doi.org/10.36721/PJPS.2026.39.1.REG.14163.1

Adjunctive nutritional intervention improves glycaemia and quality of life in dapagliflozin-treated diabetic patients

Yifan Liu[1]*, Xuejian Hu[1] and Jintang Jia[2]*
[1]Department of Endocrinology, The Second Hospital of Lanzhou University, Lanzhou, Gansu, China
[2]Department of General Surgery, Gansu Provincial Maternity and Child-care Hospital, Lanzhou, Gansu, China

Abstract: **Objectives**: This study aimed to evaluate the added benefits of a structured nutritional intervention combined with dapagliflozin in patients with DN. **Methods**: In this prospective, randomized, open-label trial, 108 patients with DN were assigned to a control group (CG, conventional care), a treatment group (TG, CG + dapagliflozin 10 mg/day), or an observation group (OG, TG + Mediterranean diet and oral nutritional supplements). Key outcomes included glycaemic control (FBG, PBG, HbA1c), renal function (BUN, sCr, UACR, eGFR), nutritional status (albumin, ferritin, SGA), inflammation (CRP, TNF-α, IL-6), safety and quality of life (SF-36), assessed at baseline, 3 and 6 months. **Results**: Both TG and OG showed significant improvements over CG in glycaemic control and renal parameters ($P<0.05$). The OG demonstrated superior outcomes compared to TG: greater reductions in HbA1c (-1.5% vs. -0.9%), FBG, PBG and UACR (-48% vs. -35%) (all $P<0.05$). Nutritional markers (albumin, ferritin) and SF-36 scores improved significantly more in the OG. Inflammatory markers decreased in both treatment groups, with a trend favoring OG. Adverse event rates did not differ significantly among groups. **Conclusion**: Adjunctive nutritional intervention significantly enhances the glycaemic, renal, nutritional and quality-of-life benefits of dapagliflozin in patients with DN, offering a promising integrated therapeutic strategy.

Keywords: Adverse reaction; Dapagliflozin; Diabetic nephropathy; Glycaemia; Inflammatory; Nutritional intervention; Renal function

Submitted on 21-02-2025 – Revised on 03-12-2025 – Accepted on 09-12-2025

INTRODUCTION

Untreated intervention after the onset of diabetes mellitus induces a variety of complex complications and diabetic nephropathy (DN) is one of the most frequent and symptomatic complications, causing a high mortality rate among patients (Samsu, 2021). The earliest clinical evidence of classic DN is early nephropathy leading to microalbuminuria. The prevalence of diabetes mellitus has been reported to be increasing globally, especially in developing countries and 1/3 of these diabetic patients will have latent development of DN (Xue *et al.,* 2017). The incidence of chronic kidney disease (CKD) in China was 10.6% in 2019, with 196,726 deaths, causing a serious socio-economic burden (Y. Li *et al*., 2023). Established risk factors for DN include persistent hyperglycaemia, hypertension and dyslipidemia ("KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease," 2021). Furthermore, contemporary guidelines underscore the importance of early screening for albuminuria and declining eGFR in all patients with type 2 diabetes mellitus (T2DM) ("KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease," 2020). In addition, CKD results in varying degrees of malnutrition (20%-76%) due to abnormal protein metabolism *(Slee and Reid, 2022*) and malnutrition is also an independent risk factor for DN. Therefore, early diagnosis and treatment of DN should be developed.

Sodium-glucose cotransporter protein-2 (SGLT2) inhibitors are a popular class of drugs for the treatment of T2DM. By inhibiting the glucose transporter SGLT2, these drugs reduce glucose reabsorption and promote glucose excretion through the urine and are able to reduce glucose levels independently of insulin action (Hsia *et al*., 2017; Wilding *et al*., 2018). Dapagliflozin is more widely used in the treatment of T2D, especially for patients with DN (Plosker, 2014). For patients with renal insufficiency, glucose can be metabolised by the liver and excreted as an inactive metabolite in the urine, reducing the damage and burden on the kidneys (Balant *et al*., 1973; Palmer and Brogden, 1993). Studies have shown that dapagliflozin improves iron death by inhibiting activation of the HIF1α/HO1 axis thereby exerting a renoprotective effect and alleviating DN (Wang *et al*., 2024). In addition, the cost of incorporating dapagliflozin into the standard treatment of DN has been calculated in the United States to be cost-effective based on the low adverse effects of dapagliflozin (Abegaz *et al*., 2022).

In this study, we aimed to evaluate the efficacy of an integrated therapeutic approach in patients with DN. To this end, we designed a prospective, randomized controlled

**Corresponding author:* e-mail: yifamliu1980@126.com; wolf916715@163.com

trial comparing standard care alone, standard care plus dapagliflozin and a combination of dapagliflozin with a structured nutritional intervention. The primary outcomes focused on glycaemic control and renal function, with secondary assessments of nutritional status, inflammatory markers, safety profile and health-related quality of life.

MATERIALS AND METHODS

Study subjects

A total of 108 patients with DN were treated from April 2022 to April 2024 in our hospital. They were randomly divided into three groups of CG, TG and OG with 36 cases in each group. There was no obvious difference in the general data of groups (P>0.05), details are shown in table 1.

Inclusion criteria: (1) age between 20-70 years old; (2) meeting the diagnostic criteria for DN (Kaneshiro and Kimura, 2010); (3) patients with unsatisfactory glycaemic control and good adherence.

Exclusion criteria: (1) patients with non-DN; (2) patients with severe cardiovascular disease; (3) patients with severe hepatic and renal impairment; (4) patients with diabetes mellitus combined with acute complications; and (5) patients who were treated with SGLT2 medication in the last month prior to the enrolment, or patients who were allergic to this type of medication.

Randomization

Eligible patients were randomly assigned (1:1:1) to one of the three groups using a computer-generated random number sequence (Scholte *et al*., 2025). The allocation sequence was prepared by an independent statistician not involved in patient recruitment or assessment. To ensure concealment, assignments were placed in sequentially numbered, opaque, sealed envelopes (SNOSE) (Tang *et al*., 2025). The envelope was opened by the study coordinator only after the patient had signed the informed consent form and completed baseline assessments.

Study design and duration

This was a prospective, randomized, open-label, controlled clinical trial. Each enrolled patient underwent an active intervention and assessment period of 6 months. Evaluations were performed at baseline (0 months), at the midpoint (3 months) and at the end of the intervention period (6 months).

Treatment methods

CG: Patients received conventional intervention for DN, which included standard medical care (e.g., blood pressure and lipid management as per guidelines), bed rest as needed, environmental disinfection and comprehensive health education focusing on diabetes self-management.

TG: In addition to the conventional intervention provided to the CG, patients received dapagliflozin (AstraZeneca Pharmaceuticals Ltd., specification: 10 mg/tablet) at a fixed dose of 10 mg orally, once daily.

OG: Patients received the same dapagliflozin treatment as the TG, combined with a structured, multi-component nutritional intervention. The nutritional intervention was designed and supervised by a clinical dietitian and consisted of the following three key components:

(1) Dietary pattern: Implementation of a Mediterranean-style diet (Mazza *et al*., 2021). The dietary plan emphasized: high daily consumption of vegetables, fruits, whole grains and legumes; moderate intake of nuts, seeds and olive oil as the primary fat source; consumption of fish at least twice weekly; limited intake of red and processed meats, sweets and refined grains. Total daily caloric intake was individualized to meet energy requirements, with approximately 50-55% from carbohydrates (focus on low glycemic index sources), 15-20% from protein (adjusted within safe limits for CKD stage) and 25-30% from fats (predominantly unsaturated).

(2) Oral nutrition supplements (ONSs): To address the common risk of protein-energy wasting in CKD, patients were prescribed a specific, commercially available ONS product: Fresubin® 2.0 kcal Fibre (Fresenius Kabi). Each 200 mL ready-to-drink bottle provides 200 kcal of energy and 10 g of high-quality, readily digestible protein (50% casein, 50% whey). It is also enriched with dietary fiber (3.0 g/200mL), vitamins and minerals. Patients were instructed to consume one bottle (200 mL) three times daily, taken one hour after the main meals (breakfast, lunch and dinner). This regimen provided an additional 600 kcal and 30 g of protein per day to their baseline Mediterranean diet.

(3) Individualized fluid management: Patients were educated on strict monitoring and control of their daily fluid intake. The allowable daily fluid volume (including water, beverages and fluid content of foods like soups and fruits) was calculated for each patient as: Total daily urine output (measured over 24 hours) + 500 mL to 800 mL. This was to prevent fluid overload while ensuring adequate hydration. Intake from milk was accounted for within this limit, while the water content of solid fruits was generally not strictly restricted but monitored.

Observation indicators

1. *Blood glucose level*: Fasting blood glucose (FBG), postprandial blood glucose (PBG) and glycated hemoglobin (HbA1c) levels were measured for all participants before the initiation of treatment and at the end of the study (6 months). FBG and PBG (measured 2 hours after the start of a standard breakfast) were measured using a glucose oxidase method with a fully automated biochemical analyzer (Hitachi 7600, Hitachi, Japan).

HbA1c was quantified by high-performance liquid chromatography (HPLC) using the Bio-Rad D-10™ Hemoglobin Testing System (Bio-Rad Laboratories, USA).

2. *Renal function*: To assess renal function, fasting venous blood and first-morning urine samples were collected at baseline and after 6 months of treatment. Blood urea nitrogen (BUN) and serum creatinine (SCr) were measured using standard enzymatic and kinetic colorimetric methods, respectively, on the Hitachi 7600 automated analyzer. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation (*Heerspink et al., 2025*). Urinary albumin excretion rate (UAER) was determined from 24-hour urine collections and urinary albumin-to-creatinine ratio (UACR) was measured from spot urine samples. Urinary albumin concentration was assayed by immunoturbidimetry (Roche Cobas c501, Roche Diagnostics, Switzerland) and urinary creatinine was measured using the Jaffe method (Dogara *et al*., 2025).

3. *Inflammatory factors*: Fasting venous blood was collected in EDTA tubes at baseline and 6 months. Plasma levels of C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) were measured. CRP was quantified by particle-enhanced immunoturbidimetric assay on the Roche Cobas c501 analyzer. TNF-α and IL-6 concentrations were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN, USA), following the manufacturer's instructions, with absorbance read on a BioTek ELx800™ microplate reader (BioTek Instruments, USA).

4. *Nutritional status*: Body mass index (BMI) was calculated from measured height and weight. Fasting blood samples were analyzed for albumin (ALB), total protein (TP), hemoglobin (HGB) and serum ferritin (SF). ALB and TP were measured by the bromocresol green method and biuret method, respectively, using the Hitachi 7600 analyzer. HGB was analyzed as part of a complete blood count performed on a Sysmex XN-550 hematology analyzer (Sysmex Corporation, Japan). SF was measured using a chemiluminescent immunoassay on the Abbott Architect i2000SR analyzer (Abbott Laboratories, USA). Additionally, the Subjective Global Assessment (SGA) scale (*Sayed et al., 2025*) was administered by a trained dietitian or clinician at baseline and at 3 and 6 months to subjectively evaluate nutritional status, with higher scores indicating better status.

5. *Adverse reactions*: All patients were monitored for adverse events throughout the 6-month study period. Specific adverse reactions of interest included hypoglycemia (defined as blood glucose < 3.9 mmol/L with or without symptoms), hypotension (systolic blood pressure < 90 mmHg or a drop > 20 mmHg from baseline with symptoms), dizziness, vomiting and urinary tract infections (diagnosed based on symptoms and confirmatory urinalysis/culture). Events were recorded in case report forms.

6. *Quality of life*: Health-related quality of life was assessed using the 36-Item Short Form Health Survey (SF-36). The questionnaire, covering physical, emotional and social functioning dimensions, was administered to all participants at baseline, 3 months and 6 months by research staff in a quiet, private setting.

Statistical analysis

SPSS 20.0 was used to process and analyze the data and GraphPad Prism 8.0 was used to plot the graphs. Count data and measurement data were expressed as n (%) and mean ± SD, respectively and differences were tested using the χ^2 test and t-test. $p < 0.05$ was statistically significant.

RESULTS

Changes in blood glucose levels

The blood glucose levels of patients in TG and OG improved after intervention, with FBG, PBG and HbA1c of OG remarkably lower than those of TG, indicating that dapagliflozin combined with nutritional intervention was more effective in ameliorating patients' blood glucose ($P < 0.05$). The mean reduction (Δ) in HbA1c from baseline to 6 months was -0.9% in the TG and -1.5% in the OG ($P < 0.05$ for OG vs. TG). Similarly, FBG decreased by -1.8 mmol/L and -2.7 mmol/L and PBG by -3.1 mmol/L and -4.5 mmol/L in the TG and OG, respectively (all $P < 0.05$ for OG vs. TG). Details are listed in Fig. 1.

Changes in renal function parameters

The BUN, sCr, UAER and UACR of TG and OG were lower than those of CG ($P < 0.05$), while the eGFR had an increasing trend but was not statistically insignificant ($P > 0.05$). There was no statistically significant difference between OG and TG indexes, indicating that dapagliflozin could effectively improve the renal function of patients. The UACR, a key marker, showed a mean reduction of -35% in the TG and -48% in the OG from baseline. Details are listed in Fig. 2.

Changes in inflammatory marker levels

After treatment, the inflammatory factors of both TG and OG decreased. The level of inflammatory factors in TG was significantly lower than that in CG ($P<0.05$) and the level of inflammatory factors in OG showed a decreasing trend compared to TG, but there was no statistically significant difference ($P>0.05$) Details are listed in Fig. 3.

Changes in nutritional status indicators

After treatment, BMI was significantly lower in TG and ALB, TP, HGB and SF indicators were expressed at remarkably higher levels in OG than in TG ($p < 0.05$).The nutritional status of OG patients was better on the SGA scale and scores increased with the duration of the intervention. Details are listed in Fig. 4.

Table 1: Baseline characteristics of the study participants

Characteristic	CG (n=36)	TG (n=36)	OG (n=36)	*P*-value
Age (years)	53.27 ± 9.26	54.51 ± 9.01	54.05 ± 9.17	> 0.05
Gender (Male/Female)	20 / 26	21 / 25	22 / 24	> 0.05
BMI (kg/m²)	25.64 ± 1.75	25.79 ± 1.67	25.51 ± 1.63	> 0.05
Hypertension, n (%)	24 (66.7)	21 (58.3)	21 (58.3)	> 0.05
Disease duration (years)	8.78 ± 2.56	8.93 ± 2.37	8.88 ± 2.39	> 0.05

Notes: Data are presented as mean ± standard deviation or number (percentage). CG: Control Group; TG: Treatment Group (dapagliflozin); OG: Observation Group (dapagliflozin + nutritional intervention). BMI: Body Mass Index. P-values were derived from ANOVA or Chi-square test as appropriate; P > 0.05 indicates no statistically significant difference among groups at baseline.

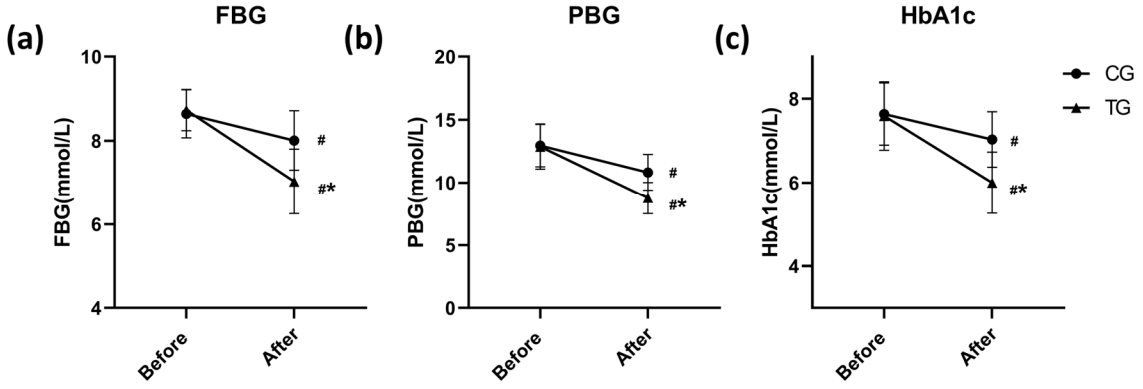

Fig. 1: Evaluation of blood glucose levels. (a) FBG; (b) PBG; (c) HbA1c. #P<0.05 compared with before treatment, *P<0.05 compared with TG. Abbreviations: CG: control group; TG: treatment group; FBG: fasting blood glucose; PBG: postprandial blood glucose; HbA1c: glycated hemoglobin.

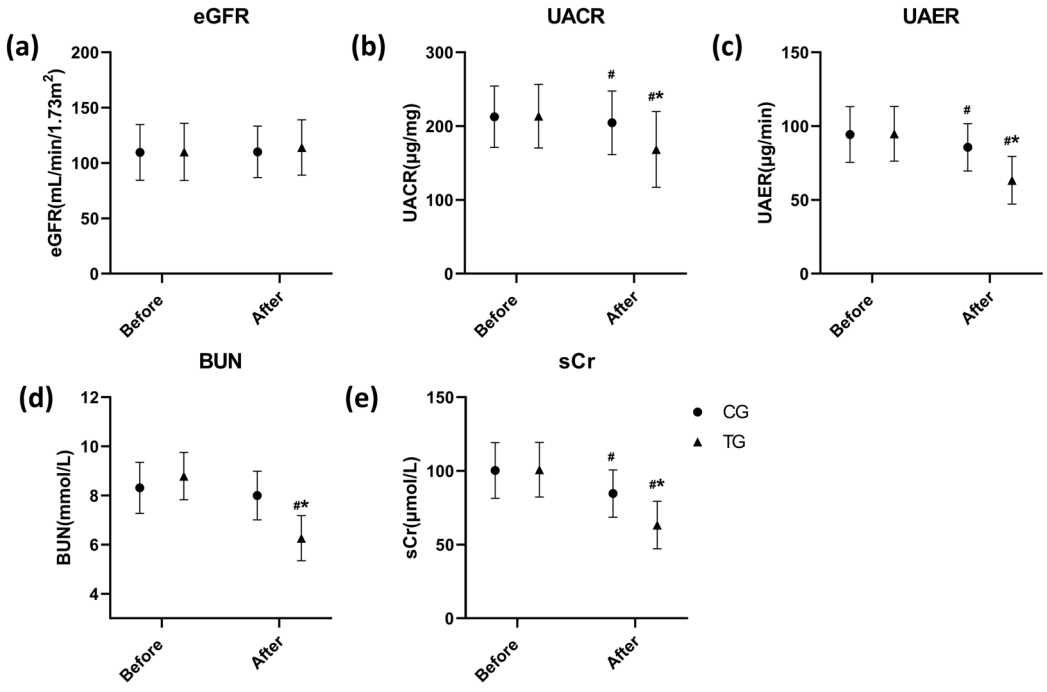

Fig. 2: Evaluation of renal function. (a) eGFR; (b) UCER; (c) UCAR; (d) BUN; (e) SCr. #P<0.05 compared with before treatment, *P<0.05 compared with TG. Abbreviations: CG: control group; TG: treatment group; eGFR: estimated glomerular filtration rate; UAER: urinary albumin excretion rate; UCAR: urinary albumin-to-creatinine ratio; BUN: blood urea nitrogen; SCr: serum creatinine.

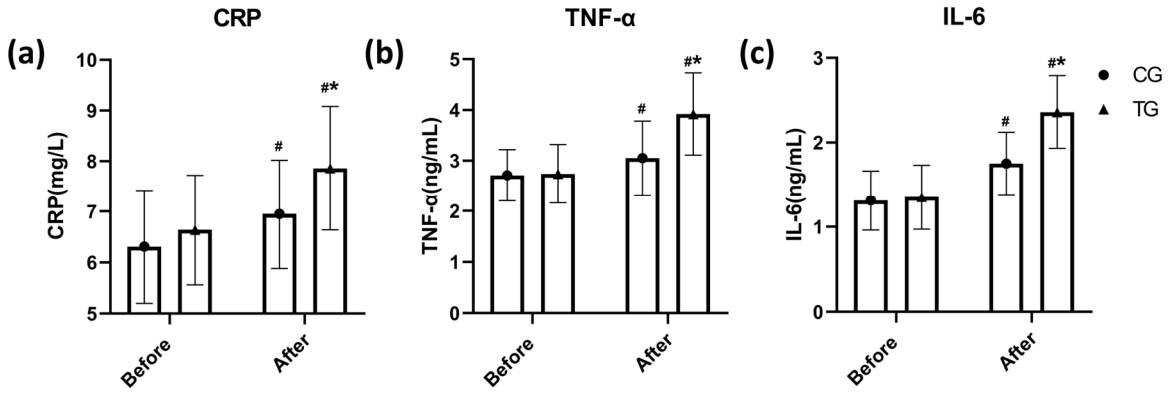

Fig. 3: Evaluation of inflammatory factor. (a) CRP; (b) TNF-α; (c) IL-6. #P<0.05 compared with before treatment, *P<0.05 compared with TG. Abbreviations: CG: control group; TG: treatment group; CRP: C-reactive protein; TNF-α: tumor necrosis factor-alpha; IL-6: interleukin-6.

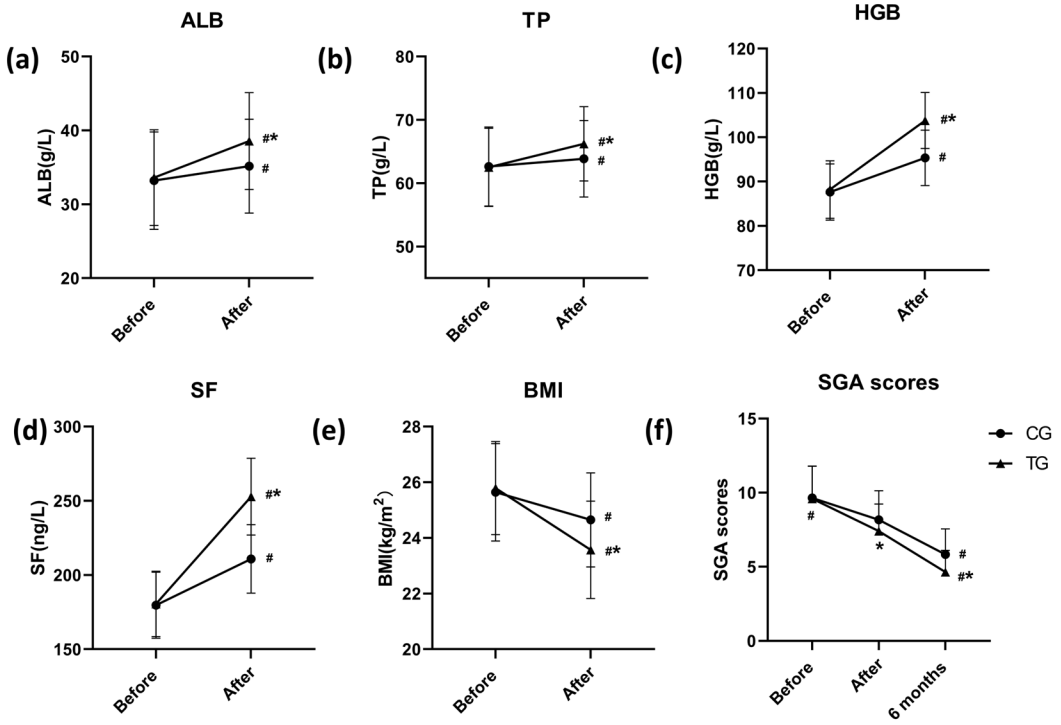

Fig. 4: Evaluation of nutritional status. (a) ALB; (b) TP; (c) HGB; (d) SF; (e) BMI; (f) SGA.#P<0.05 compared with before treatment, *P<0.05 compared with TG. In SGA scores, #P<0.05 compared with after treatment, *P<0.05 compared with TG. Abbreviations: CG: control group; TG: treatment group; ALB: albumin; TP: total protein; HGB: hemoglobin; SF: serum ferritin; BMI: body mass index; SGA: Subjective Global Assessment.

Table 2: Evaluation of adverse reaction in three groups

Groups	Hypoglycaemia	Hypotension	Urinary infection	Nausea and dizziness	Total incidence rates
CG (n=36)	1 (2.78)	1 (2.78)	0 (0.00)	1 (2.78)	3 (8.33)
TG (n=36)	1 (2.78)	2 (5.56)	2 (5.56)	2 (5.56)	7 (19.44)
OG (n=36)	1 (2.78)	1 (2.78)	2 (5.56)	2 (5.56)	6 (16.67)
P1					0.307
P2					0.478

P1 represents CG versus TG, P2 represents CG versus OG.

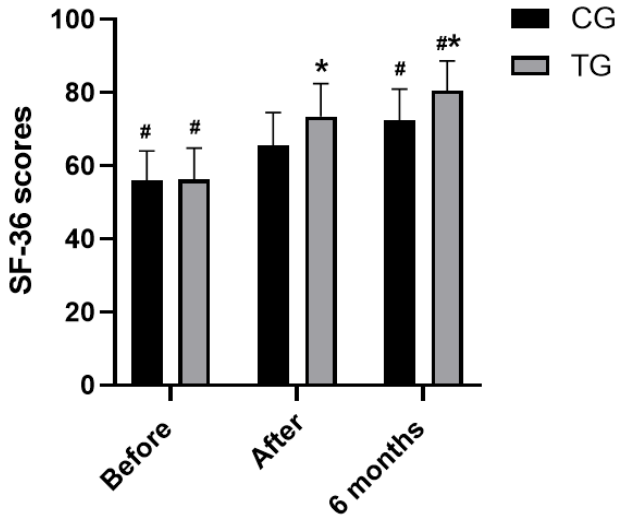

Fig. 5: Evaluation of SF-36 scores. #P<0.05 compared with after treatment, *P<0.05 compared with TG. Abbreviations: CG: control group; TG: treatment group.

Comparison of adverse reactions

There was no obvious difference of all three groups in adverse reactions such as hypoglycaemia and hypotension, dizziness and vomiting and urinary tract infection ($P > 0.05$, Table 2).

Changes in quality of life scores

The quality of life of both TG and OG patients after treatment was better than before treatment, with the quality of life of TG being better than that of CG and that of OG being better than that of TG. The scores at 6 months of intervention were higher than those at 3 months of intervention ($p < 0.05$). Details are listed in Fig. 5.

DISCUSSION

Diabetes mellitus is a chronic metabolic disease that poses a serious public health risk and, if left untreated, produces microangiopathy within a few years of its onset, affecting small vessels in the kidneys, eyes and nerves. DN is one of the most common complications of diabetes and cardiovascular disease or end-stage renal failure are the main causes of high morbidity and mortality rates (Gupta *et al*., 2023; Rossi and Gesualdo, 2017). Historically, persistent proteinuria was associated with a high risk of progression to end-stage kidney disease. However, the advent of novel therapies such as SGLT2 inhibitors has significantly altered this trajectory, demonstrating marked reductions in renal and cardiovascular events in contemporary clinical trials (Heerspink *et al*., 2020; Liu *et al*., 2025; Perkovic *et al*., 2019). Due to the complexity of the pathogenesis of DN, its diagnostic and therapeutic methods are still immature. The traditional pathogenesis of DN is due to metabolic and haemodynamic abnormalities in the body (Tavafi, 2013). DN is determined by decreased renal function, diabetic retinopathy, proteinuria and decreased GFR (Bermejo *et al*., 2017). ADA recommends annual screening for kidney function and proteinuria is required for T2DM (ElSayed *et al*., 2023).

Dapagliflozin is a type of SGLT-2 inhibitor that inhibits glucose reabsorption in renal tubules thereby effectively controlling blood glucose. Our clinical study found that nutritional intervention combined with dapagliflozin treatment for three months was effective in improving FBG, PBG and HbA1c levels and controlling the development of hyperglycaemia. It has been proven that a 1% increase in HbA1c increases the risk of microvascular complications by 40% (Zoungas *et al*., 2012). Additionally, dapagliflozin can effectively reduce urinary microalbumin level in nephritis patients, which can alleviate the occurrence and development of proteinuria. Our results showed that after three months of treatment, the renal function indexes such as sCr, UAER and UACR of TG were lower than those of CG, indicating that dapagliflozin plays a role in protecting kidney and improving renal function. Van *et al*. (2020) revealed that dapagliflozin slowed down the decline of eGFR and improved renal function in chronic kidney patients. In addition, dapagliflozin can delay renal tubulointerstitial fibrosis in DKD rats by inhibiting YAP/TAZ activation and renal inflammatory effect (Feng *et al*., 2023). The analysis of our study revealed that the levels of inflammatory factors such as CRP, TNF-α and IL-6 were lower in the dapagliflozin experimental group than in CG, which is accordance with the above findings.

Clinical studies have shown that diet quality affects the development of diabetes and insulin resistance. Consumption of large amounts of fructose and saturated fatty acids (Newman and Verdin, 2014; Puchalska and Crawford, 2017) are independent risk factors for the development of insulin resistance and diabetes. Findings revealed that reduced 25(OH)D2 concentrations were related to a growing prevalence of proteinuria (Chokhandre *et al*., 2015). On the basis of the study of Khan *et al*. (2009) on the assessment of malnutrition, we monitored the nutritional status of the patients. After three months of nutritional intervention, the patients' biochemical indices such as ALB, TP and SF improved, BMI and SGA scores also improved and the nutritional status at six months was better than that at three months of intervention. Our findings align with recent evidence supporting the role of dietary patterns in CKD management. The Mediterranean diet, in particular, has been associated with reduced inflammation and slower eGFR decline in patients with kidney disease, as shown in recent cohort studies and trials (Kwon *et al*., 2024; Picard *et al*., 2021). The adjunctive use of ONS in our protocol addresses the prevalent issue of protein-energy wasting, a critical target in modern nutritional therapy for CKD (Kang *et al*., 2025). The adverse effects of dapagliflozin drug were not significantly different from those of conventional treatment, in which

the chances of reproductive tract infections were somewhat increased after dapagliflozin treatment. Studies have reported that SGLT-2 inhibitors are well tolerated, with the most common adverse effect being fungal infections of the genital tract, but these are generally mild and easily treatable (Fitchett, 2019). Several studies have demonstrated the safety of dapagliflozin treatment, which makes it a commonly used drug in the clinical management of T2DM (Anderson, 2014; Li *et al*., 2023). Furthermore, we investigated the quality of life of our patients after three months and six months of treatment intervention and the analysis indicated that the life treatment was remarkably improved after treatment and the quality of life at six months was also significantly win upon that at three months of treatment. This further confirms the clinical value of our therapeutic intervention.

It is important to acknowledge the limitations of this study. First, the sample size was relatively small and the study was conducted at a single center, which may limit the generalizability of the findings. Second, the follow-up duration (6 months) was moderate; while it was sufficient to observe significant changes in several biochemical parameters (e.g., HbA1c, UACR), a longer observation period might be necessary to detect statistically significant improvements in slower-changing indices such as estimated glomerular filtration rate (eGFR). Longer-term studies are needed to assess the sustained effects of the combined intervention on renal outcomes and cardiovascular events. Third, while we implemented a structured Mediterranean diet and ONS, individual dietary compliance was monitored but not quantified using tools such as food diaries, which might introduce variability. Future multi-center randomized controlled trials with larger samples and longer follow-up are warranted to confirm our conclusions.

CONCLUSION

Nutritional intervention combined with dapagliflozin treatment can control blood glucose and inflammation development, improve renal function, nutritional level and quality of life in patients with DN to a certain extent, which has certain clinical value.

Acknowledgement
He authors would like to express their sincere gratitude to all the patients who participated in this study. We also thank the nursing staff and clinical dietitians at our hospital for their invaluable assistance in patient care, data collection, and the implementation of the nutritional intervention. We acknowledge the technical support provided by the Department of Clinical Laboratory for conducting the biochemical and immunological assays. Finally, we thank our colleagues for their insightful discussions and support throughout this research project.

Author's contributions
Conceptualization, methodology, formal analysis, writing - original draft: Yifan Liu. Yifan Liu: Investigation, data curation, project administration. Xuejian Hu: Resources, supervision, writing - review & editing. Jintang Jia: Validation, visualization, software. All authors have read and agreed to the published version of the manuscript.

Funding
This study was supported by Gansu Provincial Science and Technology Plan Project (Natural Science Foundation) (No. 20JR5RA338) and the Gansu Higher Education Innovation Fund Project (No. 2020B-39).

Data availability statement
The datasets generated during and/or analysed for the current study are available from the corresponding author on reasonable request.

Ethical approval
This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Second Hospital of Lanzhou University (Approval No.: 2020GS_L0012). Written informed consent was obtained from all participants.

Conflict of interest
The authors state that there are no conflicts of interest to disclose.

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