The Effect of GLP-1 Receptor Agonist as Add-on Therapy to SGLT-2 Inhibitor on Albuminuria in Type 2 Diabetes with Chronic Kidney Disease

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Abstract

Background: The effectiveness GLP-1 receptor agonist as an add-on therapy to SGLT-2 inhibitor in reducing albuminuria in diabetic kidney disease remains largely underexplored. This trial aims to evaluate the impact of this dual therapy compared to SGLT-2 inhibitor alone on albuminuria reduction over 6 months in patients with type 2 diabetes and chronic kidney disease

Methods: This retrospective cohort study included patients with type 2 diabetes and albuminuria between January 2018 and December 2023. A total of 122 patients who received either SGLT-2 inhibitors alone or in combination with GLP-1 receptor agonists were included. The primary outcome was the difference in the mean percent change in the urine albumin-to-creatinine ratio (UACR) at 6 months. Secondary outcomes included changes in HbA1c, blood pressure, body weight, serum creatinine, estimated glomerular filtration rate (eGFR), and adverse events.

Results: The mean percent change in UACR from baseline was 7.26% (-21.84, 36.36) in the SGLT-2 inhibitor group and -5.43% (-28.1, 17.25) in the combination therapy group. The between-group difference was -12.7% (-48.8, 23.4) (P=0.491). While the combination group showed a trend toward HbA1c and blood pressure reductions, these differences did not reach statistical significance. Neither group had significant changes in body weight, serum creatinine, or eGFR. Adverse events were similar between the two groups.

Conclusion: Adding GLP-1 receptor agonist to SGLT-2 inhibitor did not significantly reduce albuminuria, blood pressure, or HbA1C after 6 months of follow-up in patients with diabetic kidney disease.

Keywords: DM; renal function; proteinuria; diabetic nephropathy; SGLT2i; GLP-1RA; CKD; DKD

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Received: 4 September 2024; Revised: 31 October 2024; Accepted: 1 November 2024

ผลของการได้รับยากลุ่ม GLP-1 Receptor Agonist เสริมกับยา SGLT-2 Inhibitor ต่อปริมาณอัลบูมินในปัสสาวะในผู้ป่วยเบาหวานชนิดที่ 2 ที่เป็นโรคไตเรื้อรัง

พลวุฒิ แจ่มฟ้า และ อรรถพล วนาเดช

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บทคัดย่อ

บทนำ: ปัจจุบันการศึกษาผลของการเพิ่มยาในกลุ่ม GLP-1 receptor agonist ในผู้ป่วยเบาหวานชนิดที่ 2 และเป็นโรคไตเรื้อรังที่ได้รับยา SGLT-2 inhibitor อยู่แล้ว ในการลดปริมาณอัลบูมินในปัสสาวะยังมีไม่เพียงพอ การศึกษานี้มีวัตถุประสงค์เพื่อประเมินประสิทธิภาพของการเพิ่มยา GLP-1 receptor agonist ให้กับผู้ป่วยที่ได้รับยา SGLT-2 inhibitor อยู่แล้วในการลดระดับอัลบูมินในปัสสาวะ เปรียบเทียบกับการได้รับยา SGLT-2 inhibitor แต่เพียงชนิดเดียว

ระเบียบวิธีวิจัย: การศึกษานี้เป็นการศึกษาย้อนหลังในผู้ป่วยนอกที่เป็นโรคเบาหวานชนิด 2 ที่มีโรคไตเรื้อรังและมีการรั่วของอัลบูมินในปัสสาวะระหว่าง เดือนมกราคม 2561 ถึง เดือนธันวาคม 2566 จำนวนทั้งหมด 122 ราย โดยแบ่งผู้ป่วยเป็น 2 กลุ่ม คือ กลุ่มที่ได้รับยา SGLT-2 inhibitor เพียงอย่างเดียว และกลุ่มที่ได้รับยา SGLT-2 inhibitor ร่วมกับยา GLP-1 receptor agonist โดยมีผลลัพธ์หลักคือความแตกต่างของการเปลี่ยนแปลงของปริมาณอัลบูมินในปัสสาวะภายหลังจากได้รับการรักษาเป็นระยะเวลา 6 เดือน ผลลัพธ์รองคือการเปลี่ยนแปลงของระดับ HbA1c, ความดันโลหิต น้ำหนักตัว ซีรั่มครีเอตินีน อัตราการกรองของไต และการเกิดภาวะไม่พึงประสงค์

ผลการวิจัย: กลุ่มที่ได้รับยา SGLT2 inhibitor เพียงอย่างเดียวมีค่าเฉลี่ยของการเปลี่ยนแปลงของปริมาณอัลบูมินในปัสสาวะหลังจาก 6 เดือนเมื่อเปรียบเทียบกับก่อนได้รับยาที่ร้อยละ 7.26 (-21.84, 36.36) ในขณะที่กลุ่มที่ได้รับยา SGLT2 inhibitor ร่วมกับ GLP-1 receptor agonist มีการเปลี่ยนแปลงที่ร้อยละ -5.43 (-28.1, 17.25) โดยมีความแตกต่างระหว่างกลุ่มอยู่ที่ร้อยละ -12.7 (-48.8, 23.4) (P=0.491) กลุ่มที่ได้รับยาผสมมีแนวโน้มของการลดลงของความดันโลหิต และ ระดับของ HbA1C แต่ไม่มีนัยสำคัญทางสถิติ นอกจากนี้ไม่พบการเปลี่ยนแปลงของน้ำหนักตัว ซีรั่มครีเอตินีน อัตราการกรองของไต และภาวะไม่พึงประสงค์

สรุป: ในการศึกษานี้การเพิ่มยากลุ่ม GLP-1 receptor agonist ให้กับผู้ป่วยที่มีโรคไตจากเบาหวานและได้รับยากลุ่ม SGLT2 inhibitor มาก่อนแล้ว ไม่สามารถช่วยลดระดับอัลบูมินในปัสสาวะ ความดันโลหิต หรือ ระดับ HbA1C ได้

คำสำคัญ: เบาหวานลงไต; โปรตีนรั่วในปัสสาวะ; ไตวาย; ยาเบาหวาน; ไตเสื่อม

Introduction

Diabetic kidney disease (DKD) is a common complication of diabetes. Despite the newer and more effective therapies, DKD frequently progresses to chronic kidney disease (CKD) and end-stage kidney disease (ESKD). Additionally, DKD substantially increases the risk of death from cardiovascular diseases such as ischemic heart disease and stroke.[1]

Albuminuria is commonly used to estimate the risk of CKD progression. Increased albuminuria is an indicator of the severity of DKD. A meta-analysis suggested that a 30% reduction in the urine albumin-creatinine

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ratio (UACR) is associated with a decreased risk of CKD progression, ESKD, and major adverse cardiovascular events.[2] Furthermore, elevated levels of albuminuria coupled with reduced estimated glomerular filtration rate (eGFR) are associated with a higher risk of cardiovascular disease and mortality.[3]

In recent years, several drugs, including sodium-glucose co-transporter-2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA), have shown efficacy not only in reducing blood glucose levels but also in decreasing albuminuria through distinct mechanisms. These medications offer new avenues for managing DKD.[3]

SGLT-2i can effectively reduce blood glucose levels by inhibiting the reabsorption of both sodium and glucose via SGLT-2 co-transporters in the proximal renal tubules. This action results in an increase in glucose concentration in the urine. The higher urine glucose concentration stimulates the macula densa to induce afferent arteriole vasoconstriction, thereby reducing pressure in the kidney glomeruli. Consequently, this mechanism leads to a decrease in albuminuria. Additionally, the increased supply of oxygen to the kidney tubular cells enhances fuel utilization and modifies the balance of renal metabolism.[1,4]

GLP-1 RA is another class of drugs that can effectively reduce blood glucose levels. GLP-1, an incretin hormone, is secreted from L-cells lining the small intestine, stimulated by oral fat and sugar intake. GLP-1 stimulates neogenesis and inhibits apoptosis of beta cells in the pancreas, leading to increased insulin secretion without causing hypoglycemia. In the kidneys, GLP-1 inhibits the sodium–hydrogen exchanger 3 in the proximal renal tubules, resulting in natriuresis and diuresis, which reduces intraglomerular pressure. Additionally, GLP-1 helps reduce oxidative stress, inflammation, and glucose toxicity in the proximal renal tubules, ultimately reducing albuminuria.[1,5,6]

There is insufficient information and evidence to support that using SGLT-2i in combination with GLP-1 RA can further reduce albuminuria. This study aims to determine the efficacy of adding GLP-1 RA to SGLT-2i in reducing albuminuria in patients with DKD.

Methods

Study design

This retrospective cohort study was conducted at Police General Hospital, Bangkok, Thailand. The study conforms with the principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of Police General Hospital with a waiver of signed informed consent.

Population

The present study used the data from the electronic medical record system between January 2018 and December 2023. The inclusion criteria were: age ≥ 18 years, type 2 diabetes with albuminuria ≥ 30 mg/g, eGFR ≥ 20 ml/min/1.73 m², treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers at the maximum tolerated doses, and use of SGLT2 inhibitors for at least 2 months. Exclusion criteria included the presence of other conditions known to cause albuminuria (e.g., type 1 diabetes, pregnancy, or active malignancy), prior treatment with GLP-1 RA before SGLT-2i, and missing or incomplete data.

Exposure

All diabetic patients who met the inclusion criteria were divided into two groups. Group 1 consisted of patients receiving only SGLT-2i (dapagliflozin 10 mg, empagliflozin 10 mg, or luseogliflozin 2.5 mg daily). Group 2 included patients who had been treated with SGLT-2i for at least 2 months before the addition of a GLP-1 RA (dulaglutide 0.75 mg, semaglutide 0.5 mg, liraglutide 1.2 mg subcutaneously once a week, or semaglutide 7 mg orally once daily). The follow-up period after the introduction of the GLP-1 receptor agonist was 6 months.

Outcomes

The primary outcome was the difference in the change in UACR between the two groups. Secondary outcomes included differences in the changes in HbA1c, systolic and diastolic blood pressure, body weight (BW), and eGFR. Differences in adverse events, such as dehydration, renal events, hypoglycemia, bone fractures, limb amputations, and diabetic ketoacidosis, were also investigated.

Data collection

Demographic and laboratory data were obtained from the electronic medical record system. Drug prescribing information was sourced from the Drug Information Services. The stages of CKD were determined based on eGFR and albuminuria levels, following the Kidney Disease Improving Global Outcomes (KDIGO) criteria. Adverse events, including acute kidney injury, dehydration, and hypoglycemia, were identified using ICD-10 CM codes. All data were de-identified to protect patient privacy and confidentiality.

Sample size calculation

A survey of data on changes in UACR among diabetic patients from Police Hospital was conducted. Random samples of 10 individuals per group were selected based on the inclusion criteria. The results showed that the mean percentage change in UACR was -36.4% ± 6.52% for the group receiving SGLT-2i alone, while the group receiving SGLT-2i combined with GLP-1 RA had a mean percentage change in UACR of -43.4% ± 17.23%. The study used an alpha error (α) of 0.05 and a beta error (β) of 0.20 (power of 80%). The calculated sample size was 55 patients per group. Accounting for a 10% data loss rate, the required sample size increased to 61 patients per group, resulting in a total of 122 patients for the study.

Statistical analysis

Pairing between the two groups was conducted to control for confounding variables. The criteria for the pairing process involved strict matching to ensure comparability. A one-to-one pairing strategy was employed, using the following variables for matching: sex, levels of albuminuria (A2 and A3), age difference (≤ 1 year), body mass index (BMI) difference (≤ 1 kg/m²), and systolic blood pressure difference (≤ 10 mmHg).

Categorical variables were presented as numbers and percentages, while continuous variables were expressed as mean with standard deviation or median with interquartile range. Between-group comparisons were performed using the Chi-square test or Fisher's exact test for categorical variables and the Student's t-test or Mann-Whitney U test for continuous variables.

A linear marginal model with mixed effects was employed, using restricted maximum likelihood regression to analyze repeated measures. Within-patient correlations were accounted for using an unstructured covariance pattern. Two-tailed P-values < 0.05 were considered statistically significant. All data analyses were performed using Stata 18.0 (Stata Corp., College Station, TX, USA).

Results

Study population and patient characteristics

The study flow diagram is shown in Figure 1. Among 758 patients diagnosed with type 2 diabetes and received SGLT-2i, a total of 139 patients met the inclusion and exclusion criteria. After a pair matching, 122 patients were included in the final analysis.

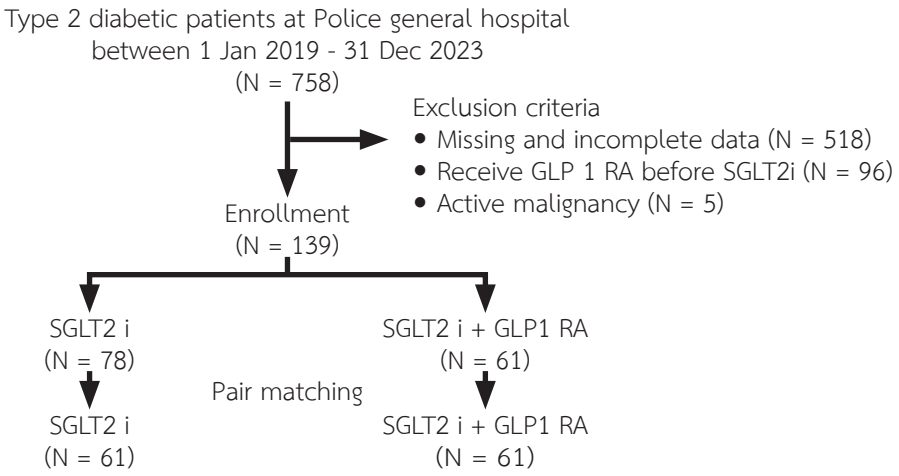

Figure 1 Study flow diagram

SGLT2i, SGLT-2 inhibitors; GLP1 RA, GLP1 receptor agonists

Table 1 presents the baseline characteristics of all patients according to the interventions. There were no significant differences between the two groups in terms of sex, BW and BMI, blood pressure, HbA1c, eGFR, or underlying diseases. The group receiving combined SGLT-2i and GLP-1 RA showed a trend toward a higher percentage of male patients and greater BW, but these differences were not statistically significant.

Table 1 Baseline characteristics of all participants by intervention group

Parameters	All (N=122)	SGLT-2i (N=61)	SGLT-2i + GLP-1 RA (N=61)	P-value
Male sex (N/%)	74 (61)	32 (53)	42 (70)	0.095
Age, years	66.2±11.2	68.1±11.3	64.2±10.9	0.055
Body Weight, kg	74.9±14.9	72.5±14.1	77.4±15.5	0.067
Body mass index, kg/m^2	28.2±4.2	27.6±4.3	28.8±4.1	0.108
Blood pressure, mmHg				
Systolic blood pressure	136.1±14.6	136.9±14.5	135.1±14.2	0.401
Diastolic blood pressure	72.9±11.6	71.6±11.1	74.1±12.0	0.233
HbA1c, %	7.83±1.55	7.60±1.6	8.1±1.5	0.138
eGFR (ml/min/1.73 m^2) (N/%)	65.3±21.8	64.3±20.5	66.4±23.2	0.601
≥90	66 (54)	33 (54)	33 (54)	0.212
60 - 89	30 (25)	14 (23)	16 (26)	-
45 - 59	22 (18)	14 (23)	8 (13)	-
30 - 44	3 (2)	0	3 (5)	-
15 - 29	1 (1)	0	1 (2)	-
UACR (mg/g) (N/%)	195.8 (66.7-636)	165.3 (53.8-533.5)	288.9 (89.0-1076.0)	0.095
30-299	73 (60)	42 (70)	31 (51)	0.064
300-3000	49 (40)	19 (30)	30 (49)	-
Underlying diseases (N/%)				
Hypertension	122 (100)	61 (100)	61 (100)	1.000
Cardiovascular disease	33 (27.0)	14 (22.9)	19 (31.2)	0.415
Dyslipidemia	98 (80.3)	53 (86.9)	45 (73.8)	0.110
Hypothyroidism	5 (4.1)	4 (6.6)	1 (1.6)	0.365
Benign prostatic hyperplasia	3 (2.5)	1 (1.6)	2 (3.3)	1.000
Medications (N/%)				
Alpha-blockers	32 (26.2)	16 (26.2)	16 (26.2)	1.000
Beta blockers	38 (31.1)	14 (22.9)	24 (39.3)	0.078
Mineralocorticoid RA	7 (57.4)	3 (4.9)	4 (6.6)	1.000
Calcium channel blockers	68 (55.7)	34 (55.7)	34 (55.7)	1.000
Thiazides	7 (5.74)	2 (3.28)	5 (8.20)	0.439
Vasodilators	14 (11.5)	4 (6.6)	10 (16.4)	0.154
Statin	107 (87.7)	55 (90.2)	52 (85.3)	0.583
Ezetimibe	25 (20.5)	13 (21.3)	12 (19.7)	0.980

Table 1 Baseline characteristics of all participants by intervention group (continued)

Parameters	All (N=122)	SGLT-2i (N=61)	SGLT-2i + GLP-1 RA (N=61)	P-value
Levothyroxine	5 (4.1)	4 (6.6)	1 (1.6)	0.365
Insulin	59 (48.4)	27 (44.3)	32 (52.5)	0.469
Metformin	90 (73.8)	46 (75.4)	44 (72.1)	0.837
Sulfonylureas	43 (35.2)	17 (27.9)	26 (42.6)	0.129
DPP4i	45 (36.9)	26 (42.6)	19 (31.2)	0.260
Thiazolidinediones	19 (15.6)	12 (19.7)	7 (11.5)	0.318

Data are presented as mean ± standard deviation or median (interquartile range)

SGLT-2i, SGLT-2 inhibitor; GLP-1 RA, GLP-1 receptor agonist; eGFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio; RA, receptor antagonists; DPP4i, Dipeptidyl Peptidase IV inhibitors

The changes in UACR, blood pressure, and other laboratory data at 6 months are presented in **Table 2**. A reduction in UACR was observed in the group receiving combined SGLT-2i and GLP-1 RA; however, the changes within and between groups did not reach statistical significance (**Figure 2**). Similarly, the reduction in HbA1c and blood pressure appeared more pronounced in the combination group, but these differences were also not significant. Neither group exhibited significant changes in BW, BMI, serum creatinine, or eGFR.

Table 2 Changes in albuminuria, blood pressure, and laboratory data

Parameters	Group	Time	Mean (95% CI)	Within-group changes Mean % changes from baseline (95% CI)	Between-group change % difference from SGLT-2i (95% CI)	P- value
UACR, mg/g	SGLT-2i	Baseline	165.3 (53.8-533.5)			
		Follow-up	89.5 (46.9-585.6)	7.26 (-21.84, 36.36)		
	GLP-1 RA+SGLT-2i	Baseline	288.9 (89-1076)			
		Follow-up	167.1 (50-771.5)	-5.43 (-28.1, 17.25)	-12.7(-48.8, 23.4)	0.327
HbA1c, %	SGLT-2i	Baseline	7.6±1.6			
		Follow-up	7.7±1.7	0.11 (-0.18, 0.41)		
	GLP-1 RA+SGLT-2i	Baseline	8.1±1.5			
		Follow-up	7.7±1.5	-0.37 (-0.81, 0.06)	-0.49 (-0.99, 0.03)	0.064
SBP, mmHg	SGLT-2i	Baseline	136.9±14.5			
		Follow-up	138.3±15.6	1.3 (-2.7, 5.4)		
	GLP-1 RA+SGLT-2i	Baseline	135.1±14.2			
		Follow-up	133.4±12.7	-1.7 (-5.5, 2.2)	-3.1 (-8.5, 2.4)	0.276

Table 2 Changes in albuminuria, blood pressure, and laboratory data

Parameters	Group	Time	Mean (95% CI)	Within-group changes Mean % changes from baseline (95% CI)	Between-group change % difference from SGLT-2i (95% CI)	P- value
DBP, mmHg	SGLT-2i	Baseline	71.6±11.1			
		Follow-up	70.7±12.4	-1.04 (-4.21, 2.11)		
	GLP-1 RA+SGLT-2i	Baseline	74.1±12.0			
		Follow-up	74.1±12.4	0 (-3.16, 3.16)	1.05 (-3.33, 5.43)	0.638
BW, kg	SGLT-2i	Baseline	72.5±14.1			
		Follow-up	71.9±13.9	-0.6 (-1.3, 0.2)		
	GLP-1 RA+SGLT-2i	Baseline	77.4±15.5			
		Follow-up	77.3±15.7	-0.6 (-1.4, 0.3)	0.03 (-1.07, 1.13)	0.953
eGFR,	SGLT-2i	Baseline	64.3±20.5			
ml/min/1.73m^2		Follow-up	60.9±20.4	-3.4 (-6.4, -0.5)		
	GLP-1 RA+SGLT-2i	Baseline	66.4±23.2			
		Follow-up	64.2±22.8	-2.2 (-5.1, 0.6)	1.2 (-2.8, 5.2)	0.555
Cr, mg/dL	SGLT-2i	Baseline	1.13±0.35			
		Follow-up	1.17±0.38	0.04 (0.00, 0.08)		
	GLP-1 RA+SGLT-2i	Baseline	1.19±0.40			
		Follow-up	1.24±0.45	0.05 (-0.01, 0.10)	0.01 (-0.06, 0.07)	0.818

GLP-1 RA, GLP-1 receptor agonist; SGLT-2i, SGLT-2 inhibitor; CI, confidence interval; UACR, urine albumin-creatinine ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; BW, body weight; Cr, creatinine; eGFR estimated glomerular filtration rate

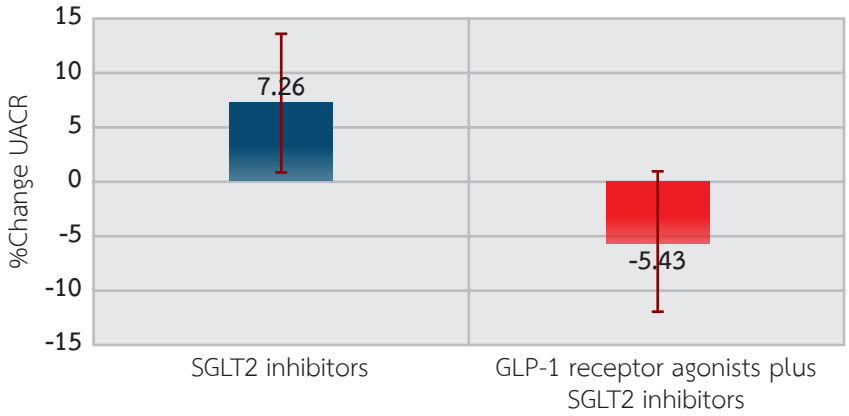

Figure 2 Box plot graph of the change in urine albumin/creatinine ratio at 6 months
UACR, urine albumin-creatinine ratio

Adverse events are summarized in **Table 3**. No serious adverse events occurred in either group. Hypoglycemia was observed more frequently in the combination group; however, the hypoglycemic symptoms were rated as mild, and no hospital admissions were required. The doses of hypoglycemic agents were adjusted, except for those of SGLT-2i or GLP-1 RA. One patient in the SGLT-2i group developed mild dehydration, while another in the same group experienced elevated AST and ALT levels due to hepatitis B virus infection. A urinary tract infection was reported in one patient in each group.

Table 3 Adverse events during the follow-up

Adverse events	SGLT-2 inhibitors (N=61)	SGLT-2 inhibitors + GLP-1 receptor agonists (N=61)
Urinary tract infection	1 (1.6%)	1 (1.6%)
Acute kidney injury	1 (1.6%)	1 (1.6%)
Dehydration	1 (1.6%)	0
Ketoacidosis	0	0
Hepatitis	1 (1.6%)	0
Amputation	0	0
Fracture	0	0
Hypoglycemia	1 (1.6%)	3 (4.9%)

Discussion

In this small retrospective cohort study of patients with type 2 diabetes and albuminuria, combination therapy with GLP-1 RA and SGLT-2i resulted in a non-significant reduction in albuminuria compared to SGLT-2i alone. The combination group also showed a tendency toward improved glycemic and blood pressure control. There were no differences in BW, BMI, serum creatinine, or eGFR between the two treatment groups.

In kidney outcome trials involving diabetic patients with impaired kidney function and albuminuria, GLP-1 RA have been shown to reduce the risk of kidney disease progression by lowering albuminuria.[7-13] Similarly, SGLT-2i have also been shown to slow CKD progression.[14-16] Therefore, it is possible that combining these two types of medications could provide an additive benefit in reducing albuminuria and CKD progression.

The DECADE trial, a randomized, placebo-controlled crossover trial, evaluated the effect of combined dapagliflozin and once-daily exenatide in participants with type 2 diabetes and albuminuria.[17] A mean reduction in UACR of 26% was observed during the combination therapy period. Similarly, in the DECREASE trial, a randomized, double-blind, placebo-controlled clinical trial in obese patients with type 2 diabetes, a 32% reduction in UACR was observed in the group receiving combined dapagliflozin and twice-daily exenatide after 16 weeks.[18] Another randomized open-label, placebo-controlled, double-blind, parallel study involving 60 individuals with type 2 diabetes and albuminuria reported a 22% reduction in UACR from baseline in the combined empagliflozin and semaglutide group.[19]

In the present study, the reduction in albuminuria was small and non-significant. This difference may stem from the variable efficacy of different drugs within the same class. The GLP-1 RA used in this study were dulaglutide, semaglutide, and liraglutide, whereas exenatide was used in other studies.[20] Additionally, the difference in dosage may also play a role. For example, in the study that used semaglutide, the prescribed dose was 1 mg weekly, while the dose in our study was 0.5 mg weekly.

The larger reduction in albuminuria observed in the combination group in our study could be attributed to the higher baseline albuminuria. The albuminuria-lowering effect of GLP-1 RA may be more pronounced in individuals with higher levels of albuminuria.[18-19,21-23] Evidence from the ELIXA trial supports the efficacy of GLP-1 RA in reducing albuminuria, particularly in patients with higher baseline levels. For instance, lixisenatide reduced albuminuria by 2% in patients with normoalbuminuria and 39% in patients with macroalbuminuria.[21] Conversely, the SEMPA trial, which used the combination of empagliflozin and semaglutide in patients with normal albuminuria, found no reduction in albuminuria compared to empagliflozin alone.[24] This lack of reduction may be due to overlapping effects on blood pressure and BW when adding GLP-1 RA to SGLT-2i.

In the present study, participants were enrolled based on a recent measurement of albuminuria (≥ 30 mg/g), with 60% having microalbuminuria. This characteristic may have contributed to the lack of albuminuria-lowering effect. Additionally, the albuminuria level was already low in the SGLT-2 inhibitor group, resulting in a less pronounced difference.

The metabolic benefits of combining GLP-1 RA and SGLT-2i are well established. For instance, the DURATION-8 and SUSTAIN-9 trials demonstrated reductions in systolic blood pressure, HbA1c, and BW in the combination group compared to SGLT-2i alone.[25,26] In the present study, we observed reductions in HbA1c and blood pressure in the combination group, though the between-group differences did not reach statistical significance. The relatively low baseline systolic blood pressure may have limited the potential for further reductions. Additionally, the long duration of diabetes in our patients suggests the presence of calcified vascular beds and reduced vascular elasticity, which may diminish the antihypertensive effects of GLP-1 RA.

The limitations of this study include its retrospective design, which may introduce biases and confounders. The sample size was small, and the follow-up duration may have been too short to assess CKD progression. However, the strength of this study lies in its use of real-world data, making the findings highly generalizable to the broader population.

In conclusion, the addition of GLP-1 RA to SGLT-2i did not significantly reduce albuminuria, blood pressure, or HbA1c over a 6-month follow-up period in patients with DKD. Additionally, there were no differences in the adverse events reported between the two groups.

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