Potential impact of sodium glucose co-transporter (SGLT2) inhibitors on cholesterol fractions in stage 3 chronic kidney disease

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Abstract

Introduction Data on sodium glucose co-transporter 2 inhibitors impact on lipids in patients with diabetes are available and only a handful of studies have explored this effect in individuals with both diabetes and renal impairment; lipid parameters were not the primary focus of those earlier studies. However, there is a significant research gap specifically addressing the influence of SGLT2 inhibitors on cholesterol fractions in patients exclusively with chronic kidney disease. This aim constitutes the central objective in this particular study.

Methods In this 3-month randomized controlled study, 30 patients with stage 3 chronic kidney disease and dyslipidemia were randomly assigned to receive either dapagliflozin 10 mg or placebo. Lipid profiles, renal function, and urinary albumin levels were assessed at baseline and after 3 months.

Results Compared to baseline, patients receiving dapagliflozin for 3 months showed significant improvements in serum creatinine ($p < .001$) and eGFR ($p = .001$). Total cholesterol and LDL-C levels decreased significantly ($p = .010$ and .006, respectively). While albumin-creatinine ratio also decreased, this change was not statistically significant. Additionally, HDL-C and TG not significantly increased. The control group without intervention experienced deterioration in serum creatinine and eGFR ($p = .008$, and .011, respectively), but no statistically significant lipid changes were observed. Furthermore, post-intervention total cholesterol moderately correlated with BMI ($p = .032$, $R = .554$), yet no predictors significantly influenced lipid levels in the multiple linear regression analysis.

Conclusions Dapagliflozin has a favorable effect on cholesterol fractions in stage 3 CKD patients without diabetes mellitus and this effect was different from that observed in patients with diabetes alone.

Keywords Dapagliflozin, Lipids, Cholesterol, Chronic kidney disease

Introduction

Undoubtedly, sodium glucose co-transporter 2 (SGLT2) inhibitors offer benefits beyond the main action for glycemic control. SGLT2 inhibitors are now recognized as crucial for slowing chronic kidney disease progression

in real-world studies [1, 2]. Consequently, these medications are frequently prescribed for individuals with chronic kidney disease.

Recently, SGLT2 inhibitors have been linked to lipids. They impact fat storage and substrate utilization and regulate lipid synthesis, transportation, and fatty acid oxidation. They also promote weight loss and reduce body fat which in turn also affects the lipids level [3].

Meta-analyses of 60 randomized trials involving 147,130 individuals documented that SGLT2-inhibitor treatment was associated with increased total cholesterol, LDL cholesterol, and HDL cholesterol, while

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triglyceride levels decreased [4]. Elevated (LDL-C) levels can occur due to diminished lipid transfer between triglyceride-rich lipoprotein (TRL)-TG and LDL-C. Additionally, enhanced insulin sensitivity leads to increased lipoprotein lipase activity, promoting the conversion of very-low-density lipoprotein-C (VLDL-C) to LDL-C. However, these changes were documented mainly for patients diagnosed with diabetes, and this elevation in LDL-C in patients who used SGLT2-inhibitor was not accompanied with an increased cardiovascular diseases risk [5].

There is currently no existing literature specifically addressing the impact of SGLT2-inhibitor on cholesterol fractions in patients with exclusive chronic kidney disease (CKD).

Dyslipidemia frequently occurs in patients with chronic kidney disease (CKD). In this context, dyslipidemia refers to elevated triglyceride (TG) levels and low high-density lipoprotein cholesterol (HDL-C) levels [6]. Patients with chronic kidney disease (CKD) are at high risk for cardiovascular disease (CVD). Dyslipidemia, along with other factors like chronic inflammation, vascular remodeling, and metabolic disturbances, contributes to coronary artery disease, heart failure, atherosclerosis, arrhythmias, and sudden cardiac death in these patients [7].

CKD patients are often undertreated with cholesterol lowering agents due to lacked evidence to evaluate LDL-C levels' impact across different CKD stages on cardiovascular disease risk or mortality and due to the fact that individuals with chronic kidney disease (CKD) face an increased risk of side effects from lipid medications due to reduced renal excretion and the associated poly pharmacy [8].

The accumulating evidences that SGLT2 inhibitors have potential benefits in preventing complications associated with dyslipidemia in diabetes patients [9, 10] prompt us to study the impact of dapagliflozin on cholesterol fractions in chronic kidney disease (CKD) patients. It is possible that SLUT2 inhibitor effects may differ from those observed in individuals with diabetes alone.

Therefore, the objective of our study is to investigate how dapagliflozin influences blood cholesterol profiles in stage 3 CKD patients.

Methods

Thirty stage 3 chronic kidney disease patients with dyslipidemia were enrolled in this single blinded randomized–placebo controlled study (only patients were unaware of the allocated treatment) from outpatient clinic of Cairo University Hospitals between August and November 2023. The sample size was determined based on the formula for clinical trials of mean differences. Specifically, with $n=15$ patients per group, the study aimed to detect a significant 15% difference compared to baseline in cholesterol fractions.

Following the acquisition of informed consent, participants were allocated randomly by sealed envelope (1:1) either to receive a daily regimen of dapagliflozin 10 mg in the morning or using placebo alongside their existing conservative CKD medications. The intended duration of the treatment is 3 months.

Intervention group ($n=15$) received dapagliflozin 10 mg + conservative CKD medications.

Control group ($n=15$) received placebo + conservative CKD medications.

The study enrolled adults diagnosed with stage 3 CKD (who had an estimated glomerular filtration rate (GFR) between 30 and 59 ml/min per 1.73 m^2) with disease duration of at least 6 months and had dyslipidemia required to be receiving a consistent dose of statins for minimum 3 months before enrollment in the study.

All enrolled patients in both groups received a moderate-intensity statins (10–20 mg atorvastatin).

Individuals were excluded if they had diabetes mellitus, altered their statin dosage or therapy within the last 3 months, had an active urinary tract infection at the time of inclusion, suffered from alcoholism, had triglyceride levels of 600 mg/dl or higher, were allergic to dapagliflozin, had an eGFR below 30, were taking omega-3 fatty acids, were pregnant or breastfeeding, or were unable to provide informed consent.

Age, gender, body mass index (BMI), systolic and diastolic blood pressure, smoking assessment of the enrolled participants alongside with, serum creatinine, eGFR, urinary albumin/creatinine ratio ACR (mg/g), HbA1c at the baseline, and after 3 months were recorded.

Ten-hour fasting blood samples were obtained at baseline and after 12 weeks for assessment lipid profile (total cholesterol, HDL-C and LDL-C, and triglycerides (TGs)).

Primary outcome was the change in cholesterol fractions (total cholesterol, LDL-C, HDL-C) and TG levels 3 months of intervention versus baseline.

The CKD-EPI formula was used to estimate glomerular filtration rate (eGFR) [11]. Microalbuminuria in spot urine specimens is defined as excretion of 30–300 mg of albumin/gram creatinine [12]. Lipid fractions were measured by conventional direct methods.

All patients were aware by symptoms and signs of hypoglycemia for safety issue.

Ethical committee approval.

The study protocol obtains approval from the Faculty of Medicine, Cairo University Research Ethics Committee (REC), at 27–5-2023, with the approval number N-152–2023.

Statistical analysis

Microsoft Excel 2013 was employed for data entry, while the Statistical Package for the Social Sciences (SPSS) version 23 (SPSS, Armonk, NY: International Business Machines Corporation) was utilized for statistical analysis. Simple descriptive statistics (average and standard deviation) provided a concise overview for the quantitative data and frequencies express qualitative data. Bivariate relationship was explored in cross-tabulations and comparison of proportions was done using the chi-square test or fisher exact whenever appropriate. *T*-independent test and paired *T*-test were applied to compare normally distributed quantitative data. Pearson correlation was performed to detect correlation between quantitative variables. Multiple linear regression models were used to assess the impact of several factors on the lipid profile parameters in the intervention group. The level of significance was set at probability (*P*) value < 0.05.

Results

Thirty patients with stage 3 chronic kidney disease (CKD) and dyslipidemia were enrolled in the study. Fifteen participants were administered dapagliflozin for 3 months as an intervention, in addition to conservative care for CKD, while the remaining fifteen participants were assigned to the control group, receiving a placebo alongside their conservative care for CKD too.

Demographic data and laboratory measurements are presented in Table 1. Both the intervention and control groups displayed comparable baseline results, with no statistically significant differences observed in levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG)—the primary variables of interest.

Compared to control group, after 3 months, the intervention group exhibited a significant lower serum creatinine levels (*p*-value = 0.005) and a corresponding higher estimated glomerular filtration rate (eGFR) (*p*-value = 0.005), and regarding the lipid profile of the patients, the intervention group showed lower levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C), while high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels were elevated. However, these differences were statistically significant only for LDL-C (*p*-value = 0.022, Table 1).

Compared to baseline, patients who received dapagliflozin showed improvement in serum creatinine and eGFR levels after 3 months with highly significant *p*-values of less than 0.001 and 0.001, respectively. Additionally, there was a notable reduction in total cholesterol and LDL-C levels among those receiving the treatment, evidenced by significant *p*-values of 0.010 and 0.006, respectively. While there was an increase in HDL-C levels and a decrease in TG, these changes did not reach statistical significance. Tendency towards significance were observed post-treatment in the decrease of ACR levels suggesting a positive trend, although this finding was not statistically significant (Table 2).

Same laboratory variables were tested after 3 months for the control group without intervention. The results indicated significant deterioration in serum creatinine levels, and estimated glomerular filtration rate (eGFR) (*p* value = 0.008 and 0.011, respectively). However, there was no statistically significant increase in total cholesterol, LDL-C, HDL-C, triglycerides (TG), or albumin-to-creatinine ratio (ACR) in this group (as shown in Table 2).

Male sex exhibited significantly higher eGFR at baseline and after 3 months in the intervention group compared to female sex (*p* value = 0.025 and 0.048, respectively). In contrast, smoking demonstrated a non-specific correlation with the tested variables (*p* value > 0.05, Table 3).

Total cholesterol at baseline showed a moderate significant correlation with BMI (*p* value = 0.028, *R* value = 0.566). The same correlation was observed for total cholesterol after 3 months (*p* value = 0.032, *R* value = 0.554) (Table 4).

A multiple linear regression was conducted to predict post-intervention total cholesterol levels based on certain independent variables. However, none of these variables significantly predicted the decrease in cholesterol levels ($F_{(10, 15)} = 1.218$, $p = 0.460$, $R^2 = 0.135$, Table 5). Similarly, another multiple linear regression aimed to predict post-intervention LDL-C levels using the same independent variables. Again, none of these variables significantly predicted LDL-C levels ($F_{(10, 15)} = 0.638$, $p = 0.743$, $R^2 = -0.349$, Table 5). However, when predicting post-intervention urinary albumin/creatinine levels, only the baseline urinary albumin/creatinine level emerged as a statistically significant predictor ($F_{(10, 15)} = 17.460$, $p = 0.007$, $R^2 = 0.922$). This variable significantly contributed to the prediction ($p < 0.05$, Table 6).

Discussion

There is currently no existing literature addressing the impact of dapagliflozin on cholesterol fractions in patients with chronic kidney disease (CKD). To our knowledge, this is the first trial examining the impact of SGLT2 inhibitors on lipids in chronic kidney patients. We found that dapagliflozin has a favorable effect on cholesterol fractions in stage 3 CKD patients without diabetes mellitus.

Data regarding SGLT2 inhibitors and lipids in patients with diabetes exist. Only a few relevant studies have included the effect of SGLT2 inhibitors on cholesterol fractions in patients with both diabetes and renal

Table 1 Patients' characters at baseline and after 3 months of follow-up in both groups, *N*=30

		Group				*P*.value
		Intervention group *N*=15		Control group *N*=15		
		N	*N*	*N*	*N*	
Sex	Male	11	73.3%	11	73.3%	1.000
	Female	4	26.7%	4	26.7%	
Smoking	Yes	6	40.0%	5	33.3%	.705
	No	9	60.0%	10	66.7%	

*Chi-square test

Variable	Group	Mean	Std. deviation	*P*.value
Age	Intervention group	48.67	8.449	.666
	Control group	47.13	10.676	
BMI	Intervention group	27.893	4.7358	.645
	Control group	27.100	4.6067	
SBP	Intervention group	144.33	22.109	.490
	Control group	139.67	13.425	
DBP	Intervention group	87.67	13.998	.822
	Control group	88.67	9.722	
Creatinine-baseline	Intervention group	1.580	.3448	.909
	Control group	1.593	.2840	
eGFR- baseline	Intervention group	52.73	14.921	.723
	Control group	51.07	10.138	
Total cholesterol- baseline Reference: < 200 mg/dl	Intervention group	204.60	30.577	.467
	Control group	192.13	57.969	
LDL-C- baseline Reference: < 100 mg/dl	Intervention group	133.87	32.876	.190
	Control group	111.67	54.846	
HDL-C- baseline Reference: ≥ 40 mg/dl	Intervention group	39.73	11.554	.336
	Control group	34.67	16.369	
TGs- baseline Reference: < 150 mg/dl	Intervention group	176.27	62.920	.239
	Control group	142.13	90.140	
HbA1C- baseline	Intervention group	5.298	.9938	.741
	Control group	5.213	.9410	
Urinary albumin/creatinine ratio- baseline	Intervention group	174.40	155.989	.890
	Control group	166.47	155.983	
Creatinine-after 3 months	Intervention group	1.273	.4367	**.005***
	Control group	1.693	.2865	
e-GFR- after 3 months	Intervention group	72.67	28.575	**.005***
	Control group	47.53	10.134	
Total cholesterol- after 3 months Reference: < 200 mg/dl	Intervention group	177.00	42.842	.110
	Control group	202.93	43.125	
LDL-C- after 3 months Reference: < 100 mg/dl	Intervention group	103.20	21.508	**.022***
	Control group	133.40	42.291	
HDL-C- after 3 months Reference: ≥ 40 mg/dl	Intervention group	43.47	11.507	.196
	Control group	39.00	6.199	
TGs- after 3 months Reference: < 150 mg/dl	Intervention group	171.20	79.575	.819
	Control group	164.93	68.532	
HbA1c- after 3 months	Intervention group	5.295	.8312	.898
	Control group	5.301	.8117	
Urinary albumin/creatinine- after 3 months	Intervention group	157.33	151.919	.694
	Control group	179.67	155.466	

*T-independent test

N Number, *BMI* Body mass index, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *eGFR* Estimated glomerular filtration rate, *LDL-C* Low-density lipoprotein-cholesterol, *HDL-C* High-density lipoprotein-cholesterol, *TG* Triglycerides, *Std.* Standard

Table 2 Baseline laboratory data compared to follow-up after 3 months within the studied groups

Variables		Intervention group $N=15$			Control group $N=15$		
		Mean	Std. deviation	*P* value	Mean	Std. deviation	*P* value
Pair 1	**Creatinine- baseline**	1.580	.3448	**<.001***	1.593	.2840	**.008***
	Creatinine- after 3 months	1.273	.4367		1.693	.2865	
Pair 2	**eGFR- baseline**	52.73	14.921	**.001***	51.07	10.138	**.011***
	e-GFR- after 3 months	72.67	28.575		47.53	10.134	
Pair 3	**Total cholesterol- baseline**	204.60	30.577	**.010***	192.13	57.969	.571
	Total cholesterol- after 3 months	177.00	42.842		202.93	43.125	
Pair 4	**LDL-C- baseline**	133.87	32.876	**.006***	111.67	54.846	.197
	LDL-C- after 3 months	103.20	21.508		133.40	42.291	
Pair 5	**HDL-C- baseline**	39.73	11.554	.091	34.67	16.369	.311
	HDL-C- after 3 months	43.47	11.507		39.00	6.199	
Pair 6	**TGs- baseline**	176.27	62.920	.727	142.13	90.140	.270
	TGs- after 3 months	171.20	79.575		164.93	68.532	
Pair 7	**HbA1C- baseline**	5.298	.9938	.823	5.213	.9410	.715
	HbA1c- after 3 months	5.295	.8312		5.301	.8117	
Pair 8	**Urinary albumin/creatinine- baseline**	174.40	155.989	*.058*	166.47	155.983	.105
	Urinary albumin/creatinine- after 3 months	157.33	151.919		179.67	155.466	

eGFR Estimated glomerular filtration rate, *LDL-C* Low-density lipoprotein-cholesterol, *HDL-C* High-density lipoprotein-cholesterol, *TG* Triglycerides, *Std.* Standard

* Paired sample *T*-test

impairment. It is worth noting that this was not the primary focus of those studies [13–16].

In our study, compared to baseline, patients who received dapagliflozin exhibited a significant decrease in LDL-C and total cholesterol values. Favorable outcomes were observed regarding triglyceride (TG) and HDL-C levels. In contrast, there was no significant change in the lipid profile of patients in the control group. These findings partially align with multiple clinical trials that have demonstrated SGLT-2 inhibitors' ability to decrease plasma TG levels and increase HDL-C levels [17]. However, it is important to note that these studies were conducted in patients with type 2 diabetes [18, 19]. In our study, we did not discern the anticipated increase in LDL-C levels associated with dapagliflozin treatment. While the precise impact of dapagliflozin on LDL-C levels remains incompletely understood, several mechanisms may contribute. These mechanisms include promoting weight loss, enhancing insulin sensitivity, increasing urinary glucose excretion, and potentially influencing liver function and lipid metabolism, which could ultimately lead to reduced LDL-C production. Although these mechanisms hint at a potential association between SGLT2 inhibitors and decreased LDL-C, further research is necessary to fully comprehend this relationship in patients with chronic kidney disease (CKD) [3]. Individual responses to statins vary due to genetic factors [20], with some people exhibiting better responsiveness. Additionally, the intervention group may have adhered more rigorously to dietary modifications, exercise, or weight management, or demonstrated better adherence to statin therapy. Furthermore, unmeasured confounders in our study could also play a role. However, these factors could introduce bias to the results.

Studies on individuals with DM reported that people whose LDL-C levels increased after receiving dapagliflozin experienced higher triglyceride (TG) levels (which were already slightly elevated compared to the reference range at baseline in our patients). This suggests a pivotal role of TG in the SGLT2 inhibitor-induced LDL-C elevation [21, 22].

Proteinuria shows a correlation with an atherogenic subspecies of LDL. Reducing proteinuria has a beneficial effect on lipid levels, regardless of the method used (such as medication or dietary changes). This effect was observed in the intervention group, as evidenced by a notable reduction in albumin-to-creatinine ratio (ACR), which may contribute to a reduction in LDL-C levels [23, 24].

While the dapagliflozin group experienced an approximate 22% reduction in LDL-C levels from the initial values, this decrease did not meet the desired target. According to current recommendations and large-scale observational studies, adults with CKD stages 1–4 who have been diagnosed with atherosclerotic cardiovascular disease (ASCVD), diabetes mellitus, or apparent proteinuria (similar to our patients) should strive for LDL cholesterol levels below 70 mg/dl [6].

Table 3 Comparison between the qualitative independent variables and parameters pre- and post-dapagliflozin administration (intervention group, $N = 15$)

	Sex					Smoking				
	Variable	N	Mean	Std. deviation	P value	Variable	N	Mean	Std. deviation	P value
Creatinine- baseline	Male	11	1.545	.3671	.540	Yes	6	1.733	.3882	.167
	Female	4	1.675	.2986		No	9	1.478	.2906	
eGFR- baseline	Male	11	57.73	13.915	.025*	Yes	6	46.33	12.817	.184
	Female	4	39.00	7.118		No	9	57.00	15.354	
Total cholesterol- baseline	Male	11	208.00	29.896	.496	Yes	6	207.67	19.775	.735
	Female	4	195.25	34.999		No	9	202.56	37.149	
LDL-C- baseline	Male	11	134.55	32.463	.900	Yes	6	133.67	42.359	.985
	Female	4	132.00	39.047		No	9	134.00	27.749	
HDL-C- baseline	Male	11	40.27	12.924	.776	Yes	6	41.50	17.830	.709
	Female	4	38.25	7.890		No	9	38.56	5.570	
TGs- baseline	Male	11	183.64	67.518	.472	Yes	6	170.33	68.342	.778
	Female	4	156.00	50.326		No	9	180.22	62.968	
HbA1C- baseline	Male	11	5.223	.8269	.384	Yes	6	5.300	.5582	.648
	Female	4	5.278	.0165		No	9	5.208	.8019	
Urinary albumin/creatinine- baseline	Male	11	170.55	166.716	.881	Yes	6	228.00	225.161	.389
	Female	4	185.00	143.875		No	9	138.67	85.468	
Creatinine- after 3 months	Male	11	1.209	.4527	.364	Yes	6	1.367	.4320	.519
	Female	4	1.450	.3873		No	9	1.211	.4540	
e-GFR- after 3 months	Male	11	81.27	27.178	.048*	Yes	6	65.50	29.084	.448
	Female	4	49.00	18.166		No	9	77.44	28.914	
Total cholesterol- after 3 months	Male	11	167.82	40.541	.177	Yes	6	174.67	36.517	.871
	Female	4	202.25	43.904		No	9	178.56	48.701	
LDL-C- after 3 months	Male	11	103.00	24.787	.955	Yes	6	104.00	25.314	.911
	Female	4	103.75	10.500		No	9	102.67	20.205	
HDL-C- after 3 months	Male	11	45.00	13.153	.412	Yes	6	46.17	18.659	.582
	Female	4	39.25	2.986		No	9	41.67	2.236	
TGs- after 3 months	Male	11	176.00	92.116	.713	Yes	6	178.50	74.629	.784
	Female	4	158.00	30.800		No	9	166.33	86.797	
HbA1c- after 3 months	Male	11	5.209	.9300	.718	Yes	6	5.210	.9423	.885
	Female	4	5.225	.5188		No	9	5.233	.7984	
Urinary albumin/creatinine- after 3 months	Male	11	152.73	159.322	.854	Yes	6	203.33	210.666	.435
	Female	4	170.00	150.997		No	9	126.67	100.031	

N Number, *BMI* Body mass index, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *eGFR* Estimated glomerular filtration rate, *LDL-C* Low-density lipoprotein-cholesterol, *HDL-C* High-density lipoprotein-cholesterol, *TG* Triglycerides, *Std.* Standard

asterisk means statistically significant

The synergistic effect of using SGLT2 inhibitors (SGLT2i) and statins together in humans remains unclear due to the limited availability of studies. However, research conducted on mice has demonstrated that combined treatment with dapagliflozin and atorvastatin improves lipid oxidation and reduces kidney lipid accumulation. This combination yields favorable effects on metabolic parameters and contributes to the reduction of oxidative stress, fibrosis, and apoptosis in an insulin-resistant model induced by a high-fat, high-fructose diet [25, 26].

In this study, we anticipated that either the estimated glomerular filtration rate (eGFR) would decrease or remain stable upon initiation of SGLT2 inhibitors (SLUT2i). However, we observed a noticeable improvement in these parameters within the intervention group, which contradicted the expected trend. In contrast, the control group experienced significant worsening. Despite these findings, predicting the duration and identifying individuals who will experience an acute eGFR dip remain challenging. In SGLT2 inhibitor trials, individuals who did experience an acute

Table 4 Comparison between the quantitative independent variables and parameters pre- and post-dapagliflozin administration (intervention group, $N = 15$)

		Age	BMI	SBP	DBP
Creatinine- baseline	*R* value	−.184	.268	−.058	−.203
	P value	.512	.334	.837	.469
	N	15	15	15	15
eGFR- baseline	*R* value	.070	−.262	−.133	.134
	P value	.806	.345	.637	.635
	N	15	15	15	15
Total cholesterol- baseline	*R* value	−.056	**.566**[a]	.028	.065
	P value	.843	**.028**[a]	.922	.817
	N	15	15	15	15
LDL-C- baseline	*R* value	−.494	.376	.079	−.006
	P value	.061	.167	.780	.983
	N	15	15	15	15
HDL-C- baseline	*R* value	.321	−.419	−.143	.170
	P value	.243	.120	.610	.544
	N	15	15	15	15
TGs- baseline	*R* value	−.431	.432	−.063	−.255
	P value	.109	.108	.823	.359
	N	15	15	15	15
HbA1C- baseline	*R* value	.115	.170	−.178	−.320
	P value	.683	.546	.526	.245
	N	15	15	15	15
Urinary albumin/creatinine- baseline	*R* value	−.201	−.040	−.038	.208
	P value	.472	.889	.894	.457
	N	15	15	15	15
Creatinine- after 3 months	*R* value	−.140	.068	−.231	−.145
	P value	.619	.811	.407	.605
	N	15	15	15	15
e-GFR- after 3 months	*R* value	.094	.014	.096	.087
	P value	.740	.959	.733	.757
	N	15	15	15	15
Total cholesterol- after 3 months	*R* value	−.235	**.554**[a]	.239	.162
	P value	.399	**.032**[a]	.392	.564
	N	15	15	15	15
LDL-C- after 3 months	*R* value	−.397	.256	−.122	−.221
	P value	.143	.356	.665	.428
	N	15	15	15	15
HDL-C- after 3 months	*R* value	.223	−.298	−.237	.047
	P value	.425	.280	.394	.867
	N	15	15	15	15
TGs- after 3 months	*R* value	−.228	−.064	−.068	−.359
	P value	.413	.820	.809	.189
	N	15	15	15	15
HbA1c- after 3 months	*R* value	.106	.229	−.138	−.401
	P value	.706	.412	.623	.139
	N	15	15	15	15
Urinary albumin/creatinine- after 3 months	*R* value	−.150	.021	−.079	.170
	P value	.594	.941	.778	.544
	N	15	15	15	15

N Number, *BMI* Body mass index, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *LDL-C* Low-density lipoprotein-cholesterol, *HDL-C* High-density lipoprotein-cholesterol, *TG* Triglycerides, *Std.* Standard

[a] Pearson correlation

Table 5 Predictors of total cholesterol level and LDL-C post-intervention (logistic regression)

| Model | Total cholesterol level-post intervention | | | | | | LDL-C level -post intervention | | | | | |
| | Unstandardized coefficients | | Standardized coefficients | P value | 95.0% confidence interval for B | | Unstandardized coefficients | | Standardized coefficients | P value | 95.0% confidence interval for B | |
	B	Std. error	Beta		Lower bound	Upper bound	B	Std. error	Beta		Lower bound	Upper bound
1 (Constant)	220.557	633.370		.745	−1537.960	1979.073	495.018	396.982		.280	−607.181	1597.216
Sex	10.861	84.335	.116	.904	−223.291	245.013	−35.717	52.859	−.760	.536	−182.478	111.044
Age	−1.164	1.978	−.230	.588	−6.655	4.327	−2.164	1.240	−.850	.156	−5.606	1.277
BMI	3.610	6.310	.399	.598	−13.911	21.130	−.692	3.955	−.152	.870	−11.673	10.290
SBP	.554	1.866	.286	.781	−4.627	5.735	.725	1.170	.745	.569	−2.523	3.972
DBP	−1.604	3.175	−.524	.640	−10.420	7.213	−2.110	1.990	−1.373	.349	−7.636	3.416
Smoking	32.805	81.367	.388	.707	−193.107	258.717	37.156	50.999	.876	.507	−104.440	178.753
Creatinine-baseline	−31.083	143.993	−.250	.840	−430.873	368.706	−68.047	90.252	−1.091	.493	−318.626	182.532
eGFR- baseline	−1.221	4.352	−.425	.793	−13.304	10.863	−1.962	2.728	−1.361	.512	−9.536	5.612
HbA1C- baseline	−1.405	7.901	−.055	.868	−23.342	20.532	−.330	4.952	−.026	.950	−14.079	13.420
Urinary albumin/ creatinine- baseline	.175	.156	.636	.325	−.258	.607	.071	.098	.512	.510	−.201	.342

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate

Table 6 Predictors of urinary albumin/creatinine ratio-post intervention (logistic regression)

Model		Unstandardized coefficients		Standardized coefficients	P value	95.0% confidence interval for B	
		B	Std. error	Beta		Lower bound	Upper bound
1	(Constant)	− 518.816	675.931		.486	− 2395.500	1357.868
	Sex	76.713	90.002	.231	.442	− 173.174	326.599
	Age	1.962	2.111	.109	.405	− 3.898	7.822
	BMI	4.784	6.734	.149	.517	− 13.914	23.482
	SBP	− 1.049	1.992	− .153	.626	− 6.578	4.481
	DBP	.463	3.389	.043	.898	− 8.946	9.872
	Smoking	− 14.579	86.835	− .049	.875	− 255.671	226.514
	Creatinine- baseline	118.224	153.669	.268	.485	− 308.431	544.878
	eGFR- baseline	3.394	4.645	.333	.505	− 9.502	16.290
	HbA1C- baseline	− 6.498	8.432	− .071	.484	− 29.909	16.913
	Urinary albumin/creatinine- baseline	.949	.166	.974	**.005***	.487	1.411

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate

eGFR dip generally had a lower absolute eGFR than non-dippers [27].

The findings from two studies involving patients with diabetes and chronic kidney disease (CKD) were matched with our results. In a study by Barnett et al., patients with stage 2–4 CKD who received empagliflozin treatment experienced only minor reductions in estimated glomerular filtration rate (eGFR). Importantly, these slight decreases promptly returned to baseline levels by the end of the 3-week follow-up after treatment completion [13]. Similarly, in the study by Haneda M et al., patients with type 2 diabetes mellitus and CKD initially saw a decline in eGFR during the first 2 weeks of luseogliflozin treatment. However, shortly thereafter, eGFR rebounded and consistently remained above baseline levels across all eGFR groups [14]. These findings highlight the impact of SGLT2 inhibitors on kidney function and suggest that any initial declines in eGFR may be reversible or even followed by improvement.

SGLT-2 inhibitors (SGLT2i) confer several indirect benefits for kidney function. They enhance glycemic control, promote weight loss, and reduce blood pressure. Furthermore, SGLT2 inhibitors (SGLT2i) may have a valuable impact on reducing proteinuria, not only in cases of microalbuminuria but also in more severe nephrotic-range proteinuria. This reduction in proteinuria contributes to slowing down the progression of chronic kidney disease. In the intervention group of this study, micro albuminuria significantly decreased following dapagliflozin administration [28–30]. The control group did not achieve the benefit of slowing down the progression of CKD with SGLT2 inhibitor use [31].

Regardless the dapagliflozin use, it has been found that, despite the typical relentless decline in renal function among most patients with chronic kidney disease (CKD), certain studies (REIN follow-up study, MDRD study, and the African-American Study of Kidney Disease and Hypertension (AASK) trial) have shed light on an intriguing phenomenon: a notable proportion of CKD patients experience sustained improved kidney function over time. These observations suggest that GFR improvement is possible at any CKD stage even through stage 4–5 [32–35].

Although this study had limitations due to a small patient cohort and short treatment duration, additionally, it lacked measurements of some confounders which may affect LDL-C levels; it underscores the need for additional research, particularly long-term clinical trials, to comprehensively explore the lipid-lowering and lipid-modifying effects of these medications in patients with chronic kidney disease.

Conclusion

Dapagliflozin favorably influences cholesterol fractions and kidney function in patients with stage 3 chronic kidney disease. SGLT2 inhibition is associated with a decrease in total cholesterol, LDL-C, triglycerides (TG), serum creatinine, and albumin-creatinine ratio, as well as increases in HDL-C, and estimated glomerular filtration rate (eGFR) in this population.

Abbreviations

ACR	Albumin/creatinine ratio
BMI	Body mass index
CKD	Chronic kidney disease
CVD	Cardiovascular disease

DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
HDL-C	High-density lipoprotein-cholesterol
LDL-C	Low-density lipoprotein-cholesterol
SBP	Systolic blood pressure,,
SGLT2 inhibitors	Sodium glucose co-transporter 2 inhibitors
TG	Triglycerides
TRL-TG	Triglyceride-rich lipoprotein

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Authors' contributions
All authors contributed to study design, screening of all citations from full-text papers retrieved, data collection, and final revision of the manuscript.

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Availability of data and materials
All data generated in this study are included in this published article.

Declarations

Ethics approval and consent to participate
This study was reviewed and approved by Faculty of Medicine, Cairo University Research Ethics Committee (REC), with the *approval number N-152–2023* and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the all patients participated in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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