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Evaluation of effects of glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors on estimated glomerular filtration rate, albuminuria and weight in diabetic kidney disease: A prospective cohort study

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A R T I C L E   I N F O

A B S T R A C T

Introduction: Albuminuria and baseline estimated glomerular filtration rate (eGFR) are the main predictors for progression of diabetic kidney disease (DKD).
Objectives: The objectives of the study were to assess the effects of GLP1-RA (glucagon-like peptide-1 receptor agonists) and SGLT2i inhibitors therapy on estimated GFR, albuminuria, and weight in patients with DKD stage 3 and 4.
Patients and Methods: This was a prospective cohort study of patients with stage 3 and 4 DKD over 6 months at Basra teaching hospital from November 1, 2020, to May 1, 2020. Baseline weight, UACR (urine albumin creatinine ratio), and eGFR were measured, and 6-months values were assessed between and within the group.
Results: The baseline characteristics for the GLP-1 RA (GLP-1 receptor agonists) versus SGLT2i (sodium-glucose co-transporter-2 inhibitors) groups were mean ages 65 years versus 62.5 years, male (54.5% versus 50%), median weight (75 versus 80 kg), median eGFR (23.5 versus 39 ml/min/1.73 m^2) and median UACR (925 mg/g versus 327 mg/g). In the GLP-1 RA group, after 6-months of therapy, there was 32% increase in eGFR ($P < 0.001$), 29% decrease in UACR ($P < 0.001$) and 4.5% decrease in weight while in the SGLT2i group, there was 4.5% decrease in eGFR ($P = 0.345$), 34% decrease in UACR ($P < 0.001$) and 2.8% decrease in weight ($P = 0.005$). With cox-regression analysis, the HR for eGFR decline with SGLT2i therapy was 3.25 (95% CI: 1.1-9.97; $P = 0.039$).
Conclusion: GLP-1 RA, compared to SGLT2i therapy, caused an increase in eGFR in stages 3 and 4 CKD and caused more weight reduction but slightly less albuminuria reduction.

Implication for health policy/practice/research/medical education:
Evaluation of the effectiveness of GLP1-RA (glucagon-like peptide-1 receptor agonists) and SGLT2i (sodium-glucose co-transporter-2 inhibitors) on albuminuria, weight, and estimated glomerular filtration rate (eGFR) in patients with stages 3 and 4 diabetic kidney disease (DKD) showed more weight and preservation of eGFR in stage 4 CKD (chronic kidney disease) with GLP1-RA compared to SGLT2i which showed more albuminuria reduction and eGFR preservation in stage 3 CKD.

Introduction

Diabetes mellitus accounts for approximately 50% of incident CKD (1). Tight glycemic control slows progression of diabetic kidney disease (DKD) as seen in the ADVANCE-ON study, but at the expense of hypoglycemia (2). Independent risk factors for CKD progression are albuminuria and reduced estimated glomerular filtration rate (eGFR) (3). Albuminuria typically precedes and accelerate GFR decline (4). Both albuminuria and eGFR decline are correlated with an increased hazards of

adverse cardiovascular and renal outcomes and mortality (5). Reduction in albuminuria by 30% is associated with decrement risk of renal failure by 1% over 10 years (6). Both GLP-1 RA and SGLT2i therapy reduce progression of microalbuminuria to macroalbuminuria by 20%-30% and progression of macroalbuminuria by 30%-40% (7,8). The SGLT2i showed reduction in eGFR decline in albuminuric CKD whereas only dulaglutide in the REWIND trial reduces progression in albuminuric CKD (9, 10). The SGLT2i may be initiated in patients with a baseline eGFR >30 mL/min/1.73 m²; two studies are undergoing addressing the efficacy and safety of SGLT2i initiation in patients with eGFR <30 mL/min/1.73 m²; DAPA-CKD) and EMPA-Kidney. GLP-1 RA may be used If there are contraindications for the use of SGLT2i as in stage 4 CKD or intolerance to SGLT2i.

Objectives

Our study was to evaluate the effects of GLP-1 RA and SGLT2i therapy on weight and kidney outcome measures, including eGFR and Urine albumin/creatinine ratio (UACR), in patients with DKD stages 3 and 4.

Patients and Methods

Study design

This study was a prospective cohort conducted on patients with DKD stages 3 and 4 who consulted outpatient clinic at Basra teaching hospital from November 1, 2020, to May 1, 2020, and received routine treatment with GLP-1 RA and SGLT2i. The study was approved by the ethical committee of the University of Basra and Iraqi Ministry of Health. Two groups were studied, the first 38 patients received SGLT2i, and the second 22 patients received GLP-1 RA. A propensity match score was used to reduce the impact of selection bias in an observational study and 2 groups with 22 patients in each were analyzed. Liraglutide has initiated at a dose of 0.6 mg subcutaneous injection and escalated to 1.2 mg and dapagliflozin was initiated at a dose of 10 mg orally. Baseline and serial measurement (1, 3 and 6 months) of weight, UACR and eGFR was done. Drugs were stopped if there was >50% decline in eGFR.

Patients ≥ 18 years old with DKD stage 3 and 4 with micro- and macroalbuminuria were included in the study. Patients AKI, CKD stage 5 on no dialysis, end-staged kidney disease (ESKD) on dialysis therapy and kidney transplantation were excluded from the study.

Definitions and measurements

Chronic kidney disease (CKD) was defined as eGFR less than 60 mL/min/1.73 m², CKD 3 was defined as eGFR of 30-60 mL/min/1.73 m², and CKD stage 4 was defined as eGFR of 15-30 mL/min/1.73 m² (estimated GFR was calculated using the CKD-EPI equation) (11). Hypertension was defined as BP > 130/80 mm Hg according to American Heart Association guidelines or patients on antihypertensive medications (12). Coronary artery disease was defined as positive treadmill test or stress echocardiogram or CT coronary angiography or percutaneous intervention (13). Heart failure with preserved ejection fraction (HFpEF) was defined as ejection fraction of >50% and heart failure with reduced ejection fraction (HFrEF) was defined as ejection fraction of <40% (14). UACR was classified as microalbuminuria if 30-300 mg/g and macroalbuminuria if >300 mg/g (15).

Covariates

Patients' demographics and history of chronic diseases were collected. Echocardiography was reviewed to classify patients with HFrEF and HFpEF. Baseline serum creatinine was used to classify stages of CKD into stage 3 or 4. Serum creatinine was measured by modified Jaffe colorimetric method. Urine albumin/creatinine ratio was measured by immunonephelometry method. Percent changes per patient's eGFR for each therapy per CKD status was calculated by the following formula: (6-months eGFR – baseline eGFR)/baseline eGFR × 100.

Outcomes

The outcome of the study was to estimate the effects of GLP- RA and SGLT2i therapy on eGFR, UACR and weight after 6-months duration of treatment.

Statistical analysis

The assumption of normality of the continuous variables were analyzed using Shapiro-Wilk test. Propensity score was used to match the 2 groups of therapy to reduce the selection bias. Comparisons between the two groups of therapy for the unmatched and matched groups were conducted by Mann-Whitney U test categorical variables and Kruskal-Wallis test for continuous variables. Wilcoxon signed-rank test was used for comparison between median eGFR, weight and UACR changes before and after six months of therapy. A one-way analysis of covariance (ANCOVA) was conducted to determine statistically significant difference between therapy (GLP-1 RA and SGLT2i) on six-month eGFR controlling for baseline eGFR. Post-hoc analysis was used to examine the mean differences in 6-month eGFR between the two groups of therapy. Cox-regression was performed to show the hazard ratio (HR) of decline eGFR among patients on SGLT2i therapy. A P value <0.05 was considered statistically significant. Statistical analysis was conducted using SPSS version 25.

Results

A total of 44 patients with DKD, 22 patients in each group of therapy, were studied. Only one patient in the SGLT2i group discontinued treatment due to doubling serum creatinine. Table 1 shows the baseline characteristics of the patients; for GLP-1 RA versus SGLT2i groups, the mean age was 65 years versus 62.5 years, more males in 54.5% versus 50%, less weight (75 kg versus 80 kg), more smokers

(45.5% versus 31.8%) and fewer cardiovascular diseases apart from similar HTN frequency. GLP-1 RA therapy has been more frequently in stage 4 CKD and SGLT2i therapy has been used more frequently in stage 3 CKD. Baseline eGFR was lower in the GLP-1 RA group compared to the SGLT2i group (23.5 versus 39, $P<0.001$) and baseline UACR was lower in the SGLT2I group compared to the GLP-1 RA group (327 versus 925, $P=0.004$).

Table 2 shows the effects of 6-months therapy on the outcome variables, with GLP-1 RA therapy, there was 32% increase eGFR ($P<0.001$), 29% decrease UACR ($P<0.001$) and 4.5% decrease weight ($P<0.001$) while with SGLT2i therapy, there was 4.5% decrease eGFR ($P = 0.345$), 34% decrease UACR ($P<0.001$) and 2.8% decrease weight ($P=0.005$).

One-way ANCOVA test
There was a significant effect of therapy on 6-months eGFR after controlling for baseline eGFR, F(2, 41) = 11.71 ($P<0.001$). Also, there was a significant effect of therapy on eGFR differences of 6-months eGFR from baseline eGFR after controlling for baseline eGFR, F(1, 41) = 4.34, $P = 0.044$.

Post hoc
For the main effect of therapy, the mean of six-month eGFR for GLP-1 RA (39.16 ± 75.77) was significantly larger than for SGLTI2i (27.47 ± 75.77) ($P=0.044$).

Cox regression
The HR for decrease eGFR in the SGLT2i therapy group was 3.25 (95% CI: 1.1,9.97; $P=0.039$) compared to GLP-1 RA therapy.

Figure 1 shows the percentage of changes in eGFR per CKD status. With GLP-1 RA therapy, 100% of CKD 3 and 80% of CKD 4 showed improvement in eGFR and with SGLT2i therapy, 41.2% of CKD3 and 40% of CKD 4 showed improvement in eGFR.

The median baseline and serial eGFR values for both therapies during treatment duration were illustrated in Figure 2. GLP-1 RA showed a substantial increase in eGFR during therapy and SGLT2i showed a major decrease in

Table 1. Baseline characteristics of the study cohort before and after propensity match score

Characteristics	GLP-1 RA (n=22)	SGLT2i (n=38)	P value	GLP-1 RA (n=22)	SGLT2i (n=22)	P value
Age (y), mean ± SD	65 ± 9.4	65.4 ± 9.3	0.912	65 ± 9.4	62.5 ± 8.9	0.361
Male, No. (%)	12 (54.5)	21 (55.3)	0.957	12 (54.5)	11 (50)	0.763
Weight (kg), No. (%)	75 (70, 81)	80 (70, 90)	0.599	75 (70, 81)	80 (69, 92)	0.573
Smoking, No. (%)	10 (45.5)	14 (36.8)	0.512	10 (45.5)	7 (31.8)	0.353
HTN, No. (%)	21 (95.5)	36 (94.7)	0.902	21 (95.5)	21 (95.5)	1.000
HFpEF, No. (%)	16 (72.7)	30 (78.9)	0.583	16 (72.7)	19(86.4)	0.262
HFrEF, No. (%)	4 (18.2)	10 (26.3)	0.473	4 (18.2)	6 (27.3)	0.472
CAD, No. (%)	9 (40.9)	17 (44.7)	0.773	9 (40.9)	10 (45.5)	0.761
CKD3, No. (%)	2 (9.1)	32 (84.2)	<0.001	2 (9)	17 (77)	<0.001
CKD4, No. (%)	20 (90.9)	6 (15.8)	<0.001	20 (91)	5 (23)	<0.001
Baseline eGFR (mL/min/1.73 m²), median (interqunatile range)	23 (17, 26)	40.5 (36, 47)	<0.001	23.5 (17, 26)	39 (32, 47)	<0.001
Baseline UACR (mg/g), median (interqunatile range)	825 (500, 4500)	350 (108, 650)	0.008	925 (500, 4500)	327 (100, 774)	0.004

GLP-1 RA, glucagon like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitors; HTN, hypertension; DM, diabetes mellitus; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; CAD, coronary artery disease; CKD, chronic kidney disease; GFR, glomerular filtration rate; UACR, urine albumin/creatinine ratio.
Comparisons between the 2 groups of therapy was done by Mann-Whitney test categorical variables and Kruskal-Wallis test for continuous variables.

Table 2. Median eGFR, weight and UACR changes before and after therapy with GLP-1 RA and SGLT2i

| Characteristics	GLP-1 RA				SGLT2i			
	Baseline values	Six-months values	P value	%	Baseline values	Six-months values	P value	%
eGFR (mL/min)	23.5 (17, 26)	28 (23, 38)	<0.001	+32	39 (32, 47)	30.5 (22, 48)	0.435	-4.6
Weight (kg)	75 (70, 81)	72.5 (65, 67)	<0.001	-4.5	80 (69, 92)	77.5 (68, 89)	0.005	-2.8
UACR (mg/g)	925 (500, 4500)	633 (190, 3400)	<0.001	-29	327 (100, 774)	125.5 (42, 420)	<0.001	-34

GLP-1 RA, glucagon like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitors.
Values were expressed as median (interquartile ranges).
Wilcoxon signed-rank test was used for comparison between median eGFR, weight and UACR changes before and after therapy.
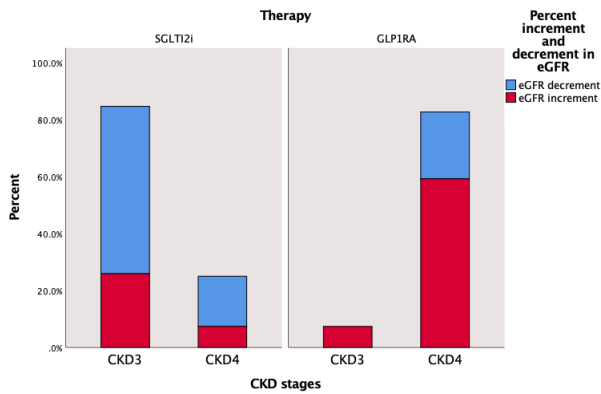
Figure 1. Percent increment and decrement in eGFR according to CKD stages by therapy status.
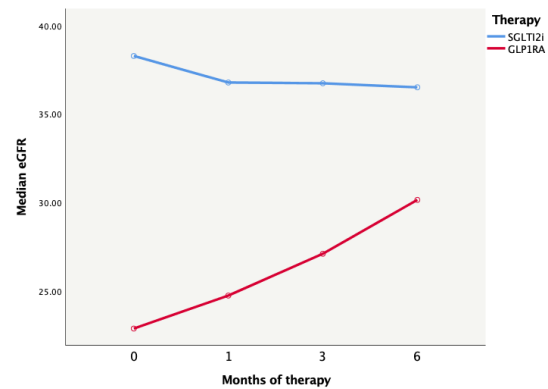
Figure 2. Slop of eGFR by therapy.

eGFR during therapy.

The main results of the present study were statistically significant improvement in 6-months eGFR, weight, and UACR reduction from the baseline values in the GLP-1 RA and statistically significant reduction in 6-months weight and UACR but, decline albeit non-statistically significant in eGFR from the baseline in the SGLT2i group. The GLP-1 RA therapy showed a 32% increase in eGFR (81.8% of patients had increased eGFR from baseline values), a 29% decrease in UACR (100% of patients had decreased UACR from baseline values), and a 4.5% decrease in weight (100% of patients had decreased weight from baseline values). The SGLT2i treatment reported a 4.6% decrease in eGFR (59.1% of patients had decreased eGFR from baseline values), a 34% decrease in UACR (90.9% of patients had decreased UACR from baseline values), and 2.8% decrease in weight (86.4% of patients had decreased weight from baseline values).

In the LEADER trial, which is double-blind RCT using liraglutide for a median of 3.84 years, 21% had entry eGFR of 30-59 mL/min/1.73 m^2 and 2% had entry eGFR < 30 mL/min/1.73 m^2, 26.3% had severely increased albuminuria and 10.5% had moderately increased albuminuria; 22% decreased composite kidney outcome with eGFR loss of only 7.44 per 36 months, 17% decrease UACR and weight loss of 2.3 kg (16). In the LIRA-RENAL trial using 1.8 mg liraglutide, 99.3% of patients were CKD3 with a mean baseline eGFR of 45.4 ± 0.23 and moderately increased albuminuria with a baseline median UACR of 55.5 ± 7.58, eGFR loss of 0.35 over 26 weeks, a 13% decrease in UACR and a weight loss of 2.4 kg (17). In a trial using once-weekly dulaglutide with a mean baseline eGFR of 89.4 ± 17.1, a baseline mildly increased albuminuria with a mean value of 8.9, no significant changes were reported in eGFR, a 16.7% reduction in UACR compared to 10% for placebo, and no weight changes (18). In the AWARD-7 which is a multicenter, open-label, randomized trial using dulaglutide with a mean baseline eGFR of 38.3 ± 12.8 and baseline median UACR of 200 mg/g, there was an eGFR change of -0.4 for 0.75 mg dose and -0.1 for 1.5

mg dose, 26.7% reduction of UACR for 0.75 mg dose and 27.7% reduction of UACR for 1.5 mg dose and weight loss of 1.27 kg (19). In the EXSCEL trial using exenatide ER with 21.2% of patients in the CKD3-5, the percentage of discontinuation due to eGFR <30 mL/min/1.73 m^2 was 1.1% versus 1.3% in placebo and in ESKD was 0.7% versus 0.9% in placebo, UACR change in moderately increased albuminuria in 7.2% versus 7.5% in placebo and in severely increased albuminuria in 2.2% versus 2.8% in placebo with weight loss of 1.27 kg (20). In the ELIXA trial which is double-blind RCT using lixisenatide for a median of 25 months and entry mean eGFR of 67 mL/min/1.73 m^2 and 22.5% with eGFR <60 mL/min/1.73 m^2 with eGFR <30 mL/min/1.73 m^2 was excluded and mean baseline UACR of 10.4 mg/g; the renal composite endpoint was change in UACR over 24 months and it showed 34% versus 24% with a *P* value of 0.004 (21). In the SUSTAIN-6 trial which is double-blind RCT using semaglutide for a duration of 2.1 years and entry eGFR of <60 mL/min/1.73 m^2 in 24.1%; HR of the renal composite endpoint which is persistent macroalbuminuria and two times increase in serum creatinine with eGFR <45 mL/min/1.73 m^2 was 0.64, 95% CI 0.46-0.88 and HR for 2 times increase serum creatinine was 1.28, 95% CI 0.64-2.58 (22). In the Harmony Outcome trial which is double-blind RCT using albiglutide for an average duration of 1.6 years and stage 4 CKD was excluded with 19% had nephropathy; no difference in eGFR at 16 months with HR of -0.43, 95% CI -1.26 to 0.41 (23). In the REWIND trial which is double-blind RCT using dulaglutide with 22% had baseline eGFR <60 mL/min/1.73 m^2; sustained decrease in eGFR >40% with HR of 0.77 (0.68-0.87; *P*<0.0001) and sustained decrease in eGFR > 50% with HR of 0.74 (0.66-0.84; *P*<0.0001) (24). In the SCALE trial, the mean weight reduction was 8.4 kg but that with the use of 3 mg liraglutide which was much higher than the dose used in the present study (25).

In the EMPA-REG outcome trial which is double-blind RCT using empagliflozin 10 and 25 mg inn patients with DM and established CVD for a median duration of 3.1

years, the mean baseline eGFR <60 mL/min/1.73 m², stage 4 CKD was excluded, 26% with UACR >300 mg/g; the HR for renal composite was 0.61, 2 times increase of serum creatinine and eGFR <45 mL/min/1.73 m²: HR 0.56; progression to severely increased albuminuria: HR 0.62 (26). In the CANVAS trial which is double-blind RCT using canagliflozin 100 and 300 mg for patients with DM and established CVD for an average duration of 47 months; baseline eGFR of 76.5 mL/min/1.73 m², eGFR <60 mL/min/1.73 m² with 20% macroalbuminuria, eGFR <30 mL/min/1.7 m² was excluded, HR for 40% reduction in eGFR was 0.60, HR for 2 times increase of serum creatinine was 0.50, ESKD HR was 0.77 (27). In the DECLARE-TIMI which is double-blind RCT using dapagliflozin 10 mg for patients with DM and established CVD for an average duration of 3.2 years but baseline eGFR <60 mL/min/1.73 m² was excluded; the HR for renal composite endpoint which is 40% reduction in eGFR <60 mL/min/1.73 m² was 0.76 (28). In the CREDENCE trial which is double-blind RCT using canagliflozin, the mean entry eGFR was 56.2 mL/min/1.73 m², normoalbuminuria in 1%, microalbuminuria in 11% and macroalbuminuria in 88%, HR for the primary kidney composite endpoint which is two times increase of serum creatinine and sustained eGFR <15 mL/min/1.73 m² was 0.70 (0.59-0.82) and HR for ESKD was 0.68 (0.53-0.86) (29).

Conclusion
GLP-1 RA, compared to SGLT2i therapy, caused an increase in eGFR in stages 3 and 4 CKD and caused more weight reduction but slightly less albuminuria reduction

Limitations of the study
The limitations of the present study were: First, it was not RCT, so lacking the control arm may decrease the power of the study. Second, few patients were studied, which may affect the results of the study. Third, a short duration of follow-up which may affect the conclusions of the study. Fourth, the CKD groups for both therapies were not matched.

Authors' contribution
Conceptualization: HA.
Methodology: HA, JR.
Validation: HA, SS.
Formal analysis: HA, JR.
Investigations: HA, SS.
Resources: HA, JR.
Data curation: HA, JR.
Visualizations HA, JR, SS.
Supervisions HA, JR.
Project administration: HA, SS.
Funding acquisition: HA, JR, SS.
Writing-original draft: HA.
Writing-review and editing: JR, SS.

Conflicts of interest
The authors declare that they have no competing interests.

Ethical issues
The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of University of Basrah, College of Medicine approved this study (ref #03040872-2020). Accordingly, written informed consent was taken from all participants before any intervention.

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