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A Comparison of Renal Effects between Empagliflozin and Linagliptin in Diabetic Patients with Chronic Kidney Disease: A Randomized Clinical Trial

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Abstract

Objective: The current study aimed to compare the renal effects of Empagliflozin with Linagliptin combined with Metformin in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease.
Materials and Methods: We conducted a randomized clinical trial on diabetic patients aged over 18 years with chronic renal failure and an EGFR between 20 to 60 ml/minutes/1.73 m^2 corrected with the MDRD equation. Between January and December 2023, a total of 150 cases in Imam Hossein Hospital were randomized into two study arms of 75 cases receiving Empagliflozin (10 mg/day) and metformin or Linagliptin (5mg/day) and metformin for 6 months. The primary outcome was a change in chronic kidney disease (CKD) stage, while serum creatinine, fasting blood sugar (FBS), proteinuria, and blood pressure were evaluated at baseline, 3 and 6 months later.
Results: The mean age of participants was 62.20 (± 4.45) years and 50% of them were females. Study indices including serum creatinine (*P*: 0.001), estimated glomerular filtration rate (eGFR) (*P*: 0.001), FBS (*P*: 0.001), HgA1c (*P*: 0.001), proteinuria (*P*: 0.001), and blood pressure (*P*: 0.001) reduced significantly over time in both groups. After adjustment for potential confounders, Empagliflozin reduced the level of serum creatinine independent of other factors.
Conclusion: Empagliflozin significantly reduces the level of serum creatinine compared to Linagliptin in patients with T2DM and chronic renal failure.

Keywords: Chronic renal failure, Diabetes mellitus, Empagliflozin, Linagliptin

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Introduction

Diabetes mellitus is one of the major risk factors for developing chronic kidney disease (CKD) affecting 38-68% of diabetic patients (1,2). There are various mechanisms mediating diabetic nephropathy but glomerular hyper-filtration, dysregulated renin–angiotensin–aldosterone system (RAAS), advanced glycation products, inflammation, and oxidative stress come on top (3). Patients usually present with hypertension, anemia, and proteinuria who eventually might end up with end stage renal disease (ESRD), cardiovascular complications, and death (4).

Metformin is an oral agent commonly used in many countries as the standard first-line treatment to control blood sugar. However, monotherapy with metformin fails to control blood sugar or prevent from progression of complications in many cases. In the last decade, other drug classes have been introduced as add-on regimens which are currently being used as the second-line or third-line treatment options in guidelines (5). Sodium-glucose cotransporter 2 inhibitors (SGLT2is) including Empagliflozin are one of the new glucose-lowering agents that act by inhibiting sodium-glucose cotransporter 2 channels of the renal proximal tubules and increasing glycosuria (6). Clinical trials on diabetic patients have approved the efficacy and safety of SGLT2 is in glycemic control and weight loss without adding the risk of hypoglycemia (7-9). Particularly, a growing body of literature indicated its' beneficial effects in patients with cardiovascular or renal backgrounds (10,11). In this regard, based on current guidelines and a recent consensus report by the Kidney Disease Improving Global Outcomes and the American Diabetes Association, it is recommended to select SGLT2 is independent of glycemic control in patients with type 2 diabetes (T2DM) and those with kidney disease, heart failure, or at high risk of cardiovascular disease (12-14).

Linagliptinas a Dipeptidyl peptidase-4 inhibitor (DPP-4i) is from another drug class that has been introduced recently and papers showed its' potent efficacy in glycemic control (15). Moreover, there are reports that highlighted its' beneficial effects in diabetic patients with kidney disease when compared to placebo (16).

To our knowledge, there is no comprehensive head-to-head randomized clinical trial (RCT) comparing the efficacy of these therapies as an add-on regimen to metformin. On this basis, we aimed to conduct this double-blinded RCT to compare the efficacy and safety of Empagliflozin versus Linagliptin in diabetic patients with CKD in terms of renal outcome and glycemic control.

Material and methods

Study design

The present study was a randomized, double-blinded, parallel-group trial that was conducted in Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, from January to December 2023. The written informed consent was obtained from all participants after explaining the details of the study.

Participants

We enrolled type 2 diabetes mellitus (T2DM) patients aged≥ 18 years with moderate to severe stages of CKD (20≤ eGFR ≤ 60 mL/min/1.73m^2 calculated by the MDRD regardless of any background anti-diabetic therapy. The study flow chart is shown in Figure 1. Eligible individuals received a fixed dose of metformin (1000 mg/d) in combination with Empagliflozin 10 mg/d or Linagliptin 5 mg/d for 24 weeks. The study's exclusion criteria were: polycystic kidney disease, lupus nephritis, anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis, treatment with cytotoxic or immunosuppressive or other immunologic agents for kidney disease within the last 6

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months before the first visit, organ transplantation, blood pressure< 90/60 mmHg, receiving SGLT2is within 8 weeks prior recruitment or previous intolerance, recurrent urinary tract infection (UTI), NYHA class IV heart failure, active malignancy, liver failure (serum alanine aminotransferase or aspartate aminotransferase levels> 3 times the upper limit of normal and bilirubin> 2 times the upper limit of normal), pregnancy and breastfeeding

Intervention

When the researcher ensures the appropriateness of the volunteer to enter the study according to all entry and non -entry criteria, the candidate is based on the pre -determined random plan in one of the two groups of intervention; To ensure acceptance and safety, the drug will be prescribed by an internal specialist.

An intervention group: prescription 1000 mg Metformin +10 mg Empagliflozin Active Control Group: prescription 1000mg Metformin+5 mg Melijent

Follow-up and end-point

Patients in both groups followed up during the study for a maximum of 6 months (one, three and 6 months after the intervention) during the study. All the consequences of the study reviewed and recorded at zero (prior to the start of the study (drug administration) and monthly until 6 months after the intervention (one, three 6 months after the intervention).

Sample size estimation

The sample size was calculated by PASS.V21.03 software according to the result of a previous RCT by Gharabaghi et al. when the mean eGFR was 76.13 ± 15.95 mL/ min/ 1.73m^2 and 68.18± 17.56 mL/ min/ 1.73m^2 after three months' treatment with Empagliflozin and Linagliptin, respectively (3). Therefore, a total of 150 participants (75 patients in each arm) was required considering a drop-out rate of 5%, power of 80%, and 5% α -level.

Randomization

After the run-in period, using permuted block randomization (24 blocks in size of 2,4,6,8,10) with SATA. 14 software patients were randomized in a 1:1 ratio into two study arms including either Empagliflozin 10 mg/d and metformin 1000 mg/d or Linagliptin 5 mg/d and metformin 1000 mg/d. Patients did not receive metformin if they had an eGFR lower than 30 mL/ min/ 1.73m^2. Doses remained unchanged during the study. Patients were evaluated regarding demographics, medical and medication history, physical examination, and laboratory experiments at baseline. All cases continued to receive their medications according to their underlying disease and they were excluded if met any of the exclusion criteria. We visited participants during Week 12 and Week 24 to assess adherence to treatment, blood pressure, and laboratory variables. The primary endpoint was to compare the effect of Empagliflozin versus Linagliptin in addition to metformin on renal outcomes as CKD staging and status of proteinuria (<150 mg/day was considered normal) after 24 weeks. Our secondary endpoint was to assess the glycemic effect as those reaching a HgA1c≤ 8% after 24 weeks. Renal and glycemic outcomes were measured using serum creatinine, estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease (MDRD) equation and proteinuria, and fasting blood sugar (FBS) and blood pressure, respectively. Data were collected using a questionnaire designed for this study.

Blinding

This study was a double-blind, parallel-group trial. The drugs required for the participants in the study were completely covered and undetectable from each other, as provided by the DR Abidi manufacturer. The participants in the study and the statistician who analyzed the data were not aware of the treatment allocation.

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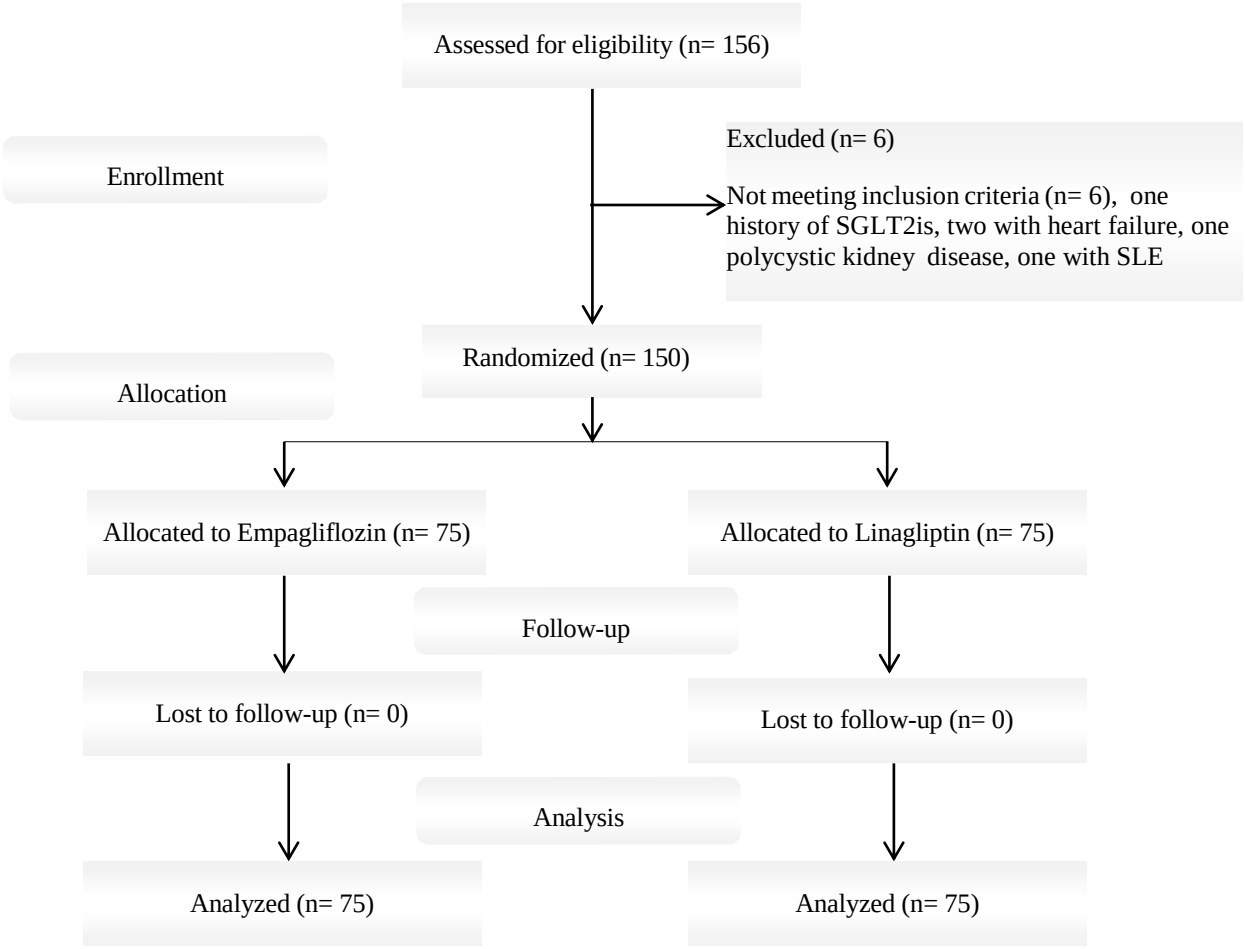
Statistical analysis

The data analysis approach in this study employed an intention-to-treat (ITT) analysis. Initially, the normality of quantitative data was assessed using a histogram and Kolmogorov–Smirnov test. Quantitative data were described using means and standard deviations, while qualitative data were presented in frequencies and percentages. The parametric student's T-test or the non-parametric Mann-Whitney U test was utilized to compare mean differences between the two groups. The chi- square test was used to examine differences in the distribution of categorized variables. To investigate changes in the distribution of outcome measures (improvement in GFR, HbA1c, and blood pressure improvement) at the sixth-month post-intervention compared to before, the McNemar or Wilcoxon signed-rank test was applied. Given the non-acceptance of assumptions for analyzing repeated measures in line with available data, this study employed Generalized Estimating Equations (GEE) with an exchangeable correlation structure for assessing the trends of repeated quantitative variables over time. Finally, a multiple GEE model with an exchangeable correlation structure was used to examine the intervention's impact in the presence of confounding variables. The final model was fitted based on the Quasi Likelihood under the Independence Model Criterion (QIC) with the minimum value. All analyses were conducted at a significance level of less than 0.05 using STATA software version 14.

Ethical considerations

After the approval of the study protocol by the institutional ethics committee (IR.SBMU.MSP.REC.1402.113). The study was registered and approved in the Iranian Registry of Clinical Trials (20230607058409N1).



CONSORT 2010 flow diagram

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Results

A total of 150 diabetic patients with a mean age of 62.2 years were recruited in this study and all of them completed the study with full adherence to treatment and without any complication. 50% were male participants. Of baseline characteristics, 24% were smokers and had a mean body mass index (BMI) of 27.95 kg/m^2 and mean blood pressure of 130/85 mmHg. Initial laboratory results were as follows; creatinine 1.82 mg/ dl, eGFR 34.02 mL/ min/ 1.73m^2, urine protein 174.76 mg/dl, FBS 151.58 mg/dl, HbA1c 8.45%. Demographics were comparable between the two groups. Data are shown in Table 1.

Regarding medical background, 20.6% and 8% had ischemic heart disease and CVA, respectively. Also, 40.3% and 10% of our patients were using angiotensin-converting enzyme (ACE) and angiotensin receptor blocker (ARB) drugs, respectively. Patients in the Empagliflozin group had significantly higher levels of BMI, diastolic blood pressure (DBP), Insulin intake, urine protein, FBS, and HgA1c ($P<$ 0.05). Despite an appropriate randomization method that was applied precisely, patients in the Empagliflozin group tended to be more obese with poorer blood sugar control.

As presented in Table 2, all study endpoints including serum creatinine, eGFR, urine protein, FBS, HgA1c, systolic blood pressure (SBP), and DBP significantly reduced in both groups over time ($P<$ 0.001). Also, given intergroup differences, patients who received Empagliflozin had a significantly greater decline in all of the mentioned endpoints compared to those with Linagliptin, except for blood pressure values ($P<$ 0.001).

Both treatments were remarkably able to slow down CKD progression; Patients in stage 4 of CKD decreased from 30.6% to 14.6% and from 30.6% to 10.6% in Empagliflozin and Linagliptin groups, respectively ($P<$ 0.05). Consistently, patients in stage 3 of CKD increased from 69.3% to 85.3% and from

Table 1. General and basic clinical information in diabetic with chronic renal failure patients

Variables	Empagliflozin + metformin (N=75)	Linagliptin + metformin (N=75)	Total (N= 150)	*P*-value
General information				
Age (years)	62.40 (±4.81)	62.01 (±4.08)	62.20 (±4.45)	0.804
Gender				
Female	36 (48.00)	39 (52.00)	75 (50.00)	0.624
Male	39 (52.00)	36 (48.00)	75 (50.00)	
Smoker (Yes)	20 (26.67)	16 (21.33)	36 (24.00)	0.444
Body mass index (BMI, kg/m^2)	28.65 (±1.72)	27.25 (±1.32)	27.95 (±1.68)	<0.001*
Initial systolic blood pressure (mmHg)	131.40 (±5.84)	130.00 ±6.62	130.70 (±6.26)	0.220
Initial diastolic blood pressure (mmHg)	86.20 (±3.27)	84.73 (±4.01)	85.46 (±3.72)	0.028*
Medical history (Yes)				
Ischemic heart diseases (IHD)	15 (20.00)	16 (21.33)	31 (20.67)	0.840
Stroke	5 (6.67)	7 (9.33)	12 (8.00)	0.547
Medication (Yes)				
ACE/ARB	35 (46.67)	30 (40.00)	65 (43.33)	0.410
Diuretic	7 (9.33)	8 (10.67)	15 (10.00)	0.785
Calcium channel blockers	13 (17.33)	15 (20.00)	28 (18.67)	0.675
ASA	15 (20.00)	16 (21.33)	31 (20.67)	0.840
Clopidogrel	6 (8.00)	9 (12.00)	15 (10.00)	0.414
Statin	15 (20.00)	16 (21.33)	31 (20.67)	0.840
Beta-blocker	15 (20.00)	16 (21.33)	31 (20.67)	0.840
Insulin	24 (32.00)	5 (6.67)	29 (19.33)	<0.001*
Initial laboratory results				
Creatinine (mg/dl)	1.87 (±0.19)	1.91 (±0.23)	1.89 (±0.21)	0.495
GFR (ml/min/1.73m^2)	34.60 (±6.83)	33.44 (±6.80)	34.02 (±6.82)	0.336
Urine protein (mg/day)	198.80 (±84.97)	150.73 (±69.48)	174.76 (±81.03)	<0.001*
FBS (mg/dl)	155.08 (±10.55)	148.08 (±11.06)	151.58 (±11.33)	0.0001*
HbA1c (%)	8.62 (±0.33)	8.27 (±0.39)	8.45 (±0.40)	<0.001*

Values described as mean ± standard deviation or n (%)
* Statistically significant, *P*-value < 0.05

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69.3% to 89.3% in the Empagliflozin and Linagliptin groups, respectively ($P< 0.05$). The percentage of patients with normal levels of proteinuria significantly increased from 22.6% to 69.3% in the Empagliflozin group and from 48% to 73.3% in the Linagliptin group ($P< 0.001$). Similarly, there was a notable increase in the proportion of patients who reached a HgA1c≤ 8% and a blood pressure≤ 130/80 mmHg in both groups ($P< 0.001$) (Table 3).

Given the difference in some basic characteristics that could act as a confounding factor that influences outcomes, we performed univariate and multivariate regression analysis to find independent factors and adjust potential confounding factors (Table 4).

In the univariate model, there was a significant indirect correlation between the level of serum creatinine and Empagliflozin (β = -0.03, CI= 95%, $P= 0.011$) or Linagliptin (β = -0.02, CI= 95%, $P= 0.012$) treatment.

Table 2. Mean changes and trend analysis of each laboratory factor between groups

Factors	Groups	Baseline	3 months after intervention	6 months after intervention	*P*_value time effect	*P*_value time × groups	Comparison of time groups [1]
Creatinine (mg/dl)	Empagliflozin + Metformin	1.87 (±0.19)	1.81 (±0.16)	1.78 (±0.14)	<0.001*	<0.001*	T1/T2* T1/T3*
	Linagliptin + Metformin	1.91 (±0.23)	1.88 (±0.20)	1.83 (±0.16)	<0.001*		T1/T2* T1/T3*
	Total	1.89 (±0.21)	1.85 (±0.18)	1.81 (± 0.15)	<0.001*		T1/T2* T1/T3*
GFR (ml/min/1.73m^2)	Empagliflozin + Metformin	34.60 (±6.83)	36.10 (±6.38)	37.16 (±6.05)	<0.001*	<0.001*-	T1/T2* T1/T3*
	Linagliptin + Metformin	33.44 (±6.80)	34.55 (±6.23)	36.46 (±5.83)	<0.001*		T1/T2* T1/T3*
	Total	34.02 (±6.82)	35.33 (±6.33)	36.81 (±5.93)	<0.001*		T1/T2* T1/T3*
Urine protein (mg/day)	Empagliflozin + Metformin	198.80 (±84.97)	158.40 (±49.46)	122.06 (±32.09)	<0.001*	<0.001*-	T1/T2* T1/T3*
	Linagliptin + Metformin	150.73 (±69.48)	135.53 (±48.21)	122.26 (±38.28)	<0.001*		T1/T2* T1/T3*
	Total	174.76 (±81.03)	146.96 (±50.01)	122.16 (±35.20)	<0.001*		T1/T2* T1/T3*
FBS (mg/dl)	Empagliflozin + Metformin	155.08 (±10.55)	141.57 (±5.79)	129.49 (±10.49)	<0.001*	<0.001*-	T1/T2* T1/T3*
	Linagliptin + Metformin	148.08 (±11.06)	138.85 (±7.36)	130.86 (±8.19)	<0.001*		T1/T2* T1/T3*
	Total	151.58 (±11.33)	140.21 (±6.74)	130.18 (±9.40)	<0.001*		T1/T2* T1/T3*
HbA1c	Empagliflozin + Metformin	8.62 (±0.33)	8.44 (±0.28)	8.24 (±0.24)	<0.001*	<0.001*-	T1/T2* T1/T3*
	Linagliptin + Metformin	8.27 (±0.39)	8.20 (±0.34)	8.14 (± 0.30)	<0.001*		T1/T2* T1/T3*
	Total	8.45 (±0.40)	8.32 (±0.33)	8.19 (± 0.28)	<0.001*		T1/T2* T1/T3*
Systolic blood pressure (mmHg)	Empagliflozin + Metformin	130.93 (±5.43)	128.86 (±5.17)	128.00 (± 5.19)	<0.001*	<0.001*-	T1/T2* T1/T3*
	Linagliptin + Metformin	130.00 (±6.62)	127.20 (±6.10)	126.80 (± 6.29)	<0.001*		T1/T2* T1/T3*
	Total	130.70 (±6.26)	128.03 (±5.70)	127.40 (± 5.78)	<0.001*		T1/T2* T1/T3*
Diastolic blood pressure (mmHg)	Empagliflozin + Metformin	86.20 (±3.27)	83.33 (±2.64)	82.53 (± 3.00)	<0.001*	<0.001*	T1/T2* T1/T3*
	Linagliptin + Metformin	84.73 (±4.01)	83.00 (±3.67)	80.40 (±3.26)	<0.001*		T1/T2* T1/T3*
	Total	85.46 (±3.72)	83.16 (±3.19)	81.46 (± 3.30)	<0.001*		T1/T2* T1/T3*

Values described as mean ± standard deviation,
* statistically significant, *P*_value< 0.05 based on Generalized Estimation Equation (GEE) analysis
[1] each visit time compared with visit time 1

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However, only Empagliflozin was able to lower the level of urine protein (β = -8.27, CI= 95%, *P*= 0.043). According to the results of multivariate analysis, after considering potential confounders such as age, sex, BMI, history of smoking, ischemic heart disease, and Insulin intake, there was a remarkable indirect correlation between both interventions and the level of serum creatinine.

Discussion

In this randomized, double-blinded, parallel-group trial, we aimed to compare the efficacy of Empagliflozin 10 mg/d and Linagliptin 5 mg/d in diabetic patients with chronic kidney disease (CKD) who were concurrently receiving metformin 1000 mg/d. Despite baseline disparities in blood sugar control, BMI, diastolic blood pressure (DBP), and proteinuria favoring the Linagliptin group, our results revealed that after 3 and 6 months of treatment, the Empagliflozin group experienced significantly greater improvements in both glycemic and renal variables compared to the Linagliptin group. Notably, our multivariate model identified an

Table 3. Changes in outcomes after sixth month intervention versus before between groups

Outcomes	Empagliflozin + Metformin			Linagliptin + Metformin		
	Baseline	After 6 months intervention	Paired comparison *P*_value	Baseline	After 6 months intervention	Paired comparison *P*_value
GFR staging						
Stage 3A (moderate CKD, 45-59 ml/min/1.73m^2)	7 (9.33)	9 (12.00)	0.010*	5 (6.67)	8 (10.67)	0.007*
Stage 3B (moderate CKD, 30-44 ml/min/1.73m^2)	45 (60.00)	55 (73.33)		47 (62.67)	59 (78.67)	
Stage 4 (severe CKD, 15-29 ml/min/1.73m^2)	23 (30.67)	11 (14.67)		23 (30.67)	8 (10.67)	
Urine protein						
Normal (<150 mg/day)	17 (22.67)	52 (69.33)	< 0.001*	36 (48.00)	55 (73.33)	< 0.001*
Abnormal (≥ 150 mg/day)	58 (77.33)	23 (30.67)		39 (52.00)	20 (26.67)	
HbA1c						
≤ 8%	5 (6.67)	20 (26.67)	0.0001*	26 (34.67)	34 (45.33)	0.007*
>8%	70 (93.33)	55 (73.33)		49 (65.33)	41 (54.67)	
Blood pressure						
≤ 130/80 mmHg	7 (9.39)	26 (34.67)	<0.001*	24 (32.00)	43 (57.33)	0.0001*
> 130/80 mmHg	68 (90.67)	49 (65.33)		51 (68.00)	32 (42.67)	

*Paired comparison of outcomes 'frequency before and after 6 months' intervention
Values described as n (%), * statistically significant, *P*-value< 0.05

Table 4. Results of univariate and multivariable linear generalized estimating equation about effect of intervention on mean changes of each factor

Factors	Groups	Model 1 ß[1] , 95% CI	*P*_value	Model 2 ß [1], 95% CI	*P*_value
Creatinine (mg/dl)	Linagliptin + Metformin	Reference	0.011*	Reference	0.012*
	Empagliflozin +Metformin	-0.03 (-0.05, -0.006)		-0.02 (-0.05, -0.006)	
GFR (ml/min/1.73m^2)	Linagliptin + Metformin	Reference	0.622	Reference	0.507
	Empagliflozin +Metformin	0.21 (-0.63, 1.06)		0.27 (-0.53, 1.07)	
Urine protein (mg/day)	Linagliptin +Metformin	Reference	0.043*	Reference	0.148
	Empagliflozin +Metformin	-8.27 (-16.29, -0.25)		-6.44 (-15.16, 2.27)	
FBS (mg/dl)	Linagliptin +Metformin	Reference	0.331	Reference	0.152
	Empagliflozin +Metformin	-0.93 (-2.80, 0.94)		-1.51 (-3.58, 0.55)	
HbA1c (%)	Linagliptin +Metformin	Reference	0.160	Reference	0.350
	Empagliflozin +Metformin	-0.04 (-0.10, 0.01)		-0.03 (-0.10, 0.03)	
systolic blood pressure (mmHg)	Linagliptin +Metformin	Reference	0.320	Reference	0.363
	Empagliflozin +Metformin	0.47 (-0.45, 1.39)		0.46 (-0.53, 1.45)	
diastolic blood pressure (mmHg)	Linagliptin +Metformin	Reference	0.051	Reference	0.189
	Empagliflozin +Metformin	0.62 (-0.001, 1.25)		0.49 (-0.24, 1.23)	

[1]Coefficient (ß), 95% Confidence Interval
Model 1: intercept, groups, initial value of each factor
Model 2: intercept, gender, age, groups, body mass index, initial value of each factor, history of smoking, history of ischemic heart disease, insulin use
* statistically significant, *P*_value< 0.05 based on Generalized Estimation Equation (GEE) analysis

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independent role for Empagliflozin treatment in reducing serum creatinine levels compared to Linagliptin.

Numerous population-based studies and real-world evidence have consistently indicated the association of SGLT2is with improved renal outcomes, including a reduced risk of ESRD and a slowed decline in eGFR compared to alternative glucose-lowering agents (17,18). The matter was further approved by large placebo-controlled clinical trials (19,20). However, it is imperative to acknowledge the warning issued by the United States Food and Drug Administration regarding the potential risk of AKI associated with SGLT2is. On the other hand, DPP-4is have been proposed to exert beneficial effects on renal outcomes based on its mechanism of action and some observations in clinical settings including a decrease in hyperglycemia and albuminuria which are risk factors for developing diabetic nephropathy. Nevertheless, the CARMELINA trial confirmed that Linagliptin lowered albuminuria progression and HgA1c while it had no effect on kidney outcome of renal death, ESRD, and a sustained ≥ 40% decrease in eGFR from baseline (21). Altogether, data on a head-to-head comparison between Empagliflozin and Linagliptin regarding renal efficacy in diabetic patients with CKD remain scarce.

Previous findings from a cohort study by Lee et al. assessing kidney outcomes in 7042 T2DM patients using Empagliflozin and/or Linagliptin reported a lesser decline in eGFR for Empagliflozin users compared to Linagliptin users. Moreover, this study highlighted that patients aged ≥ 65 years, or with a baseline eGFR <60 ml/min/1.73 m^2, or with a baseline HgA1c≤ 7% experienced attenuated benefits of Empagliflozin concerning the risk of AKI (6). Although this study had a focus on AKI as an adverse effect, the effect of these factors might be attributed to CKD condition as well. In fact, there are other studies that indicated greater prognostic effects of SGLT2is on renal outcomes in patients with higher eGFR (22). However, Reno-protective effects remained significant in low eGFR patients, regardless of their metabolic effects (23). Consequently, early treatment with Empagliflozin may offer greater benefits to patients. Importantly, the Reno-protective effects of Empagliflozin were observed for the first 3 months in Lee et al.'s study; however, this effect persisted until 6 months after treatment initiation in our study.

Recently, Mohammad zadeh Gharabaghi et al. carried out an RCT on 60 patients with T2DM to compare the renal and glycemic effects of 12-week treatment with Empagliflozin 10 mg/d vs Linagliptin 5 mg/d. [3] Similar to our observations, individuals in the Empagliflozin group had higher values of baseline FBS, HbA1C, and albuminuria in comparison to the Linagliptin group. Both interventions contributed to a reduction in eGFR and HgA1c during the study period. Yet Empagliflozin lowered the levels of FBS and albuminuria. The changes in albuminuria were greater in Empagliflozin compared to Linagliptin and this effect remained significant after adjustment for baseline values. Some discrepancies between this study and ours might be because of their smaller sample size, shorter follow-up, and restricted inclusion criteria of age (30 – 80 years) and HbA1c ≤ 9% as Empagliflozin may have more beneficial effects in younger age and higher HgA1c. Also, there are some other obstacles in this study; For instance, the background glucose-lowering agent used by participants and the proportion of patients with CKD are not presented.

As we mentioned earlier and according to the results of Lee et al., the higher baseline HgA1c levels of patients in the Empagliflozin group may be a confounding factor that contribute to greater effects of Empagliflozin. However, a comparative effectiveness study on 87274 cases by D'Andrea*et al.* demonstrated a lower risk of AKI in Empagliflozin users vs those with Linagliptin regardless of baseline HgA1c (24). Also, trials and observational studies demonstrated the role of SGLT2is in decreasing decline of

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kidney function irrespective of baseline eGFR (26-29). These findings down play the role of baseline intergroup differences on results of our study. The robustness of Empagliflozin's effects, even in the face of these discrepancies, adds a layer of resilience to its therapeutic potential. This prompts us to reconsider the significance of baseline variations and underscores the need for individualized treatment approaches.

Another population-based study on 25332 DPP-4i and 6333 SGLT2is new users evaluated associations with renal outcomes (30). The real-world evidence from this study confirmed the association of SGLT2is with reduced risks of ESRD, AKI, and a slower decline in eGFR. In line with our result, additional observational studies confirmed the association of SGLT2is with improved renal outcomes including microalbuminuria, macro albuminuria, level of serum creatinine, ESRD, eGFR decline, regardless of baseline eGFR categories, or metformin treatment (15,29). Although our results indicated Empagliflozin's efficacy in mitigating eGFR decline, it failed to prove an independent correlation. This might be due to our small sample size or some methodological considerations. Nonetheless, the call for additional research becomes imperative to validate and build upon our results. Empagliflozin's ability to independently reduce serum creatinine levels indicates a broader impact on renal markers, raising questions about its potential mechanisms beyond glucose-lowering actions.

Poor blood sugar control, hypertension, and high BMI are major risk factors for new-onset CKD. It's been well known that Empagliflozin has protective effects on cardiovascular outcomes and major adverse composite events (MACEs) (30-34). Yet, a cohort study compared SGLT2is with DPP-4i in addition to metformin in 779 patients with acute myocardial infarction and T2DMfound that MACEs and changes in HgA1c were comparable between the two groups except for changes in left ventricular ejection fraction that was significantly higher in the Empagliflozin group (35). Consistent with the trial of Inzucchi et al. that concluded that the beneficial effects of Empagliflozin on cardio-renal outcomes are independent of background glucose-lowering therapy, we assume that these benefits are apart from glucose-lowering action of Empagliflozin and it is not influenced by glycemic status (36). Similarly, The EMPEROR-Reduced trial on heart failure patients with reduced ejection fraction demonstrated that Empagliflozin significantly improved cardiovascular and renal outcomes independent diabetes status and across all HgA1c categories (37).

We provided evidence that both interventions contributed to the improvement of these risk factors at a significant level.

There are some limitation in our study including a small sample size, we didn't evaluate adverse events, we did not asses the background antidiabetic therapy, and out patients were not new-onset T2DM patients.

Conclusion

According to the results of the current study and other reports, treatment with Empagliflozin is associated with retarded kidney dysfunction progression compared to Linagliptin. We recommend using Empagliflozin in T2DM patients with CKD.

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Conflict of Interest

The authors declare that they do not have any conflict of interest.

Authors' contributions

R. ZN: Wrote original draft of the manuscript and collected the data

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R. R: collected the data and performed the analysis.

T. S and S. K: conceived and designed the analysis and performed the analysis.

All authors have accepted responsibility for the entire content of this manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved and approved the version to be published.

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