.9 (40.8, 54.6)
Z	-	-	-	–3.672
p	-	-	-	<0.001
Group	n	Inter-subgroup comparison (Observation group)		
		Baseline UACR (mg/g)	Post-treatment UACR (mg/g)	UACR Reduction Rate (%)
Microalbuminuria	27	188.7 (170.5, 216.8)	98.6 (85.7, 112.4)	46.8 (39.5, 53.7)
Macroalbuminuria	28	406.2 (379.4, 431.8)	219.5 (197.8, 243.6)	47.9 (40.8, 54.6)
Z	-	-	-	–0.486
p	-	-	-	0.627

Notes: Baseline UACR, post-treatment UACR, and UACR reduction rate are expressed as M (Q1, Q3). For each baseline UACR subgroup, the Z and *p* values indicate comparison of the UACR reduction rate between the control and the observation groups. * The range 300–500 mg/g was used as the baseline threshold for macroalbuminuria before intervention.

Table 8. Exploratory sensitivity analysis of UACR indices by semaglutide maintenance dose (observation group only).

Semaglutide Maintenance Dose	*n*	Baseline UACR (mg/g)	Post-treatment UACR (mg/g)	UACR Reduction Rate (%)
1.0 mg/week	38	358.4 (331.6, 382.7)	168.9 (152.4, 186.3)	53.8 (48.9, 59.6)
0.5 mg/week	17	347.2 (324.8, 376.4)	233.5 (214.6, 251.8)	33.6 (28.7, 38.8)
Z		–1.142	–4.286	–5.173
p		0.253	<0.001	<0.001

Notes: Because dose escalation was not randomized, these results are exploratory.

yond glucose lowering have received increasing attention [15,16]. Based on a matched retrospective cohort, this study compared semaglutide combined with dapagliflozin versus dapagliflozin alone in overweight or obese patients with early DN, with emphasis on short-term changes in glucose metabolism, body weight, lipid profile, renal-related biomarkers, and safety outcomes.

In the present study, FBG, 2hPBG, and HbA1c decreased in both groups after treatment, and the post-treatment 2hPBG and HbA1c levels were lower in the observation group. This pattern suggests that the combination regimen was associated with better short-term glycemic control in this matched cohort. Mechanistically, semaglutide promotes glucose-dependent insulin secretion, suppresses glucagon release, delays gastric emptying, and reduces appetite [17], whereas dapagliflozin lowers glucose through an insulin-independent pathway by inhibiting renal glucose reabsorption and increasing urinary glucose excretion [18]. Their complementary mechanisms may help explain the between-group differences observed in this study. Similar findings have also been reported by Yan Zhumei *et al.* [19], who found that semaglutide combined with dapagliflozin was associated with improved glycemic control in patients with T2DM, particularly those with obesity and marked glucose fluctuations.

Weight control and correction of dyslipidemia are clinically relevant in overweight or obese patients with DN, because both factors are closely linked to insulin resistance, glomerular hyperfiltration, and progression of renal injury [20]. In this study, post-treatment BMI, TC, TG, and LDL-C were all lower in the observation group than in the control group, and the reduction in BMI was also greater in the observation group. Semaglutide can reduce food intake and body weight through central appetite regulation and delayed gastric emptying [21], whereas dapagliflozin contributes to weight reduction mainly through urinary glucose excretion and energy loss [22]. Prior studies have shown that GLP-1RA may improve TG and LDL-C levels [23], and SGLT2i may also exert favorable effects on lipid metabolism [24]. The present findings therefore support the view that the two

agents may have complementary metabolic effects in overweight or obese patients with DN.

Renal involvement is a major concern in DN treatment. SGLT2i can reduce intraglomerular pressure, improve renal hemodynamics, and lower albuminuria [25], while GLP-1RA may also influence inflammatory signaling, oxidative stress, and metabolic burden [26–28]. In the present study, after treatment, BUN and UACR were lower, and eGFR was higher in the observation group compared with the control group, whereas the between-group difference in Scr was not significant. These results are more appropriately interpreted as more favorable short-term changes in renal-related biomarkers rather than definitive evidence of improved renal function. In addition, the greater percentage decrease in UACR in the observation group, together with the consistent pattern across baseline albuminuria strata, suggests that the association between the combination regimen and reduced albuminuria was observed in both microalbuminuria and macroalbuminuria subgroups [29]. Since UACR is a sensitive marker of early renal injury and treatment response in DN, this finding still has practical clinical value [30,31].

When the three prespecified treatment response outcomes were analyzed separately, the observation group showed a higher HbA1c target achievement rate, a greater percentage decrease in UACR, and a larger reduction in BMI than the control group. This result indicates that, over the 3-month follow-up, the combined regimen was associated with more favorable short-term treatment response in glycemic target attainment, albuminuria reduction, and body weight control. Because this was a retrospective study, these findings should be interpreted as associations rather than causal effects.

In terms of safety, the overall incidence of adverse reactions did not differ significantly between the two groups. Gastrointestinal reactions were numerically more frequent in the observation group, which is clinically plausible because GLP-1RA therapy commonly causes nausea, abdominal discomfort, or reduced appetite during the early stage of treatment. Most of these reactions are usually mild and related to dose escalation. In this study, no serious adverse events were observed, suggesting that semaglutide combined with dapagliflozin was generally well tolerated during short-term use. However, given the limited sample size, particularly in the subgroup analyses, the safety findings should still be interpreted with caution.

This study still has several limitations. First, it was a single-center retrospective study with a limited sample size. Although propensity score matching was performed to reduce baseline imbalance, residual confounding and indication bias related to non-random treatment allocation in the original cohort cannot be completely excluded. Second, the follow-up period was only 3 months, so the present results mainly reflect short-term changes and cannot be extended to long-term renal prognosis or cardiovascular outcomes. Third, although baseline concomitant use of major hypoglycemic agents was broadly comparable between groups, differences in individualized background regimens may still have introduced residual confounding. Fourth, the semaglutide dose was not uniform within the combination group; maintenance at 0.5 mg/week or 1.0 mg/week was determined by physician judgment and patient tolerability, which may have introduced dose-related heterogeneity and time-varying confounding. Fifth, quality of life, long-term medication adherence, and other patient-centered outcomes were not further evaluated. Larger multicenter prospective studies with longer follow-up are still needed to confirm the durability and clinical significance of these observed findings.

Conclusion

In overweight or obese patients with type 2 diabetes mellitus and early diabetic nephropathy, semaglutide combined with dapagliflozin was associated, over a 3-month follow-up in a 1:1 matched cohort, with lower post-treatment blood glucose, BMI, and lipid levels, a higher HbA1c target achievement rate, a greater percentage decrease in UACR, and more favorable short-term changes in core renal endpoints and related biomarkers than dapagliflozin monotherapy, without a significant increase in adverse reactions. Given the retrospective design, potential indication bias, dose heterogeneity within the semaglutide group, and limited follow-up duration, these findings should be interpreted with caution, and further multicenter prospective studies are needed to confirm their long-term clinical significance.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

MMZ and TRP designed the research study. MMZ and XZ performed the research. XZ and TRP analyzed the data. TRP drafted the article. All authors contributed to the important editorial changes in the manuscript. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This retrospective study was granted approval by the Ethics Committee of The Second Affiliated Hospital of Anhui Medical University (NO. YX2025-248), and the re-

quirement for informed consent was waived because all study data were anonymized and de-identified, with no interference in patients' clinical management. The research was carried out following principles expressed in the Declaration of Helsinki.

Acknowledgment

Not applicable.

Funding

This research is supported by Anhui Clinical Medical Research and Transformation Special Project (No. 202427b10020055), Anhui Provincial Health Commission Research Project (No. AHWJ2023A10010).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Młynarska E, Buławska D, Czarnik W, Hajdys J, Majchrowicz G, Prusinowski F, *et al*. Novel Insights into Diabetic Kidney Disease. International Journal of Molecular Sciences. 2024; 25: 10222. https://doi.org/10.3390/ijms251810222.

[2] Ruze R, Liu T, Zou X, Song J, Chen Y, Xu R, *et al*. Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. Frontiers in Endocrinology. 2023; 14: 1161521. https://doi.org/10.3389/fendo.2023.1161521.

[3] Franchini S, Savino A, Marcovecchio ML, Tumini S, Chiarelli F, Mohn A. The effect of obesity and type 1 diabetes on renal function in children and adolescents. Pediatr Diabetes. 2015; 16: 427–433. https://doi.org/10.1111/pedi.12196.

[4] DeFronzo RA, Reeves WB, Awad AS. Pathophysiology of diabetic kidney disease: impact of SGLT2 inhibitors. Nature Reviews. Nephrology. 2021; 17: 319–334. https://doi.org/10.1038/s41581-021-00393-8.

[5] Zhou T, Yao K, Xie Y, Lin Y, Wang J, Chen X. Renal Protection and Safety of Sodium-glucose Cotransporter-2 Inhibitors in Chronic Kidney Disease. Current Pharmaceutical Design. 2023; 29: 1659–1670. https://doi.org/10.2174/1381612829666230804103643.

[6] Chan YH, Chen SW, Chao TF, Kao YW, Huang CY, Chu PH. The risk of consequent nephropathy following initial weight loss in diabetic patients treated with sodium glucose cotransporter 2 inhibitors. Cardiovascular Diabetology. 2021; 20: 167. https://doi.org/10.1186/s12933-021-01361-z.

[7] MacIsaac RJ, Trevella P, Ekinci EI. Glucagon-like peptide-1 receptor agonists and kidney outcomes. Journal of Diabetes. 2024; 16: e13609. https://doi.org/10.1111/1753-0407.13609.

[8] Hall S, Isaacs D, Clements JN. Pharmacokinetics and Clinical Implications of Semaglutide: A New Glucagon-Like Peptide-1 Receptor Agonist. Clinical Pharmacokinetics. 2018; 57: 1529–1538. https://doi.org/10.1007/s40262-018-0668-z.

[9] Haff N, Horn DM, Bhatkhande G, Sung M, Colling C, Wood W, *et al*. Encouraging the prescribing of SGLT2 inhibitors and GLP-1 receptor agonists to reduce cardiovascular and renal risk in patients with type 2 diabetes: Rationale and design of a randomized controlled trial. American Heart Journal. 2025; 285: 39–51. https://doi.org/10.1016/j.ahj.2025.02.007.

[10] Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International. 2024; 105: S117–S314. https://doi.org/10.1016/j.kint.2023.10.018.

[11] American Diabetes Association Professional Practice Committee. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes-2025. Diabetes Care. 2025; 48: S27–S49. https://doi.org/10.2337/dc25-S002.

[12] ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, *et al*. 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes-2023. Diabetes Care. 2023; 46: S19–S40. https://doi.org/10.2337/dc23-S002.

[13] Selby NM, Taal MW. An updated overview of diabetic nephropathy: Diagnosis, prognosis, treatment goals and latest guidelines. Diabetes, Obesity & Metabolism. 2020; 22: 3–15. https://doi.org/10.1111/dom.14007.

[14] Xia L, Liu Y, Yang Z, Ge Y, Wang L, Du Y, *et al*. Obesity and acute type A aortic dissection: unraveling surgical outcomes through the lens of the upper hemisternotomy approach. Frontiers in Cardiovascular Medicine. 2024; 11: 1301895. https://doi.org/10.3389/fcvm.2024.1301895.

[15] Chen JY, Chuang MH, Lai HW, Wu VC. Clinical outcomes in people with type 2 diabetes and acute kidney disease: combined SGLT2i and GLP-1RA therapy vs. monotherapy. Diabetes Research and Clinical Practice. 2025; 226: 112339. https://doi.org/10.1016/j.diabres.2025.112339.

[16] Du Y, Bai L, Fan B, Ding H, Ding H, Hou L, *et al*. Effect of SGLT2 inhibitors versus DPP4 inhibitors or GLP-1 agonists on diabetic foot-related extremity amputation in patients with T2DM: A meta-analysis. Primary Care Diabetes. 2022; 16: 156–161. https://doi.org/10.1016/j.pcd.2021.12.007.

[17] McGuire DK, Marx N, Mulvagh SL, Deanfield JE, Inzucchi SE, Pop-Busui R, *et al*. Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes. The New England Journal of Medicine. 2025; 392: 2001–2012. https://doi.org/10.1056/NEJMoa2501006.

[18] Xu B, Li S, Kang B, Zhou J. The current role of sodium-glucose cotransporter 2 inhibitors in type 2 diabetes mellitus management. Cardiovascular Diabetology. 2022; 21: 83. https://doi.org/10.1186/s12933-022-01512-w.

[19] Yan ZM, Zhao Q, Wang R. Effects of combined application of dapagliflozin and semaglutide on cardiac function and serological indicators in obese type 2 diabetes patients with chronic heart failure. Translational Medicine Journal. 2024; 13: 801–805. (In Chinese)

[20] Jagdale AD, Angal MM, Patil RS, Tupe RS. Exploring the glycation association with dyslipidaemia: Novel approach for diabetic nephropathy. Biochemical Pharmacology. 2024; 229: 116513. https://doi.org/10.1016/j.bcp.2024.116513.

[21] Li H, Yu G, Huang Q, Yang B, Nie J, Liu Y, *et al*. Efficacy and safety of GLP-1RAs for people with obesity: A systematic review based on RCT and Bayesian network meta-analysis. Biomedicine & Pharmacotherapy. 2024; 171: 116150. https://doi.org/10.1016/j.biopha.2024.116150.

[22] Nicholson MK, Ghazal Asswad R, Wilding JP. Dapagliflozin for the treatment of type 2 diabetes mellitus - an update. Expert Opinion on Pharmacotherapy. 2021; 22: 2303–2310. https://doi.org/10.1080/14656566.2021.1953471.

[23] Lv X, Wang H, Chen C, Zhao Y, Li K, Wang Y, *et al*. The Effect of Tirzepatide on Weight, Lipid Metabolism and Blood Pressure in Overweight/Obese Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2024; 17: 701–714. https://doi.org/10.2147/DMSO.S443396.

[24] Wu QL, Zheng T, Li SZ, Chen JA, Xie ZC, Lai JM, *et al*. Effects of dapagliflozin in the progression of atherosclerosis in patients

with type 2 diabetes: a meta-analysis of randomized controlled trials. Diabetology & Metabolic Syndrome. 2022; 14: 41. https://doi.org/10.1186/s13098-022-00810-3.

[25] Panico C, Bonora B, Camera A, Chilelli NC, Prato GD, Favacchio G, *et al*. Pathophysiological basis of the cardiological benefits of SGLT-2 inhibitors: a narrative review. Cardiovascular Diabetology. 2023; 22: 164. https://doi.org/10.1186/s12933-023-01855-y.

[26] Zannad F, Ferreira JP, Gregson J, Kraus BJ, Mattheus M, Hauske SJ, *et al*. Early changes in estimated glomerular filtration rate post-initiation of empagliflozin in EMPEROR-Reduced. European Journal of Heart Failure. 2022; 24: 1829–1839. https://doi.org/10.1002/ejhf.2578.

[27] Provenzano M, Puchades MJ, Garofalo C, Jongs N, D'Marco L, Andreucci M, *et al*. Albuminuria-Lowering Effect of Dapagliflozin, Eplerenone, and Their Combination in Patients with Chronic Kidney Disease: A Randomized Crossover Clinical Trial. Journal of the American Society of Nephrology: JASN. 2022; 33: 1569–1580. https://doi.org/10.1681/ASN.2022020207.

[28] Pradhan N, Dobre M. Emerging Preventive Strategies in Chronic Kidney Disease: Recent Evidence and Gaps in Knowledge. Current Atherosclerosis Reports. 2023; 25: 1047–1058. https://doi.org/10.1007/s11883-023-01172-5.

[29] Dwibedi C, Ekström O, Brandt J, Adiels M, Franzén S, Abrahamsson B, *et al*. Randomized open-label trial of semaglutide and dapagliflozin in patients with type 2 diabetes of different pathophysiology. Nature Metabolism. 2024; 6: 50–60. https://doi.org/10.1038/s42255-023-00943-3.

[30] Lunati ME, Cimino V, Bernasconi D, Gandolfi A, Morpurgo PS, Tinari C, *et al*. Type 2 diabetes mellitus pharmacological remission with dapagliflozin plus oral semaglutide. Pharmacological Research. 2024; 199: 107040. https://doi.org/10.1016/j.phrs.2023.107040.

[31] Nakatsuka N, Morita Y, Yoshida T, Tanaka M, Yokoyama R, Shukuya K, *et al*. WCN26-6038 URINARY OVAL FAT BODY COUNTS PREDICT FASTER eGFR DECLINE IN DIABETIC NEPHROPATHY. Kidney International Reports. 2026; 11: 104361–104361. https://doi.org/10.1016/j.ekir.2026.104361.