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Research Article

Real-World Evaluation Of Dapagliflozin And Empagliflozin In Type 2 Diabetes: Cardiorenal And Metabolic Perspectives.

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Abstract

Diabetes mellitus is a global health issue with numerous complications, and SGLT-2 inhibitors can slow kidney disease progression, reduce heart failure, and lower the risk of kidney failure and death in individuals with CKD.

This study evaluated the impact of Sodium-glucose co-transporter 2 (SGLT2) inhibitors, specifically dapagliflozin and empagliflozin, on cardiovascular and renal health in Type 2 Diabetes Mellitus (T2DM) patients at Benghazi Diabetes Center (BDC). The study involved 600 T2DM patients initiating dapagliflozin or empagliflozin, and collected data from interviews, structured questionnaires, and electronic medical records. After three months of treatment, the analysis showed significant improvements in glycemic control, weight management, blood pressure, and lipid profiles, reduced albuminuria, and improved estimated glomerular filtration rate (eGFR) and ejection fraction (EF). However, drug- and sex-specific nuances were revealed. Dapagliflozin showed numerically greater improvements in BP, postprandial glucose, lipid parameters, plasma urea, and albuminuria, while empagliflozin demonstrated numerically greater reductions in weight, body mass index, fasting plasma glucose, and eGFR. Females showed greater reductions in PPG, weight, BMI, BP, and plasma urea, while males demonstrated more pronounced improvements in FPG, triglycerides, low-density lipoprotein cholesterol, albuminuria, and EF. Combined SGLT2 inhibitor use with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers did not show statistically significant differences in clinical parameters compared to SGLT2 inhibitor monotherapy. SGLT2 inhibitors show beneficial effects on cardiorenal and metabolic parameters in T2DM patients, with variations based on drug and sex, emphasizing personalized treatment plans and urging further research.

Keywords: SGLT2 inhibitors, dapagliflozin, empagliflozin, type 2 diabetes, cardiorenal effects, and metabolic parameters.

INTRODUCTION

Diabetes mellitus (DM) is a complex metabolic disorder that has become a global epidemic, posing a significant threat to public health [1]. The increasing incidence of cardiovascular disease (CVD) and chronic kidney disease (CKD) in individuals with diabetes has become a major concern, as these comorbidities elevate the risk of adverse cardiovascular events and renal complications [2-6]. The interconnectedness of diabetes, CVD, and CKD highlights the need for therapeutic strategies that extend beyond glycemic control [3-7]. SGLT2 inhibitors, emerging as a promising class of medications, have shown the potential to address both hyperglycemia and associated cardiovascular and renal complications [8]. These medications, by inhibiting the reabsorption of glucose in the kidneys, lower blood sugar levels and exert protective effects on the heart and kidneys [9]. This research aims to improve patient outcomes by establishing locally relevant data on the safety and efficacy of SGLT2 inhibitors. The study also extends to evaluating a broader range of metabolic parameters, including weight, BMI, glycemic indices, and lipid profiles. The complex and interconnected nature of T2DM as a systemic metabolic disorder justifies a comprehensive approach to understanding the therapeutic profile and protective effects of these medications. However, the precise mechanisms of these protective mechanisms are still under investigation.

The study aims to evaluate the safety and effectiveness of SGLT2 inhibitors (dapagliflozin and empagliflozin) in type 2 diabetes patients, considering factors like demographics, medication use, potential synergistic effects, prescribing practices, side effects, and cardiorenal and metabolic changes over three months, considering factors like overweight, poor glycemic control, and renal protection.

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METHODS

Study Design

The study used a mixed-methods design to assess changes in patient characteristics and baseline parameters after SGLT2 inhibitors were initiated. It included 600 patients with T2DM, aged 30 to 98, with 269 males and 331 females. Of these, 279 received dapagliflozin, and 321 received empagliflozin. The study assessed changes in patient characteristics and baseline parameters over three months.

Inclusion and Exclusion Criteria

The study objects to determine the eligibility criteria for T2DM treatment, including diagnosis, initiation of treatment, and meaningful data at the three-month follow-up visit. Exclusion criteria include T1DM, pregnancy, incomplete data, follow-up duration less than three months, and discontinuation of SGLT2 inhibitor within three months.

Data Collection

The study collected data through patient interviews, structured questionnaires, and electronic medical records. It included demographics, medical and surgical history, SGLT2 inhibitor treatment history, medication use, and clinical parameters. At baseline and three months, data was collected on weight, height, BMI, BP, EF, FPG, PPG, HbA1c, lipid profile, albuminuria, plasma urea, plasma Cr, and eGFR. BMI was calculated as weight. The non-HDL-C, and eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration.

Data Handling and Sample Size

The study focused on family history and EF analyses, with only 228 participants having complete family history data and 150 participants having complete EF data.

Statistical Analysis

The study used IBM SPSS Statistics version 23 to analyze data, calculating descriptive statistics like means, ranges, standard deviations, frequencies, and percentages for relevant variables. Change from baseline was calculated as the difference after treatment minus before treatment, with $p<0.001$ being highly significant. Pearson's correlation coefficients were used to evaluate linear relationships between variables.

Ethical Considerations

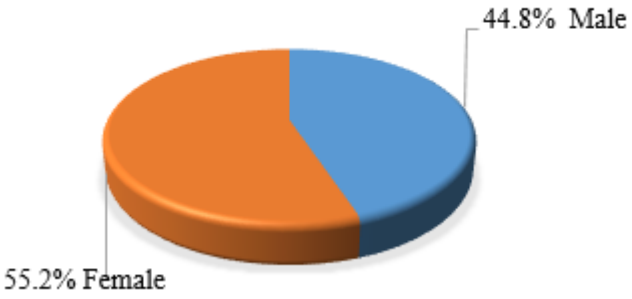
The study protocol received ethical approval from the research ethics committees of the University of Tripoli and the BDC. Verbal informed consent was obtained from all participants. Data were anonymized to maintain patient confidentiality following the Declaration of Helsinki.

RESULTS

Patient Demographics, Baseline Clinical Characteristics, and SGLT2 Inhibitor Treatment.

This study enrolled Libyan female patients (55.2%) compared to males (44.8%) in **Fig 1**. at the BDC between May 2022 and June 2023, with a majority falling within the 51-60 years age group (33.2%) and the 61-70 age group (31.8%, Table 1.). Only 6.2% had diabetes for more than 30 years with 43.3% having diabetes for 10-19 years (Table 1). Only 11.8% were smokers and 35.3% had a family history of T2DM (**Table 1**). The most commonly prescribed dosages were empagliflozin (10 mg) and dapagliflozin (5 mg, Table 1). The highest utilization was observed for dapagliflozin (36%).

Figure 1. Gender Distribution of Participants.



As initially outlined in **Figure 1**, the study cohort consisted of 600 participants, with a slightly higher prevalence of females (55.2%) compared to males (44.8%). Further analysis was conducted to delineate the specific effects of dapagliflozin and empagliflozin across different demographics and clinical categories.

Table 1. Characteristics of SGLT2 inhibitor use in patients with T2DM by gender (N=600).

Characteristic	Male	Female	Total
Gender	269 (44.8%)	331 (55.2%)	600 (100%)
Age			
≤ 40 years	10 (3.7%)	3 (0.9%)	13 (2.2%)
41 – 50 years	43 (16.0%)	26 (7.9%)	69 (11.5%)
51 – 60 years	84 (31.2%)	115 (34.7%)	199 (33.2%)
61 – 70 years	69 (25.7%)	122 (36.8%)	191 (31.8%)
71 – 80 years	51 (19.0%)	59 (17.8%)	110 (18.3%)
> 80 years	12 (4.5%)	6 (1.8%)	18 (3%)
Duration of T2DM			
< 10 years	69 (25.7%)	75 (22.7%)	144 (24%)
10-19 years	103 (38.2%)	157 (47.4%)	260 (43.3%)
20-29 years	77 (28.6%)	82 (24.8%)	159 (26.5%)
≥ 30 years	20 (7.4%)	17 (5.1%)	37 (6.2%)
Smoking			
Smoking	71 (26.4%)	0 (0%)	71 (11.8%)
Non-smoking	198 (73.6%)	331 (100%)	529 (88.2%)
Family history of T2DM			
Yes	97 (36.1%)	115 (34.7%)	212 (35.3%)
No	6 (2.2%)	10 (3.0%)	16 (2.7%)
Unavailable	166 (61.7%)	206 (62.1%)	372 (62%)
SGLT2 inhibitors members and their doses			
Empagliflozin (all doses)	**127 (47.2%)**	**194 (58.6%)**	**321 (53.5%)**
Empagliflozin 25 mg	42 (15.6%)	53 (16.0%)	95 (15.8%)
Empagliflozin 12.5 mg	20 (7.4%)	45 (13.6%)	65 (10.8%)
Empagliflozin 10 mg	65 (24.2%)	96 (29.0%)	161 (26.8%)
Dapagliflozin (all doses)	**142 (52.7%)**	**137 (41.4%)**	**279 (46.5%)**
Dapagliflozin 10 mg	98 (36.4%)	118 (35.7%)	216 (36%)
Dapagliflozin 5 mg	44 (16.4%)	19 (5.7%)	63 (10.5%)

The impact of SGLT2 inhibitor on the classification of essential cardiovascular and metabolic parameters

The study examined the effects of SGLT2 inhibitors on clinical and biochemical parameters in 600 patients, with a subset of 155 patients examining EF (**Table 2**). The administration of SGLT2 inhibitors led to significant improvements in various parameters, including weight, BMI, systolic and diastolic blood pressure, FPG, PPG, and HbA1c (*P<0.001*, Table 2,). Lipid profiles also improved, with significant reductions in TG, TC, LDL-C (*P<0.001*, Table 2) and non-HDL-C (*P=0.004*, Table 2). Renal parameters showed reduced plasma urea and Cr, an increase in eGFR, and a significant decrease in albuminuria (Table 2). The mean EF showed a notable increase, with a 47.06% decrease in albuminuria and a mean increase of 16.85% (*P<0.001*, Table 2). The study also found strong positive correlations between pre- and post-treatment values for most parameters, with the highest correlations for weight and BMI. Moderate, significant associations were found for systolic and diastolic BP, and all other correlations were also significant and moderately positive. The study found a small standard error of the mean for each parameter at baseline and post-intervention, with a mean height of 163.48 cm. Correlation analysis showed the highest correlation for pre-post changes in weight, BMI, and EF, with diastolic BP showing the lowest correlation. A paired t-test revealed a significant difference in all measured parameters due to SGLT2 administration, with several parameters showing highly significant changes with $p < 0.001$, and a significant change was noted in HDL-C. SGLT2 inhibitor administration resulted in significant improvements across several parameters, including weight, BMI, systolic BP, and diastolic BP. Renal parameters were positively affected, with reduced plasma urea and plasma Cr, an increase in eGFR, a marked reduction in albuminuria, and a notable increase in the mean EF.Paired samples correlations indicated strong, significant ($p < 0.001$) positive correlations between pre- and post-treatment values for most parameters, with the highest correlations for weight and BMI ($r = 0.99$) for both. Moderate, significant associations were found for systolic ($r = 0.68$) and

diastolic BP (r = 0.46), and all other correlations were also significant and moderately positive.

Table 2. Effects of SGLT2 inhibitors on patient's biological parameters (N = 600).

Parameter	Time point	Mean	SD	SEM	Change	% Change	P-value	r
Weight (Kg)	Before	93.61	18.17	0.74	-3.77	-4.03	< 0.001	0.99
	After	89.84	16.96	0.69				
BMI (Kg/m2)	Before	35.23	7.16	0.29	-1.43	-4.06	< 0.001	0.99
	After	33.80	6.73	0.27				
Systolic BP (mmHg)	Before	131.78	16.26	0.66	-7.06	-5.36	< 0.001	0.68
	After	124.72	13.86	0.57				
Diastolic BP (mmHg)	Before	82.09	9.38	0.38	-3.61	-4.39	< 0.001	0.46
	After	78.48	6.87	0.28				
FPG (mg/dL)	Before	186.36	64.89	2.65	-37.63	-20.20	< 0.001	0.58
	After	148.73	51.01	2.08				
PPG (mg/dL)	Before	217.59	74.43	3.04	-41.80	-19.21	< 0.001	0.65
	After	175.79	62.90	2.57				
HbA1c (%)	Before	9.47	1.79	0.07	-1.25	-13.20	< 0.001	0.70
	After	8.22	1.42	0.06				
TG (mg/dL)	Before	175.78	95.65	3.90	-39.91	-22.70	< 0.001	0.76
	After	135.87	60.07	2.45				
HDL-C (mg/dL)	Before	43.97	14.59	0.60	1.18	2.68	0.004	0.75
	After	45.15	13.56	0.55				
TC (mg/dL)	Before	171.45	46.08	1.88	-23.20	-13.53	< 0.001	0.64
	After	148.25	39.40	1.61				
Non-HDL-C (mg/dL)	Before	125.67	47.03	1.92	-23.80	-18.94	< 0.001	0.62
	After	101.87	39.08	1.60				
LDL-C (mg/dL)	Before	100.50	37.71	1.54	-15.10	-15.02	< 0.001	0.67
	After	85.40	31.61	1.29				
Plasma Urea (mg/dL)	Before	33.46	14.38	0.59	-3.85	-11.51	< 0.001	0.66
	After	29.61	10.91	0.45				
Plasma Cr (mg/dL)	Before	0.86	0.31	0.01	-0.13	-15.12	< 0.001	0.81
	After	0.73	0.24	0.01				
eGFR (mL/min/1.73m²)	Before	84.74	21.86	0.89	9.12	10.76	< 0.001	0.83
	After	93.86	19.56	0.80				
Albuminuria (mg/g Cr)	Before	120.44	287.84	11.75	-56.68	-47.06	< 0.001	0.86
	After	63.76	177.85	7.26				
EF (%)	Before	45.87	12.65	1.02	7.73	16.85	< 0.001	0.89
	After	53.60	11.27	0.91				

Abbreviations: *BMI: Body Mass Index; BP: Blood Pressure; Cr: Creatinine; EF: Ejection Fraction; eGFR: Estimated Glomerular Filtration Rate; FPG: Fasting Plasma Glucose; HbA1c: Glycated hemoglobin; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; Non-HDL-C: Non-High-Density Lipoprotein Cholesterol; PPG: Postprandial Plasma Glucose; r: Correlation Coefficient; SD: Standard Deviation; SEM: Standard Error of the Mean; SGLT2: Sodium-glucose co-transporter 2; TC: Total Cholesterol; TG: Triglycerides. Note: Paired t-tests were used to compare continuous variables from baseline to 3 months post-treatment. P < 0.05 was considered statistically significant, p < 0.01 highly significant, and p < 0.001 very highly significant.*

Table 3. Effects of SGLT2 inhibitors on male patient's biological parameters (n = 269, EF n = 79).

Parameter	Time point	Mean	SD	SEM	Change	% Change	P-value	r
Weight (Kg)	Before	95.41	17.60	1.07	-3.53	-3.70	< 0.001	0.99
	After	91.88	16.53	1.01				
BMI (Kg/m2)	Before	32.42	6.02	0.37	-1.19	- 3.67	< 0.001	0.99
	After	31.23	5.77	0.35				
Systolic BP (mmHg)	Before	132.20	17.80	1.09	-6.93	- 5.24	< 0.001	0.64
	After	125.28	14.31	0.87				
Diastolic BP (mmHg)	Before	81.80	8.08	0.49	-3.40	- 4.15	< 0.001	0.36
	After	78.40	6.37	0.39				
FPG (mg/dL)	Before	185.55	67.76	4.13	-38.55	-20.78	< 0.001	0.55
	After	147.00	51.07	3.11				
PPG (mg/dL)	Before	213.77	70.45	4.30	-39.29	-18.38	< 0.001	0.62
	After	174.48	64.08	3.91				
HbA1c (%)	Before	9.37	1.81	0.11	-1.26	- 13.44	< 0.001	0.67
	After	8.11	1.43	0.09				
TG (mg/dL)	Before	178.74	107.75	6.57	-42.54	-23.80	< 0.001	0.78
	After	136.20	65.92	4.02				
HDL-C (mg/dL)	Before	40.37	10.57	0.64	0.81	2.01	0.150	0.60
	After	41.18	10.13	0.62				
TC (mg/dL)	Before	163.74	47.82	2.92	-23.42	-14.30	< 0.001	0.63
	After	140.32	37.40	2.28				
Non-HDL-C (mg/dL)	Before	121.42	48.79	2.98	-23.72	-19.54	< 0.001	0.62
	After	97.70	38.03	2.32				
LDL-C (mg/dL)	Before	96.56	38.46	2.35	-15.30	-15.84	< 0.001	0.64
	After	81.27	31.96	1.95				
Plasma urea (mg/dL)	Before	34.78	15.13	0.92	-3.60	-10.38	< 0.001	0.63
	After	31.18	11.32	0.69				
Plasma Cr (mg/dL)	Before	0.95	0.31	0.02	-0.13	-13.80	< 0.001	0.79
	After	0.82	0.25	0.02				
eGFR (mL/min/1.73m^2)	Before	86.82	22.62	1.38	8.78	10.11	< 0.001	0.83
	After	95.60	20.82	1.27				
Albuminuri (mg/g Cr)	Before	144.53	318.03	19.39	-67.61	-46.78	< 0.001	0.85
	After	76.92	210.29	12.82				
EF (%)	Before	41.15	11.18	1.26	9.10	22.11	< 0.001	0.85
	After	50.25	10.45	1.18				

Abbreviations: *BMI: Body Mass Index; BP: Blood Pressure; Cr: Creatinine; EF: Ejection Fraction; eGFR: Estimated Glomerular Filtration Rate; FPG: Fasting Plasma Glucose; HbA1c: Glycated hemoglobin; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; Non-HDL-C: Non-High-Density Lipoprotein Cholesterol; PPG: Postprandial Plasma Glucose; r: Correlation Coefficient; SD: Standard Deviation; SEM: Standard Error of the Mean; SGLT2: Sodium-glucose co-transporter 2; TC: Total Cholesterol; TG: Triglycerides. Note: Paired t-tests were used to compare continuous variables from baseline to 3 months post-treatment. P < 0.05 was considered statistically significant, p < 0.01 highly significant, and p < 0.001 very highly significant.*

Table 4. Effects of SGLT2 inhibitors on female patient's biological parameters (n = 331, EF n = 76).

Parameter	Time point	Mean	SD	SEM	Change	% Change	P-value	r
Weight (Kg)	Before	92.14	18.51	1.02	- 3.96	-4.29	< 0.001	0.98
	After	88.19	17.15	0.94				
BMI (Kg/m2)	Before	37.49	7.21	0.40	-1.60	-4.27	< 0.001	0.98
	After	35.89	6.74	0.37				
Systolic BP (mmHg)	Before	131.44	14.90	0.82	-7.18	-5.47	< 0.001	0.71
	After	124.26	13.49	0.74				
Diastolic BP (mmHg)	Before	82.33	10.32	0.57	-3.78	-4.59	< 0.001	0.51
	After	78.55	7.26	0.40				
FPG (mg/dL)	Before	187.01	62.55	3.44	-36.88	-19.72	< 0.001	0.61
	After	150.13	50.99	2.80				
PPG (mg/dL)	Before	220.69	77.48	4.26	-43.83	-19.86	< 0.001	0.67
	After	176.86	62.00	3.41				
HbA1c (%)	Before	9.54	1.77	0.10	-1.23	-12.92	< 0.001	0.72
	After	8.31	1.41	0.08				
TG (mg/dL)	Before	173.37	84.64	4.65	-37.77	-21.78	< 0.001	0.74
	After	135.60	54.96	3.02				
HDL-C (mg/dL)	Before	46.89	16.63	0.91	1.48	3.16	0.010	0.79
	After	48.37	15.07	0.83				
TC (mg/dL)	Before	177.72	43.70	2.40	-23.03	-12.96	< 0.001	0.64
	After	154.69	39.86	2.19				
Non-HDL-C (mg/dL)	Before	129.12	45.33	2.49	-23.87	-18.49	< 0.001	0.62
	After	105.26	39.65	2.18				
LDL-C (mg/dL)	Before	103.69	36.84	2.02	-14.93	-14.39	< 0.001	0.69
	After	88.76	30.96	1.70				
Plasma urea (mg/dL)	Before	32.38	13.67	0.75	-4.04	-12.48	< 0.001	0.69
	After	28.34	10.42	0.57				
Plasma Cr (mg/dL)	Before	0.78	0.28	0.02	-0.13	-16.06	< 0.001	0.79
	After	0.66	0.21	0.01				
eGFR (mL/min/1.73m²)	Before	83.05	21.10	1.16	9.40	11.32	< 0.001	0.82
	After	92.45	18.38	1.01				
MAU (mg/g Cr)	Before	100.87	259.60	14.27	-47.81	-47.40	< 0.001	0.89
	After	53.06	145.75	8.01				
EF (%)	Before	50.78	12.29	1.41	6.30	12.41	< 0.001	0.90
	After	57.08	11.10	1.27				

Abbreviations: *BMI: Body Mass Index; BP: Blood Pressure; Cr: Creatinine; EF: Ejection Fraction; eGFR: Estimated Glomerular Filtration Rate; FPG: Fasting Plasma Glucose; HbA1c: Glycated hemoglobin; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; Non-HDL-C: Non-High-Density Lipoprotein Cholesterol; PPG: Postprandial Plasma Glucose; r: Correlation Coefficient; SD: Standard Deviation; SEM: Standard Error of the Mean; SGLT2: Sodium-glucose co-transporter 2; TC: Total Cholesterol; TG: Triglycerides.*

Note: *Paired t-tests were used to compare continuous variables from baseline to 3 months post-treatment. P < 0.05 was considered statistically significant, p < 0.01 highly significant, and p < 0.001 very highly significant.*

Figure 2. Mean Changes in Clinical Parameters by Gender and Dapagliflozin.

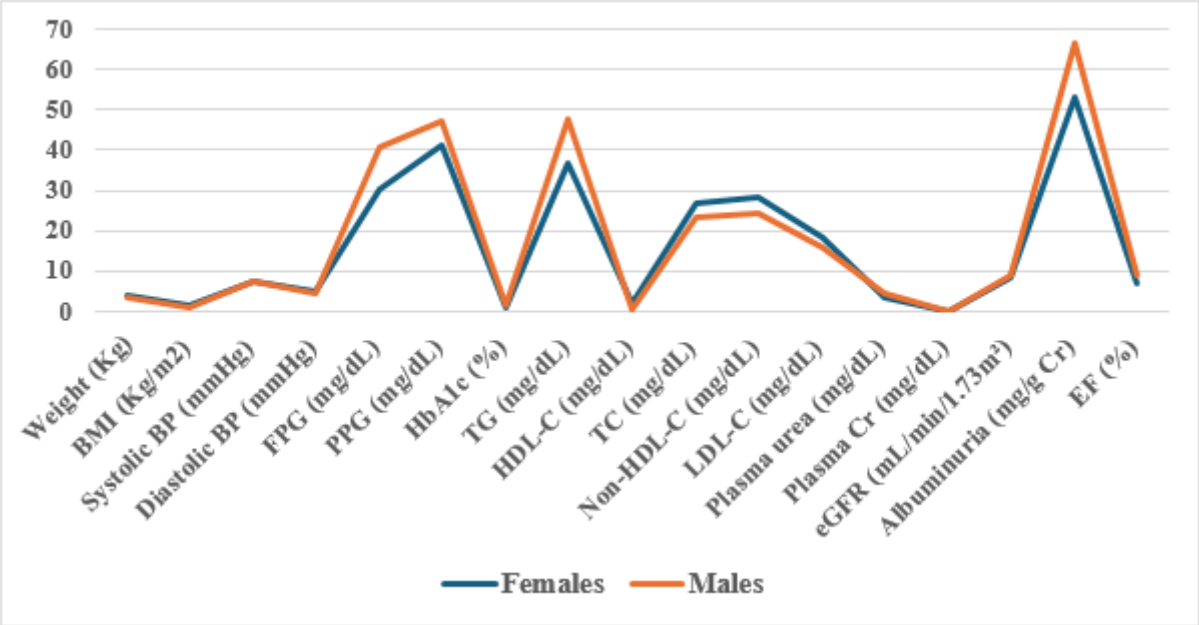


Figure 2 illustrates the mean changes in clinical parameters specifically for patients treated with dapagliflozin (n=279), stratified by gender. In this subgroup, male patients demonstrated a pronounced mean reduction in systolic blood pressure of 7.6 mmHg and a fasting plasma glucose (FPG) drop of 39.5 mg/dL. Female patients treated with dapagliflozin, conversely, showed greater improvements in different metabolic markers, experiencing a more significant mean reduction in postprandial glucose (PPG) of 44.8 mg/dL and a notable decrease in plasma urea of 4.3 mg/dL.

Figure 3. Mean Changes in Clinical Parameters by Gender and Empagliflozin.

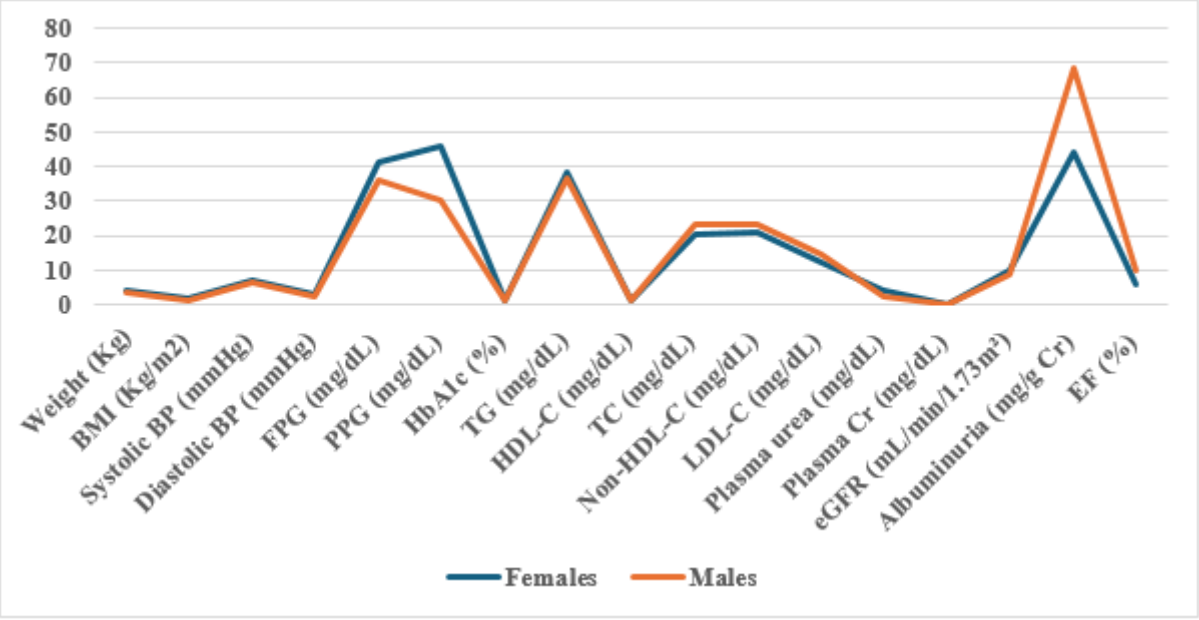
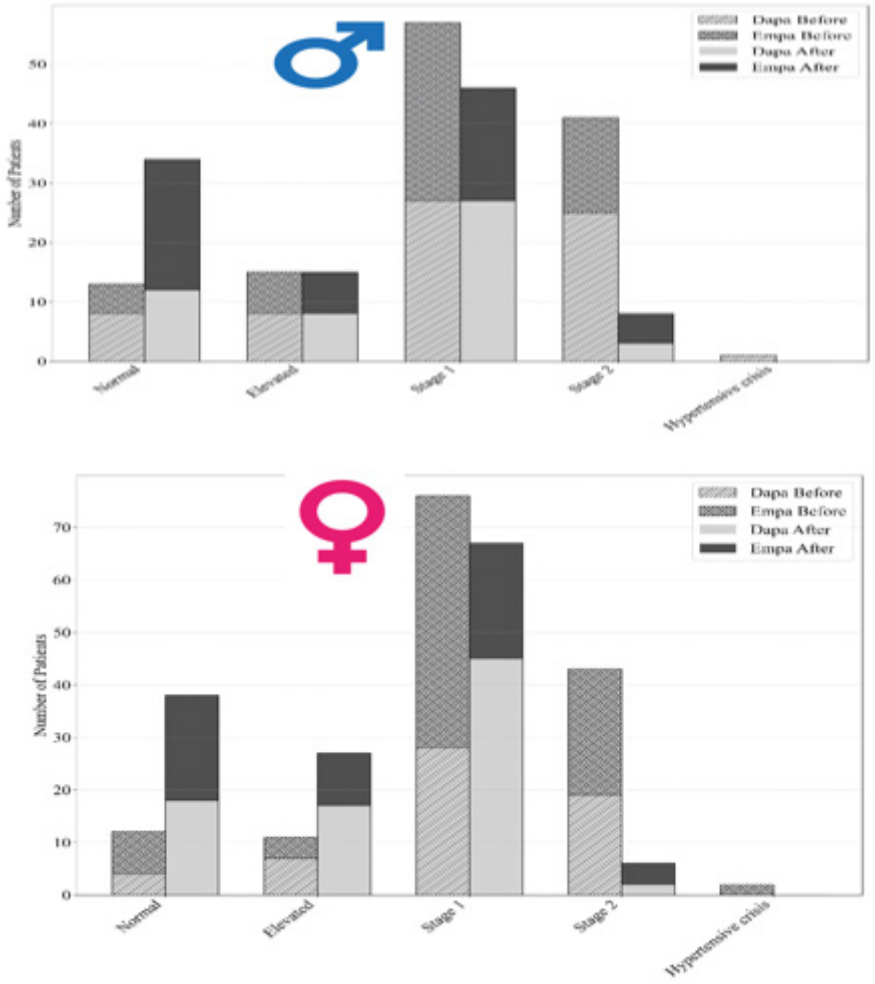


Figure 3 details the corresponding parameter changes for patients administered empagliflozin (n=321). In this cohort, females achieved a slightly greater mean weight reduction of 4.2 kg compared to a 3.5 kg reduction in males. However, male patients showed superior improvements in their lipid profiles, notably a reduction in triglycerides (TG) of 43.8 mg/dL, compared to 38.2mg/dL in females. Renal protection markers were consistent across both genders in this group, with the estimated glomerular filtration rate (eGFR) increasing by an average of 9.8 mL/min/1.73m2.

Figure 4. The Effect of SGLT2 Inhibitors on Classification of HTN Among the Participants.



The broad impact of SGLT2 inhibitors on cardiovascular strain is further highlighted by the shifts in hypertension (HTN) classification among participants, summarized in **Figure 4**. At baseline, 46% of the total cohort was classified as having Stage 2 hypertension (systolic ≥140 mmHg or diastolic ≥ 90 mmHg). Following three months of SGLT2 inhibitor therapy, this proportion significantly decreased to 29%. Concurrently, the percentage of patients classified within the "Elevated" or "Normal" blood pressure categories increased from 14% at baseline to 35% post-intervention, underscoring the systemic hemodynamic benefits of the treatment.

Table 5. BMI Changes in the Patients Treated with Dapa or Empa.

Empagliflozin			BMI	Dapagliflozin			Comment	
Change (n)	**Before (n)**	**After (n)**	**Categories**	**After (n)**	**Before (n)**	**Change (n)**	**Overall effect**	**For**
0	0	0	Underweight	1	1	0	↔	---
2	9	11	Normal	14	11	3	↑	Dapa
11	42	53	Overweight	47	40	7	↑	Empa
7-	39	32	Moderate obesity	53	54	-1	↓	Empa
1-	23	22	Severe obesity	15	20	-5	↓	Dapa
5-	14	9	Morbid obesity	12	16	-4	↓	Empa

Fig 6. Mean Changes in eGFR and Albuminuria Over 3 Months of SGLT2 Inhibitor therapy.

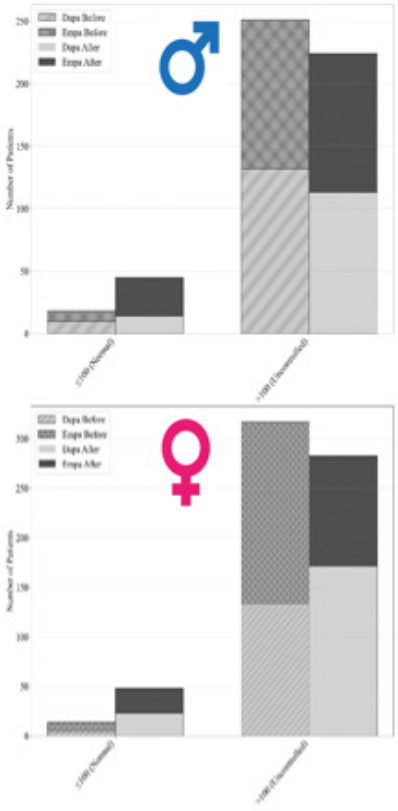


Fig 7. Pre- and Post-Treatment Ejection Fraction by Gender.

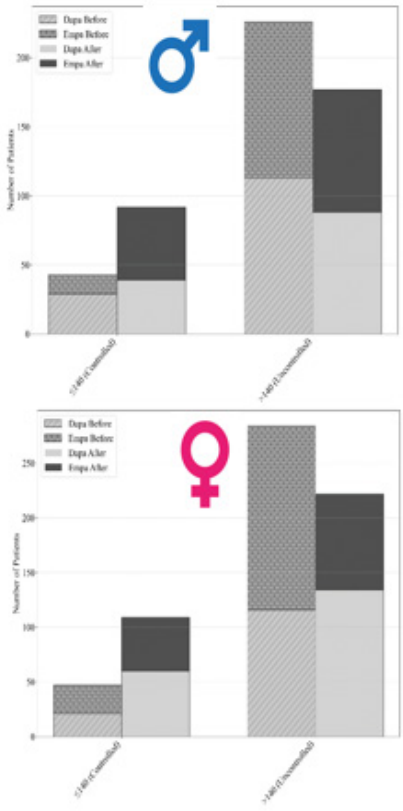


Fig 8. SGLT2 Monotherapy vs. ACEI/ARB Combination Therapy.

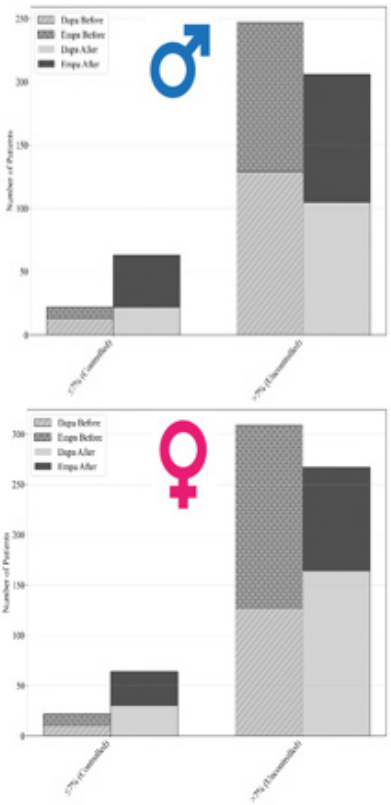


Figure 5 isolates the changes in Body Mass Index (BMI), directly comparing the efficacy of the two prescribed medications. While both drugs yielded highly significant weight loss ($p<0.001$), patients treated with empagliflozin demonstrated a numerically greater mean BMI reduction of 1.62kg/m2 (dropping from a baseline of 35.45 to 33.83 kg/m2). In comparison, the dapagliflozin group experienced a mean BMI reduction of 1.21 kg/m2 (dropping from 34.98 to 33.77 kg/m2). This aligns with the overall finding that while SGLT2 inhibitors universally improve metabolic profiles, empagliflozin shows a slightly more pronounced effect on BMI and weight management.The profound renoprotective effects of SGLT2 inhibitors within the cohort are visualized in Figure 6, which tracks the inverse relationship between estimated Glomerular Filtration Rate (eGFR) and albuminuria over the three-month period. Across the entire cohort, patients experienced a significant mean increase in eGFR from 84.7 to 93.86 mL/min/1.73m2. Concurrently, this improvement in renal filtration was paired with a drastic reduction in renal stress, depicted by a 47.06% decrease in mean albuminuria (dropping from a baseline of 120.44 mg/g Cr to 63.76 mg/g Cr). This confirms the drugs' efficacy in mitigating diabetic nephropathy progression.

Figure 7 highlights the cardioprotective benefits by detailing the changes in Ejection Fraction (EF) in the subset of patients (n=155) who had complete echocardiographic data. The bar chart demonstrates a remarkable recovery in myocardial function, with the overall mean EF increasing from a baseline of 45.87% to 53.60% post-treatment. Notably, male participants showed a more pronounced cardiac recovery, with their mean EF increasing by 22.11% compared to a 12.41% increase in female participants, suggesting potential sex-specific hemodynamic responses to the therapy.

Finally, Figure 8 addresses the evaluation of potential synergistic effects between SGLT2 inhibitors and standard antihypertensive medications. The analysis compared a subgroup of patients on SGLT2 inhibitor monotherapy against those receiving concomitant therapy with Angiotensin-Converting Enzyme Inhibitors (ACEIs) or Angiotensin II Receptor Blockers (ARBs). Contrary to expectations of a compounded effect, the data revealed no statistically significant differences in the reduction of systolic blood pressure ($p=0.31$), diastolic blood pressure ($p=0.45$), or albuminuria ($p=0.28$) between the monotherapy and combination therapy groups. Both groups achieved parallel, highly significant improvements from their respective baselines, indicating that the cardiorenal and metabolic benefits of SGLT2 inhibitors are independently robust and not reliant on ACEI/ARB co-administration. In addition, Table 6. illustrates the shifts in lipid profile classifications before and after treatment with SGLT2 inhibitors in men and women.

Table 6. Changes in Kidney Function Test Classifications Before and After SGLT2 Inhibitors.

Lipid profile Classification		Male before SGLT2 inhibitor	Male after SGLT2 inhibitor	Female before SGLT2 inhibitor	Female after SGLT2 inhibitor
TC mg/dL					
Normal	< 200	218	252	228	295
Borderline high	200 - 239	35	12	79	27
High	≥ 240	16	5	24	9
LDL-C mg/dL					
Normal	< 130	214	246	259	301
Borderline high	130 - 159	36	18	44	24
High	160 - 189	16	4	21	5
Very high	≥ 190	3	1	7	1
HDL-C mg/dL					
At risk	≤ 50 for male	235	230	127	94
	≤ 40 for female				
Normal	> 50 for male	34	39	204	237
	> 40 for female				
TG mg/dL					
Normal	< 150	128	191	158	220
Borderline high	150 - 199	70	45	83	66
High	≥ 200	71	33	90	45
Non-HDL-C mg/dL					
Normal	≤130	161	221	168	238
High	>130	108	48	163	93
Total	269	269	331	331	

DISCUSSION

The cohort included 55.2% females and 44.8% males, with the majority aged 51–70 years and a median diabetes duration of 15.4 years. Cardiovascular comorbidities were highly prevalent, with hypertension in 79.7% and ischemic heart disease in 46%. Males exhibited higher rates of PVD and IHD, while females had higher rates of hypertension. Declining eGFR was observed in individuals aged 60+ and those with longer diabetes duration.

SGLT2i initiation was more common in females, with Empagliflozin demonstrating superior reductions in weight, BMI, fasting plasma glucose (FPG), and eGFR compared to Dapagliflozin. Concomitant therapy was frequent with metformin (93%) and insulin (80.7%), alongside β blockers, ARBs, ACE inhibitors, and statins. Adverse event rates were low overall, with genitourinary tract infections (48%) and diabetic ketoacidosis (28%) being the most notable. Clinical outcomes showed significant improvements in glycemic control (FPG, PPG, HbA1c), BMI categories, lipid profiles, and kidney function classifications.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have emerged as a cornerstone in the management of type 2 diabetes (T2D), offering benefits that extend beyond glycaemic control [9]. Clinical evidence demonstrates robust cardiorenal protection, with reductions in cardiovascular death and hospitalizations for heart failure observed in both diabetic and nondiabetic patients with reduced ejection fraction [10]. These effects are mediated through inhibition of glucose reabsorption in the proximal renal tubules, leading to improved hemodynamic, enhanced sodium excretion, and reduced myocardial stress [11]. Additionally, SGLT2 inhibitors promote a metabolic shift from glucose to ketone utilization, potentially improving myocardial efficiency [12].

Landmark randomized clinical trials (RCTs) have substantiated these findings. The EMPA-REG OUTCOME trial (empagliflozin) and DECLARE-TIMI 58 trial (dapagliflozin) reported significant reductions in heart failure-related death and hospitalization [13]. Similarly, the CANVAS program (canagliflozin) demonstrated slower decline in estimated glomerular filtration rate (eGFR) and reduced albuminuria, while EMPA-REG also showed reduced progression to end-stage renal disease [14-15]. These renoprotective effects are attributed to reductions in glomerular hyperfiltration and modulation of tubuloglomerular feedback [15].

Beyond hemodynamic and metabolic mechanisms, SGLT2 inhibitors may exert cardioprotective effects through activation of nutrient deprivation pathways. By inducing a fasting-like paradigm, they appear to stimulate sirtuin-1 (SIRT1) and downstream mediators such as PGC-1α and FGF21, which are known to alleviate oxidative stress, promote autophagy, and enhance mitochondrial function [16]. Notably,

SGLT2 is not expressed in the heart, yet activation of the SIRT1/PGC-1α/FGF21 axis provides a plausible explanation for their cardioprotective profile. While no direct clinical trials have specifically investigated SIRT1 activation by SGLT2 inhibitors, preclinical evidence and overlapping biological effects strongly suggest a potential interplay that warrants further exploration.

Subgroup analyses from major RCTs have also addressed gender and obesity. Few trials have directly targeted obese populations, but several have reported consistent cardiovascular and renal protection across BMI categories, with modest weight loss and improved metabolic control [17]. Importantly, benefits are observed in both men and women, with no clinically significant sex differences. This supports the use of SGLT2 inhibitors irrespective of gender or obesity status, though lifestyle interventions remain essential for more substantial weight reduction.

Comparisons with earlier intensive glycemic control trials (UKPDS, ACCORD, ADVANCE, VADT) highlight a paradigm shift: while strict glucose lowering yielded mixed cardiovascular outcomes, SGLT2 inhibitors demonstrate multi-system protective effects independent of glycemic control [18]. Together with glucagon-like peptide-1 receptor agonists (GLP-1 RAs), they represent a new era of cardiometabolic therapy in high-risk T2D patients [19].

Total cholesterol shows a clear improvement, with more individuals in the normal category and a decrease in borderline and high categories, indicating SGLT2 inhibitors effectively normalize cholesterol levels. LDL-C, known as “bad cholesterol,” also reflects this pattern, with increased normal classifications for both sexes and fewer patients in the higher risk categories, suggesting cardiovascular risk protection, Evidence suggests SGLT2 inhibitors improve lipid metabolism, modestly lowering triglycerides and LDL-C while raising HDL-C. [20].

The study showed that HDL-C, or “good cholesterol,” improves more significantly in women compared to men, with a notable increase in those classified as normal. Triglycerides also exhibit positive changes, with more patients falling into the normal category post-treatment and reductions in borderline and high classifications. Non-HDL cholesterol, which encompasses all atherogenic particles, shows significant improvement as well, with more patients classified as normal and fewer in high-risk categories. Genetic analyses confirm that SGLT2 inhibition reduces risks of heart failure, coronary artery disease, and stroke, with part of the benefit mediated by changes in blood lipids (especially non-HDL cholesterol and LDL-C) [20-24].

Overall, SGLT2 inhibitors contribute to a healthier lipid profile by decreasing harmful cholesterol fractions and increasing beneficial ones. While both sexes benefit, women show greater improvements in HDL levels [25]. These findings suggest that SGLT2 inhibitors may also reduce cardiovascular risk in addition to their known glucose control and kidney protection benefits through favorable lipid modulation.

Conclusion and guidance for the future work

This real-world study proved that SGLT2 inhibitors act as multi-system protective agents, not merely glucose-lowering drugs. They provide consistent cardiovascular and renal protection across sexes and BMI categories, with modest improvements in diabetic dyslipidemia and metabolic control. Although direct clinical evidence linking SGLT2 inhibitors to SIRT1 activation is lacking, the overlap in biological pathways suggests a promising mechanistic connection that may contribute to their cardioprotective effects. Future research should clarify this interaction, as understanding the role of SIRT1 could inform the development of novel therapeutic strategies for diabetes and cardiovascular disease.

Limitations

This study has several important limitations. Its retrospective observational design without a control group restricts causal inference and leaves results vulnerable to confounding. Missing data for key parameters such as family history and ejection fraction may have introduced bias, while the short three month follow up captures only immediate outcomes rather than long term cardiorenal protection. Subgroup analyses were underpowered, raising the risk of Type II error, and uncontrolled confounders such as lifestyle factors and concurrent medications further limit interpretability. Patient adherence and variability in data recording were not measured, potentially influencing outcomes, and finally, the findings may have limited generalizability to other ethnicities, populations, or healthcare systems.

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