Am J Transl Res 2022;14(8):5622-5629
www.ajtr.org /ISSN:1943-8141/AJTR0142438

Original Article

The promising significance of liraglutide combined with dapagliflozin or empagliflozin in the prevention of early diabetic nephropathy

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Received February 18, 2022; Accepted July 5, 2022; Epub August 15, 2022; Published August 30, 2022

Abstract: Objective: To explore the significance of liraglutide combined with dapagliflozin or empagliflozin in the prevention of early diabetic nephropathy (DN) and its effects on renal function indices. Methods: Three hundred patients with type 2 diabetes mellitus (T2DM) treated in our hospital from April 2019 to April 2020 were retrospectively included and divided into two groups according to different treatment regimens. Among them, 150 patients who received liraglutide alone were included in the single-drug group, and 150 patients treated with liraglutide combined with dapagliflozin or empagliflozin were included in the combination group. The baseline data and the improvement of inflammatory indices, blood glucose indices and renal function-related indices were compared between the two groups of patients. Results: The baseline data such as age, body mass index, retinopathy, and course of disease had no significant difference between the two groups ($P > 0.05$). After treatment, the waist-to-hip ratio, total body fat percentage, total body fat mass, total body lean mass, and A/G ratio were significantly decreased in both groups ($P < 0.05$) compared with before treatment, and were significantly lower in the combination group than in the single-drug group ($P < 0.05$). The combination group had significantly lower urinary transferrin (Tf), neutrophil gelatinase-associated lipocalin (NGAL) and tumor necrosis factor (TNF)-α, insulin-like growth factor 1 (IGF-1), retinol-binding protein (RBP), homocysteine (Hcy), brain natriuretic peptide (BNP), 24 h urinary albumin excretion ratio (UAER), urine albumin to creatinine ratio (UACR) and urinary liver-type fatty acid binding protein (L-FABP) levels, and higher secretory frizzled-related protein 5 levels than the single-drug group after treatment ($P < 0.05$). Conclusion: Liraglutide combined with dapagliflozin or empagliflozin treatment can effectively reduce the levels of Tf, NGAL and TNF-α in patients with T2DM, and improve the renal function in terms of IGF-1, RBP, Hcy, BNP, UAER, UACR, L-FABP, showing high treatment safety.

Keywords: Diabetic nephropathy, liraglutide,dapagliflozin, renal function, early lesions

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common endocrine system diseases in China, the incidence of which has increased significantly in recent years, and long-term hyperglycemia can cause various complications [1]. Diabetic nephropathy (DN) is a common complication of T2DM and the major cause of end-stage renal disease [2]. At present, the pathogenesis of DN is not clear. Insulin resistance and hyperglycemia-induced microcirculation disorders are critical factors leading to the occurrence of DN [3]. It has been reported that strict control of blood glucose levels has a positive effect on the prevention of DN and the improvement of renal function [4]. In the past few years, accumulating studies have pointed out that some patients can also achieve good blood sugar control through insulin injections and other medications, but some patients still develop DN with the progression of the disease [5]. This may be because insulin resistance can aggravate the disorder of glucose and lipid metabolism in the body, thereby affecting the release of certain cytokines and promoting the occurrence of kidney damage [6]. Liraglutide can effectively inhibit glucagon secretion and is

a commonly used hypoglycemic drug [7]. This drug has been found to reduce the rate of urinary protein excretion and improve renal function [8]. Both dapagliflozin and empagliflozin are novel diabetes drugs, which can effectively reduce urinary glucose reabsorption, thereby lowering glucose.

Evidence has shown that liraglutide combined with dapagliflozin (empagliflozin) treatment can effectively control blood glucose levels in patients with diabetes, but there are few studies on the protective effect of liraglutide combined with dapagliflozin on renal function in patients with diabetes [9]. In this study, patients with T2DM were included, and the preventive effect of combined treatment of the two drugs on DN was analyzed by observing indicators of early pathological changes related to DN.

Materials and methods

Baseline data

Three hundred patients (161 males and 139 females) with T2DM treated in our hospital from April 2019 to April 2020 were retrospectively selected. The patients were aged 45-63 years, with a mean age of (55.32±6.23) years. Inclusion criteria: (1) patients were 40-70 years old; (2) patients diagnosed with T2DM [10]; (3) patients signed an informed consent at diagnosis to allow the use of clinical data in further research. Exclusion criteria: (1) patients with severe liver insufficiency; (2) patients diagnosed with type 1 diabetes; (3) patients combined with severe infections of other organs; (4) patients who had recent episodes of severe diabetic complications; (5) patients with abnormal thyroid function.

The study had obtained the approval from the Ethics Committee of General Hospital of the Yangtze River Shipping (approval number NCT02546324).

Methods

According to different treatment regimens, the patients were divided into a single-drug group and a combination group. Patients in the single-drug group received subcutaneous injection of liraglutide [Novo Nordisk (China) Pharmaceutical Co., Ltd. sub-package, J20160037, batch number: 20190315], 0.6 mg/time, 1 time/d, for 1 week. The reaction of patients was observed. When there was no adverse reaction, the dose was adjusted to 1.2 mg/time, 1 time/d. The daily dose did not exceed 1.8 mg/d. The dosage was adjusted according to the patient's condition.

Patients in the combination group received either oral dapagliflozin (AstraZeneca Pharmaceuticals LP, J20170040, Lot No: 20190621, 10 mg/d, 1 time/d) or empagliflozin (Boehringer Ingelheim Pharma GmbH & Co. KG, H2020-1008, Lot No: 2019041, 10 mg/dose, 1 time/d) in addition to the regimen in single-drug group. After 4 weeks of treatment, the efficacy was compared between the two groups. The dosage was adjusted according to the patient's condition.

Outcome measurements

Medical records: Age, sex, and course of diabetic patients were recorded, and the course of diabetes referred to the time (years) from diagnosis to enrollment in this study.

Body-related indicators: The weight and height of the patients were measured with accuracy of 1 cm and 0.5 kg, respectively. Body mass index (BMI) = weight/height^2. Blood pressure was measured. Before measurement, patients avoided smoking, drinking alcohol, strong tea or coffee, etc., and systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice in a resting state using an electronic sphygmomanometer.

Retinopathy detection: A digital fundus camera (CR-2, Canon) was used to observe the fundus of the patients, and an ophthalmologist read the images to determine whether there was retinopathy.

Index of body fat: The waist circumference was measured with a soft ruler around the center of the umbilical cord at the end of the exhalation and the beginning of the inhalation. The gluteal circumference was measured horizontally with a soft ruler around the symphysis pubis and the most prominent point of the gluteus maximus. Body fat and bone mineral content were measured by dual-energy X-ray bone density absorptiometry. Measurement methods: Subjects lay flat on the measuring table with the head and

sight in the middle sagittal position, shoulders horizontal, arms attached in a radial pattern to the sides, legs straight and toes adducted. Fat content in the Android region refers to fat content in the abdomen area, with parietal line of the pelvis as the lower boundary, and 20% of the distance between the submaxillary line and the parietal line of the pelvis as the upper boundary. Fat content in the Gynoid region refers to fat content in the femoral region, with level of the greater trochanter as the upper boundary and twice the height of the Android region as the lower boundary. A/G ratio is calculated by percentage of area A fat/percentage of area G fat.

Blood tests: All patients were fasted for 12 hours, and blood sample was collected in the morning. Fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), total bilirubin (TBIL), serum creatinine (Scr), cystatin C (CysC) and uric acid (UA) were measured using a biochemical analyzer (Beckman Coulter UniCei Dxc 800). Hemoglobin A1c (HbA1c) was measured by an automatic glycation analyzer (Arkray HA-8160). The lymphocyte count and neutrophil count were measured by a routine blood test (Siemens Sysmex XE-2100). Neutrophil/lymphocyte ratio (NLR) was calculated based on the above results. All serum indicators were tested in our hospital.

Urine testing: Urine (1 mL) was collected using sterile tubes for measurement of Scr, immunoglobulin G (IgG), α1 microglobulin (α1MG), transferrin (Tf), N-acetyl-β-D-glucosaminidase (NAG) and urinary albumin. A BN2 protein analyzer (Siemens) was used to measure urinary albumin by bromocresol green, urinary Cr by alkaline picric acid, NAG by nitro phenol colorimetric assay, and urinary α1MG, IgG, and Tf by immunoturbidimetric assay. The urine albumin to creatinine ratio (UACR) was calculated based on urinary albumin and Cr assays. Another tube was used for interleukin (IL)-18, podocalyxin (PCX), 8-transyl deoxyguanosine (8-OHdG), tumor necrosis factor (TNF)-α, liver-type fatty acid binding protein (L-FABP), 24 h urinary albumin excretion ratio (UAER) and UACR determination. After centrifugation of urine at 2000 rpm for 10 min, the supernatant was obtained for enzyme-linked immunosorbent assays (ELISA). All assays were conducted strictly based on the kit instructions.

Serum assay: The blood samples were taken and centrifuged at 3500 rpm for 10 min to separate and obtain the serum, and the serum samples were assayed by ELISA for serum PCX, 8-OHdG, IL-18, TNF-α, neutrophil gelatinase-associated lipocalin (NGAL), brain natriuretic peptide (BNP), insulin-like growth factor 1 (IGF-1), secretory frizzled-related protein 5 (SFRP5), homocysteine (Hcy), retinol-binding protein (RBP) and estimated glomerular filtration rate (eGFR). All assays were conducted strictly based on the kit instructions.

Statistical methods

Statistical software SPSS 22.0 was used for data analysis. Continuous variables with normal distribution were represented by mean ± standard deviation ($\bar{x} \pm s$), and independent t test was used for comparison between two groups. Data with non-normal distribution were represented by median (25th percentile, 75th percentile). Continuous variables with normal distribution among multiple groups were analyzed using repeated measure analysis of variance, and post hoc comparisons were conducted by SNK test. Categorical variables were compared using Wilcoxon's rank-sum test or Chi-square test. $P < 0.05$ was taken as the difference being statistically significant. The software for graphs in the study was GraphPad Prism 8.

Results

Comparison of baseline data

No significant difference was observed in sex, age, BMI, course of disease, retinopathy, SBP, DBP, FBG, Scr, eGFR, TC, TG, LDL, HbA1c, Tf/Ucr, IgG/Ucr, PCX/Ucr, CysC, NGAL/Ucr, NAG/Ucr, α1MG/Ucr, 8-OHdG/Ucr, TBIL, UA, TNF-α/Ucr, IL-8 and NLR between the two groups ($P > 0.05$) (**Table 1**).

Comparison of body fat between the two groups

Compared with before treatment, the waist-to-hip ratio, total body fat percentage, total body fat mass, total body lean mass, and A/G ratio were significantly decreased in both groups after treatment ($P < 0.05$). The posttreatment waist-hip ratio, total body fat percentage, total body fat mass and A/G ratio in the combination

Table 1. Comparison of efficacy and safety ($\bar{x}\pm s$)

Index	Single-drug group	Combination group	t/χ^2	P
Sex				
Male	80 (53.33)	81 (54.00)	0.013	0.908
Female	70 (46.67)	69 (46.00)		
Age (years)	56.54±4.16	56.32±4.62	0.433	0.665
Body mass index (kg/m^2)	25.45±3.52	25.43±4.56	0.043	0.966
Course of disease (years)	7.32±1.21	7.33±1.31	0.069	0.945
Retinal lesions	58 (38.67)	57 (38.00)	0.014	0.905
Systolic blood pressure (mmHg)	135.89±13.11	137.78±12.63	1.272	0.205
Diastolic blood pressure (mmHg)	82.12±7.23	81.12±8.96	1.064	0.288
Fasting blood glucose (mmol/L)	8.35±1.21	8.36±1.09	0.075	0.940
Serum creatinine (μmol/L)	82.34±12.09	82.14±13.11	0.137	0.891
Estimated glomerular filtration rate (ml/min/1.73 m^2)	97.98±6.89	98.36±7.19	0.467	0.641
Total cholesterol (mmol/L)	4.76±1.01	4.82±1.04	0.507	0.613
Triglycerides (mmol/L)	1.58±0.23	1.56±0.24	0.737	0.462
Low-density lipoprotein (mmol/L)	2.95±0.87	2.96±0.84	0.101	0.919
Hemoglobin A1c (%)	9.21±2.12	9.12±2.03	0.375	0.708
Transferrin/urine creatinine (mg/g)	23.58±4.21	23.62±4.11	0.083	0.934
Immunoglobulin G/urine creatinine (mg/g)	45.19±4.83	45.63±5.11	0.766	0.444
Podocalyxin/urine creatinine (μ/g)	7.43 (2.32-15.12)	7.45 (2.32-15.32)	0.173	0.863
Cystatin C (mg/L)	0.82 (0.56-1.96)	0.83 (0.56-1.90)	0.087	0.931
Neutrophil gelatinase-associated lipocalin/urine creatinine (μg/g)	58.24 (12.32-121.34)	58.23 (12.42-101.67)	0.087	0.931
N-acetyl-β-D-glucosaminidase/urine creatinine (U/g)	37.62 (8.24-112.87)	37.56 (8.14-100.87)	0.520	0.604
α1 microglobulin/urine creatinine (mg/g)	51.86 (7.34-121.42)	51.88 (7.97-118.33)	0.173	0.863
8-Transyl deoxyguanosine/urine creatinine (μg/g)	27.42±4.45	27.43±4.32	0.020	0.984
Total bilirubin (mmol/L)	10.11 (6.53-15.43)	10.12 (6.53-15.34)	0.087	0.931
Uric acid (μmol/L)	312.32±30.23	309.31±31.23	0.848	0.397
Tumor necrosis factor-α/urine creatinine (ng/g)	15.13±2.15	15.24±2.11	0.447	0.655
Interleukin-18 (ng/g)	74.51 (20.14-141.54)	74.42 (20.22-141.24)	0.779	0.436
Neutrophil/lymphocyte ratio	2.21±0.45	2.13±0.38	1.664	0.097

Table 2. Comparison of total body fat between the two groups ($\bar{x}\pm s$)

Indicators	Single-drug group (n=150)		Combination group (n=150)	
	Before treatment	After treatment	Before treatment	After treatment
Body mass index (kg/m^2)	25.45±3.52	25.14±3.16	25.43±4.56	25.10±3.32
Waist-to-hip ratio (%)	0.89±0.11	0.81±0.13*	0.89±0.14	0.76±0.12$^{*,\#}$
Total body fat percentage (%)	29.34±2.14	28.15±2.34*	29.41±2.34	27.26±2.16$^{*,\#}$
Total body fat mass (kg)	1865.38±168.75	1697.84±214.96*	1876.26±206.78	1598.18±210.31$^{*,\#}$
Total body lean mass (kg)	5469.78±267.62	5317.34±254.19*	5489.47±251.36	5296.75±253.84*
A/G ratio (Visceral fat)	1.13±0.06	1.11±0.05*	1.14±0.05	1.07±0.06$^{*,\#}$

Note: Compared within group before treatment, $^*P < 0.05$; compared with the single-drug group at the same time, $^\#P < 0.05$.

group were significantly lower than those in the single-drug group ($P < 0.05$) (**Table 2**).

Comparison of biomarker levels

After treatment, the urinary levels of Tf, IgG, NGAL, and TNF-α were improved noticeably in both single-drug and combination groups ($P < 0.05$), and the levels of Tf, NGAL, and TNF-α were lower in the combination group than in the single-drug group ($P < 0.05$) (**Figure 1**).

Comparison of blood glucose and lipid levels

After treatment, FPG, HbA1c, TC, and TG levels in the combination group exhibited no signifi-

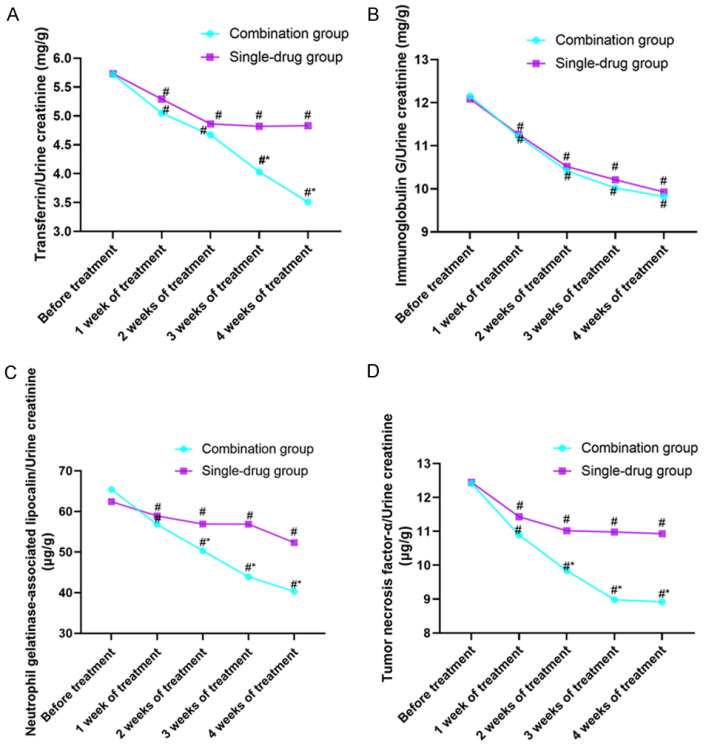

Figure 1. Urinary levels of biomarkers before and after treatment in both groups. A: Urinary transferrin; B: Immunoglobulin G; C: Neutrophil gelatinase-associated lipocalin; D: Tumor necrosis factor-α. Compared with the single-drug group, $^{*}P < 0.05$, compared with before treatment in the same group, $^{\#}P < 0.05$ (repeated measure analysis of variance, post hoc comparison performed by SNK test, inter-group comparison and intra-group comparison).

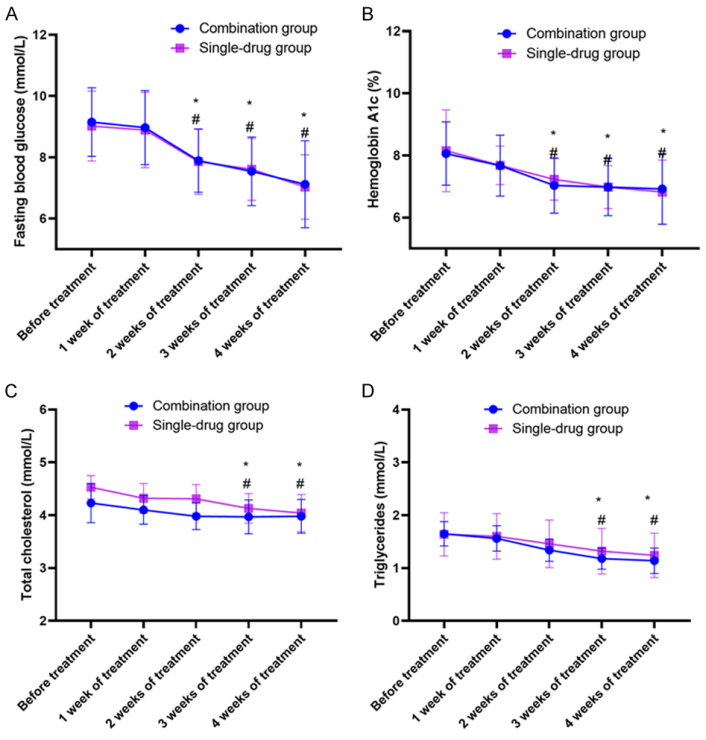

Figure 2. Blood glucose and lipid levels before and after treatment in both groups. A: Fasting blood glucose; B: Hemoglobin A1c; C: Total cholesterol; D: Triglycerides. Compared with the single-drug group, $^{*}P < 0.05$, compared with before treatment in the same group, $^{\#}P < 0.05$ (repeated measure analysis of variance, post hoc comparison performed by SNK test, inter-group comparison and intra-group comparison).

cant difference compared with those in the single-drug group ($P > 0.05$) (**Figure 2**).

Comparison of renal function levels

After treatment, the combination group showed lower IGF-1, RBP, Hcy, BNP, UAER, UACR and L-FABP levels and higher SFRP5 levels than the single-drug group ($P < 0.05$) (**Figure 3**).

Comparison of safety

The incidence of complications showed no significant difference between the two groups ($P > 0.05$) (**Table 3**).

Discussion

Liraglutide, dapagliflozin and empagliflozin are novel hypoglycemic drugs commonly used in clinical practice. A great number of studies have found that liraglutide and dapagliflozin (empagliflozin) can effectively lower the blood glucose of patients, and the combination of two can effectively improve the hypoglycemic effect [11]. However, few studies have been conducted on the protective effect of liraglutide combined with dapagliflozin (empagliflozin) on renal function [12, 13].

The degree of kidney injury is usually assessed by measuring microalbumin levels. Urine albumin alone has been found to cause underdiagnosis in approximately 20% of patients with diabetic kidney injury

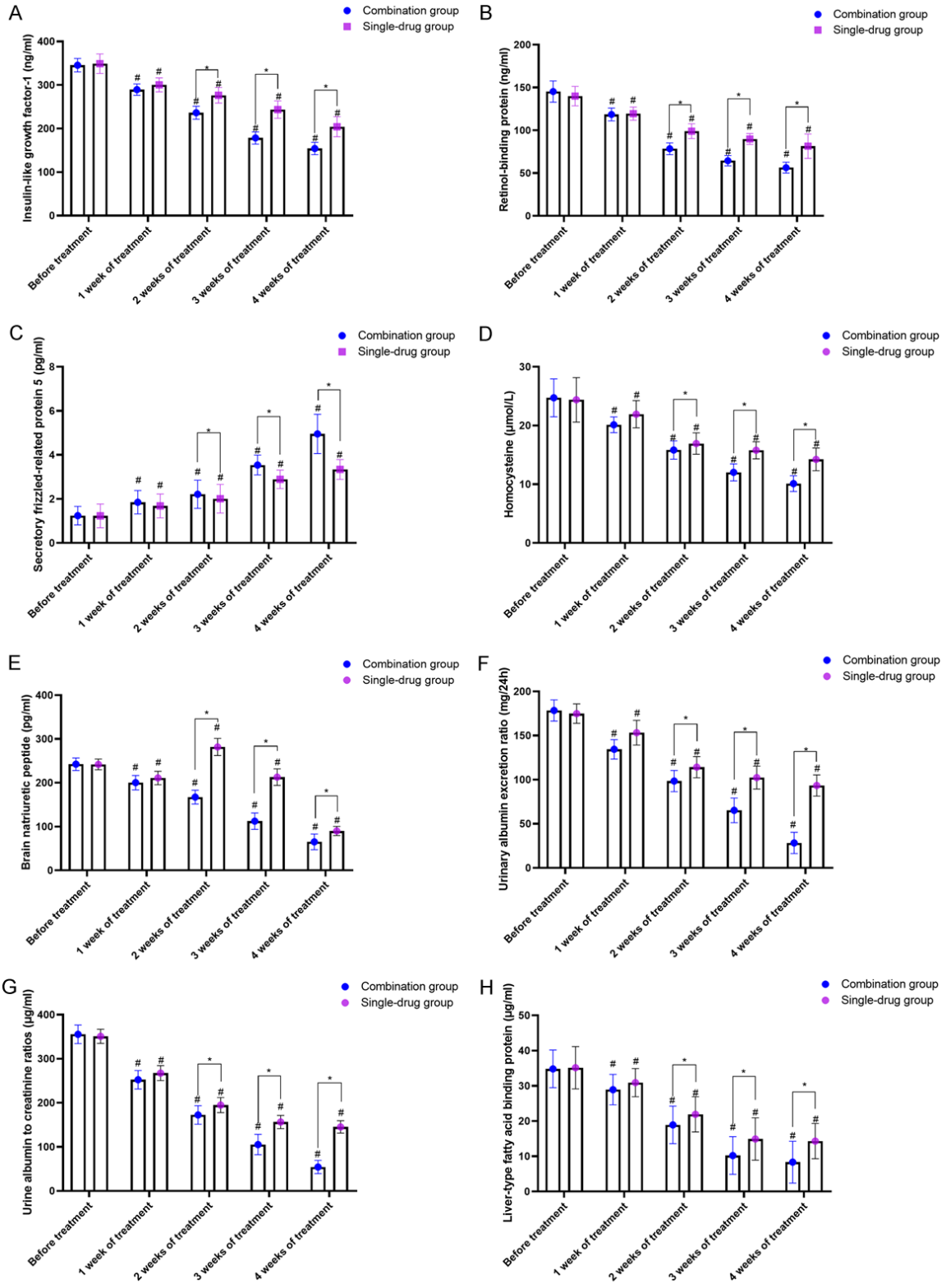

Figure 3. Levels of renal function indices before and after treatment in both groups. A: Insulin-like growth factor-1; B: Retinol-binding protein; C: Secretory frizzled-related protein 5; D: Homocysteine; E: Brain natriuretic peptide; F: 24 h urinary albumin excretion ratio; G: Urine albumin to creatinine ratios; H: Liver-type fatty acid binding protein. Compared with the single-drug group, $^{*}P < 0.05$, compared with before treatment in the same group, $^{\#}P < 0.05$ (repeated measure analysis of variance, post hoc comparison performed by SNK test, inter-group comparison and intra-group comparison).

Table 3. Analysis of treatment safety [n (%)]

Index	Combination group (n=150)	Single-drug group (n=150)	χ^2	*P*
Hypoglycemia	24 (16.00)	27 (18.00)	0.213	0.645
Inflammation of the reproductive and urinary tracts	3 (2.00)	5 (3.33)	0.585	0.444
Gastrointestinal tract symptoms	5 (3.33)	7 (4.67)	0.347	0.556
Diabetic ketoacidosis	0 (0.00)	0 (0.00)	-	-

[14, 15]. It has been found that some diabetic patients with normal urinary albumin levels still have renal injury [16-18]. In this study, the levels of Tf, IgG, NGAL and TNF-α were compared between the single-drug group and the combination group before and after treatment. We found that the combination group had lower urinary levels of Tf, NGAL and TNF-α than the single-drug group ($P < 0.05$), suggesting that liraglutide combined with dapagliflozin or empagliflozin could effectively reduce levels of Tf, IgG, NGAL and TNF-α and play a nephroprotective role. The effect of liraglutide, dapagliflozin and empagliflozin is to regulate blood glucose and lipid levels in diabetic patients, improve glucolipid metabolism of the body, and avoid complications of diabetes [19, 20]. In this study, the blood glucose and lipids were analyzed, and the results showed that both groups obtained favorable improvement in blood glucose and lipids, suggesting that both single-drug and combination therapies can achieve good glycemic control effect.

During the progression of DN, the levels of serum molecules are altered, and SFRP5 plays a protective role in renal function of patients with DN, inhibiting glomerular injury caused by oxidative stress and inflammatory response [21, 22]. IGF-1 is a crucial factor causing glomerular filtration dysfunction, while Hcy and RBP are filtered through the glomerulus, and patients with diabetic kidney injury are accompanied by glomerular damage, resulting in high levels of Hcy and RBP [23, 24]. BNP has a sodium-removal diuretic effect and is noticeably increased in patients with DN [25]. The results of this study found that the combination group showed lower levels of IGF-1, RBP, Hcy, BNP, UAER, UACR and L-FABP, and higher level of SFRP5 than the single-drug group after treatment ($P < 0.05$), suggesting that the combination of the two drugs can play a better nephroprotective role in maintaining renal function and reducing injury in diabetic patients. This study focused on the analysis of the significance of liraglutide combined with dapagliflozin or empagliflozin in the prevention of early DN and the changes of renal function indicators, and found that their clinical application is highly feasible. However, many clinical factors may affect the accuracy of the results, such as the general information of patients, the number of cases and the duration of the study. Therefore, more qualified samples should be included in the following research for further in-depth exploration, hoping to improve the accuracy of the research results and provide a theoretical basis for clinical treatment.

In conclusion, Tf, IgG, NGAL and TNF-α were predictive indicators for early DN, and liraglutide combined with dapagliflozin or empagliflozin could effectively decrease the levels of Tf, NGAL and TNF-α, and enhance the renal function, exhibiting high safety.

Acknowledgements

This work was supported by the 2019 Medical Research Project of Wuhan Health and Health Commission, "Discussion on the Therapeutic Effect and Relevant Mechanisms of Ligliptin on Non-alcoholic Fatty Liver in Type 2 Diabetic Patients" (Grant number WX19D11) and the Key Science and Technology Project of Changjiang River Administration of Navigation Affairs in 2019, "The Therapeutic Effect and Related Mechanisms of Ligliptin on Non-alcoholic Fatty Liver in Type 2 Diabetic Patients" (grant number 201910020).

Disclosure of conflict of interest

None.

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