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Empagliflozin use in cardiac transplant patients

Real world experience from Saudi Arabia

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Abstract

Objectives: Sodium-glucose transport protein 2 inhibitor |(SGLT2) drugs are used to treat patients with type 2 diabetes. In additions to their beneficial metabolic effects in lowering the glaciated hemoglobin, body weight and blood pressure, these agents have shown favorable and protective effects on the heart and the kidneys. These cardio renal benefits are seen even in people without diabetes. There is little evidence on the safety and efficacy of SGLT2 inhibitors use in cardiac transplant recipients. We wanted to study the cardiac transplant recipients who used Empagliflozin for the treatment of diabetes to evaluate its safety and efficacy in this niche sub group of patients. ***Method:*** We retrospectively identified 20 patients on the cardiac transplant recipient register taking Empagliflozin (Jardiance) or Empagliflozin combined with Metformin (Synjardy). We studied the safety and efficacy parameters. ***Results:*** Our results show improvement in HBA1c, body weight and stability in serum creatinine. There was no increased risk of genitourinary infection, hypoglycemia or diabetic ketoacidosis. ***Conclusion:*** While we need larger studies in cardiac transplant patients taking Empagliflozin, our small study provides assurance that Empagliflozin is safe to use in cardiac transplant recipients.

Keywords: Empagliflozin; Cardiac Transplant Recipients; Synjardy; Type 2 Diabetes; SGLT2 inhibitors.

Advances in Knowledge

- Empagliflozin is a safe oral antidiabetic drug option for treating patients with diabetes and cardiac transplants. It does not increase the risk of genitourinary infection even when patients are on immunosuppressive drugs, providing reassurance.
- The use of empagliflozin helps stabilize body weight and serum creatinine while improving HbA1c levels in patients with diabetes.

Applications to Patient Care

- We expect that empagliflozin (SGLT2 inhibitors) will be more widely used in patients with diabetes post-cardiac transplant and will not be limited to patients with diabetes, diabetic nephropathy, ischemic heart disease, or heart failure.

Introduction

Empagliflozin is an oral anti-diabetic agent and it belongs to the sodium-glucose transport protein 2 inhibitors class (SGLT2i). It works on the SGLT2 receptors on the proximal tubules in the nephrons and inhibits the reabsorption of filtered glucose.[1] This unique insulin-independent mechanism of action leads to glycosuria and a net loss of sodium and water to regulate glucose homeostasis.

The focus of diabetes care over many decades has been achieving reasonable glycemic control. The publication of the EMPA REG trial in 2015 led to a change in this landscape.[2] This trial demonstrated that in addition to glycemic control, Empagliflozin reduced the risk of major adverse cardiovascular events (MACE) by 13%. In addition, patients who used Empagliflozin had a reduced risk of cardiovascular mortality. This landmark trial shifted the focus of clinicians from being glucocentric to ensuring cardiovascular risk reduction in patients with diabetes. Further evidence from the Emperor reduced[3] and Emperor preserved[4] randomized control trials showed that Empagliflozin was able to reduce the risk of cardiovascular mortality and heart failure-related admissions regardless of the presence or absence of diabetes.

A meta-analysis of six randomized control trial involving over 46,000 patients with type 2 diabetes treated with four different types of SGLT2 inhibitors demonstrates that the SGLT2

inhibitors as a class has favorable effects on cardiovascular risk reduction.[5] Likewise, another meta-analysis of eight randomized controlled trials including over 60,000 patients taking another drug class, Glucagon-like peptide 1 (GLP-1), has demonstrated similar results in improving glycemic control and minimizing cardiovascular risks.[6]

Rivinius et al report that nearly one third of the cardiac transplant recipients have pre-existing type 2 diabetes which increased their risk of graft failure and mortality at five years.[7] Similarly, the cardiac transplant recipient patients are at heightened risk of developing post-transplant diabetes (PTDM) in approximately 25% of the patients.[8] The development PTDM increases the morbidity and mortality in these transplant patients.[8] While extensive evidence exists in the use of Empagliflozin in high-risk diabetes patients with enhanced cardiovascular risk[5], there is a paucity of evidence of its use in cardiac transplant recipients taking immunosuppressive drugs, which increases the risk of infections and cardiac and renal impairment.

Our aim was to study the safety and efficacy of use of Empagliflozin in cardiac transplant recipients with pre-existing type 2 diabetes. Our objective was to evaluate the efficacy parameters including HBA1c, weight, BMI, serum creatinine and the safety parameters that included genitourinary infection risk.

Methods

We identified our target patients from the cardiac transplant registry at our institution using keywords: diabetes, Empagliflozin, Synjardy, Jardiance. We identified 20 patients who met these criteria. We included all patients who initiated empagliflozin post-transplant for the treatment of pre-existing type 2 diabetes. We reviewed the electronic medical records of our study population. We included patients who used the study drug for at least six months and we had their baseline and the follow up clinical data for two clinic follow ups. We recorded the first follow-up data from 2-4 months and the second follow-up data from 5-7 months from baseline. We studied the safety parameters including the episodes of genitourinary infection and hypoglycemia. We studied the efficacy parameters including the change in HBA1c, weight, serum creatinine and e GFR. Twelve patients took Empagliflozin and metformin combination (Synjardy) and continued it, five patients took Empagliflozin 25mg daily and three patients took Empagliflozin 10 mg daily.

We summarized baseline characteristics using continuous variables and presented them as mean and standard deviation (SD). We used frequencies (n), percentages (%), and graphs to present summary data for continuous and categorical variables. We collected the data in the password protected Redcap software hosted at our institution. We anonymized the data and adhered with the institutional confidentiality guidelines. We took the approval for conducting the study from the institutional research committee. We adhered to the CARE checklist for case series during our study.

Results

We had 20 patients with mean age of 49.6 years. 75% were male patients (table 1). Mean body weight was 73 ± 18.03 kg. More than 60% of the patients were in the overweight to obese category. Mean HBA1c was 8.48%. ± 1.89 The predominant reason for requiring the cardiac transplant was cardiomyopathy followed by the coronary artery disease. Our patients had extensive prior cardiovascular disease history with 60% having coronary artery disease and 55% had heart failure and 35% of the patients had history of hospitalization due to acute heart failure during the preceding 12 months. Most patients were taking more than one anti-rejection medication. All patients were taking steroids: two patients were taking Cyclosporin, seventeen patients were taking Tacrolimus, and eighteen patients were taking Mycophenolate.

HBA1c improved from mean baseline HBA1c of 8.48% ± 1.89 to 8.02 ±2.90 at the second follow up (figure 1). The body weight changed from 73.24 Kg ± 18.03 to 72.27 Kg ± 19.40 (figure 2). The body mass index improved from 27.47 Kg/m² to 26.72 Kg/m² (figure 3). The eGFR remained stable from baseline of 62.3 ± 6.82 to 64.33 ±5.74. Serum creatinine reduced from baseline of 92.85 ± 24.25 to 79.33 ±28.80 (figure 4). All patients had a post-transplant echo within three months, and ejection fraction (EF) was >50%. Eighteen patients had echo results available at six months: EF was > 50 % in twelve patients, 40-49% in two patients and <40% in four patients. One patient had transplant rejection between 3-6 months. One patient developed genitourinary infection that required oral antibiotics treatment. No patient experienced hypoglycemic episodes or diabetic ketoacidosis that required hospitalization. Four patients were treated in the hospital for renal impairment during the follow up period. Empagliflozin was temporarily held and resumed for these patients at discharge from the hospital.

Discussion

Patients taking SGLT2 inhibitors are at increased risk of genitourinary infection.[2] This risk is enhanced further when taking immunosuppressive drugs post-cardiac transplant. Only one patient in our study group experienced the genitourinary infection, which was amicably treated with oral antibiotics and did not require hospitalization or withdrawal of Empagliflozin, which provides reassurance.

Diabetic ketoacidosis (DKA) is a rare occurrence in patients with type 2 diabetes. However, there are some reports of euglycemic ketoacidosis in patients taking SGLT2 inhibitors.[9] This risk is mitigated by temporarily omitting its use during acute illness and perioperative periods. During our study, no patient developed DKA, which provides confidence in using Empagliflozin in cardiac transplant recipients.

Hypoglycemia is an undesirable but well-recognized side effect of any diabetes care regimen. Hypoglycemia is seen often in patients taking either insulin or drugs that increase insulin secretion. Empagliflozin works in an insulin-independent mechanism by enhancing glucose excretion in the urine and therefore it does not increase the risk of hypoglycemia particularly when not used with either insulin or insulin secretagogues.[1] None of our patients reported hypoglycemia that required hospitalization or third-party assistance which is consoling.

Dehydration and renal impairment led to the hospitalization of three patients. During the acute illness and the treatment, Empagliflozin was held temporarily and restarted when the patient recovered prior to discharge from the hospital. Treatment with SGLT2 inhibitors can lead to increased urine volume by approximately 300 ml per day.[1] This fluid loss is usually of no consequence in most patient with diabetes. However, in patients with significant comorbidity such as heart transplant and possible concurrent use of diuretics can increase the risk of dehydration. This risk of dehydration is compounded by the fact that Saudi Arabia records high temperatures reading 50 degrees in summer, which can further contribute to dehydration. Clinicians should exercise caution when using SGLT2 inhibitors in patients with comorbidities and those with simultaneous use of diuretics.

Our results are similar to those observed by Cehic et al in their cohort of 22 patients in terms of safety and efficacy.[10] While these are small observational studies, concrete evidence is

expected from the currently ongoing randomized controlled trial on the use of Empagliflozin in cardiac transplant recipients.[11]

Our study draws its strength from the availability of unique data from the cardiac transplant recipients with type 2 diabetes using Empagliflozin, a population that is otherwise not well-studied or published. Diabetes is a prevalent disease, and Empagliflozin is a well-established oral anti-diabetes agent. Considering these parameters, the study sample though small should be significant. However, we focused on a niche population of heart transplant recipients, which makes this sample size reasonable.

Our study's weaknesses include the retrospective design. In addition, our results are from the Saudi population in Saudi Arabia and are not applicable to other geographical areas or ethnicities. Furthermore, most patients in our study did not have any results for proteinuria. Proteinuria is common in transplant recepient. It is multifactorial due to the use of immunosuppressive drugs such as cyclosporine, tacrolimus, Sirolimus, Everolimus, pressence of diabetes, hypertension and episodes of transplant rejection. Regular monitoring of urine protein is essential. The use of therapies such as angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) can help reduce the proteinuria. Additionally, good control of blood pressure and diabetes with be invaluable. Future studies should include measurement of proteinuria.

Conclusion

While we need larger studies in cardiac transplant patients taking Empagliflozin, our small study provides assurance that Empagliflozin is safe to use in cardiac transplant recipients.

Authors' Contribution

MIB conceptualized and designed the study. RMHA, NA and RA collected the data, while MIB, NA and RA analyzed the data. NA and RA prepared the tables and figures. MIB drafted the manuscript. All authors critically reviewed the manuscript and approved the final version.

Conflict of Interest

The authors declare no conflicts of interest.

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Table 1: Baseline clinical characteristics of cardiac transplant recipients with type 2 diabetes taking Empagliflozin (n=20)

Age (years), mean± SD	49.6 ± 16.42
Sex	
Male n (%)	15 (75%)
Female n (%)	5 (25%)
Weight (Kg), mean± SD=n=19*	73.24 ± 18.03
Body mass index (Kg/m²) , n= 19 (%) *	
Under 20	1 (5.26%)
20 to 24.99	6 (31.58%)
25 to 29.9	4 (21.05%)
30 to 34.9	7 (36.84%)
35 to 39.9	1 (5.26%)
Blood pressure mmHg n= 19*	
Systolic, mean± SD	122.15 ± 14.54
Diastolic, mean± SD	74.57 ± 11.96
Duration of Diabetes	
Less than 5 years	3 (15%)
5 up to 10 years	2 (10%)
More than 10 years	7 (35%)

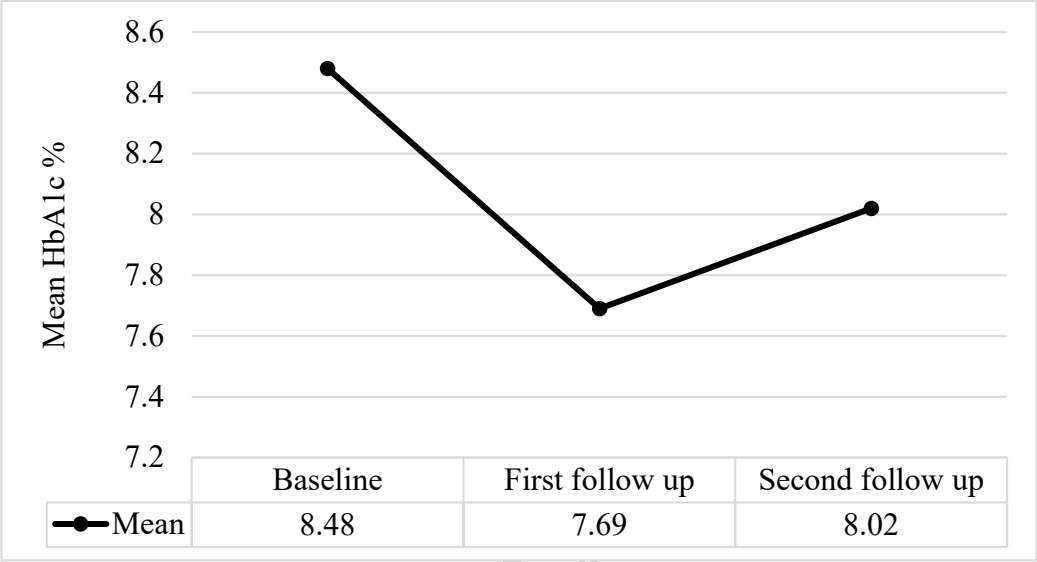
Unknown	8 (40 %)
Hemoglobin A1C	
Less than 6	2 (10%)
6-6.9%	3 (15%)
7-7.9%	2 (10%)
8-8.9%	5 (25%)
9-9.9%	2(10%)
10% and over	4 (20%)
Not done	2 (10%)
Hemoglobin A1C, % , mean±SD n= 18*	8.48 ± 1.89
Serum creatinine level, mean±SD (µmol/L)	92.85 ± 24.25
Glomerular filtration rate (GFR)	
Less than 45	0(0%)
45 to 59	7 (35%)
60 or more	13 (65%)
Reason for cardiac transplant n=20 **	
Cardiomyopathy	19 (95%)
Coronary heart disease	8 (40%)
End stage heart failure	3 (15%)
Recurrent arrhythmias not controlled with all other treatment options	1 (5%)
Cardiovascular disease past medical history n=20 (%)***	
Coronary disease	12 (60%)
Cerebrovascular disease	1 (5%)
Heart failure	11 (55%)
History in the last 12 months prior to prescription	
Genital infection	0 (0%)
Urinary tract infections	0 (0%)
Hospitalization for hypoglycemia	0 (0%)

Hospitalization for heart failure	7 (35%)

*Missing information.

**Multiple etiologies requiring transplant .

*** Patients with multiple diseases

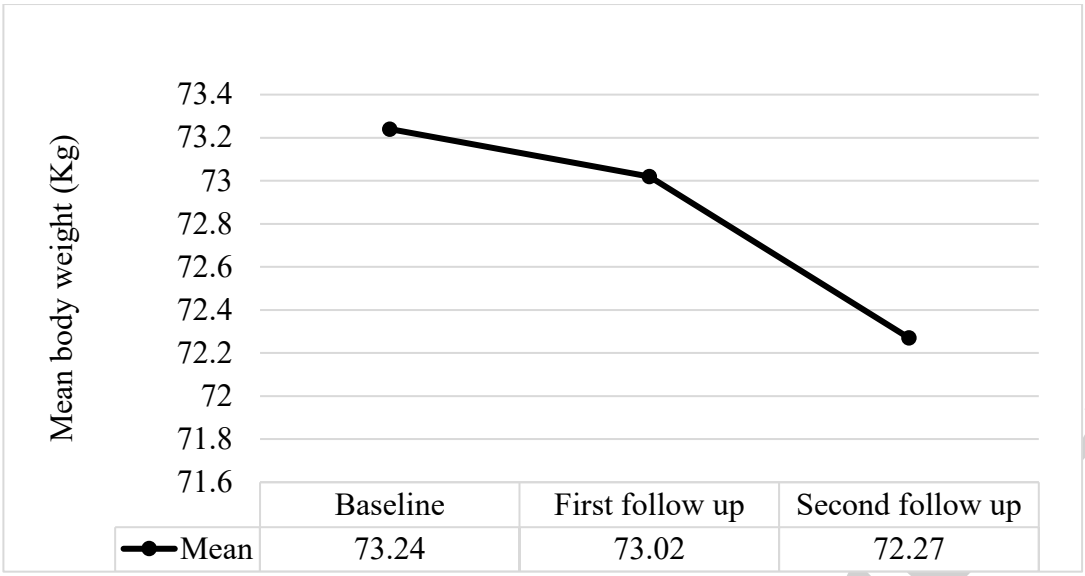


HbA1c	Mean	SD	Median	IQR	Q25	Q75	N
Baseline	8.48	1.89	8.5	2.8	6.8	9.6	18*
First follow up	7.69	1.74	7.3	2.2	6.3	8.5	11
Second follow up	8.02	2.90	7.2	1.3	6.2	7.5	9

Figure 1: Change in Glycated hemoglobin (HbA1c)

**Missing information in two patients*

HbA1c= Glycated hemoglobin; SD= Standard deviation; IQR= Interquartile range

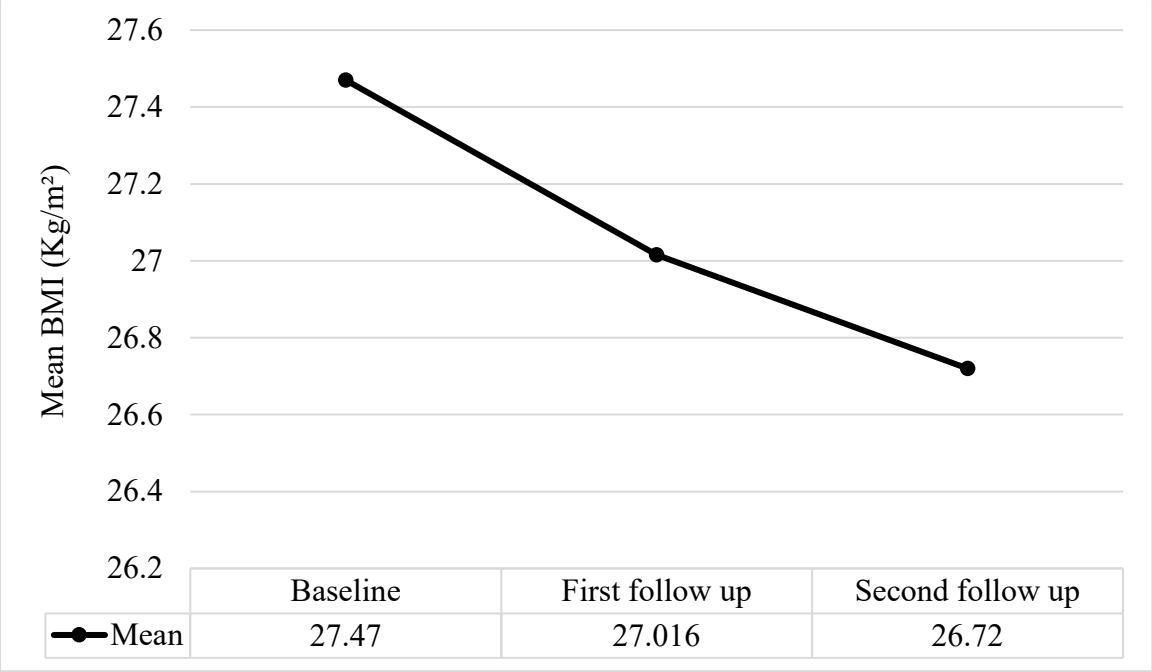


Weight	Mean	SD	Median	IQR	Q25	Q75	N
Baseline	73.24	18.03	70	23.1	60	83.1	19*
First follow up	73.02	18.69	72.55	18.3	62	80.3	18
Second follow up	72.27	19.40	71	25	60	85	15

Figure 2: Change in the body weight (Kg)

*Missing information in one patient

SD= Standard deviation; IQR= Interquartile range

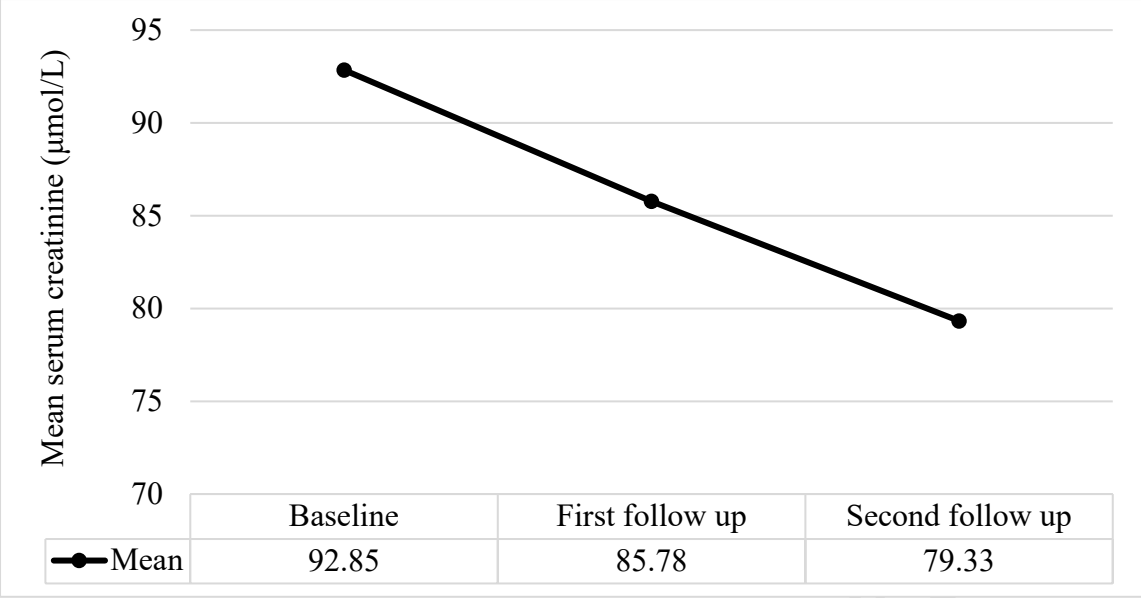


BMI	Mean	SD	Median	IQR	Q25	Q75	N
Baseline	27.47	5.47	27	8	23.1	31.1	19*
First follow up	27.016	5.32	26.35	6.29	23.7	30	18
Second follow up	26.72	5.70	28	9.5	21.5	31	15

Figure 3: Change in the body mass index (BMI)

*Missing information in one patient

SD= Standard deviation; IQR= Interquartile range; BMI= Body mass index



Serum creatinine	Mean	SD	Median	IQR	Q25	Q75	N
Baseline	92.85	24.25	97.5	25.5	82	107.5	20
First follow up	85.78	25.78	85	32	73	105	19
Second follow up	79.33	28.80	75	32	66	98	15

Figure 4: Change in serum creatinine

SD= Standard deviation; IQR= Interquartile range