

Efficacy and safety of empagliflozin: a “real-world” experience from Saudi Arabia

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BACKGROUND: Sodium-glucose cotransporter 2 (SGLT2) inhibitors are new agents for treating type 2 diabetes. In addition to the glycemic benefits, these agents provide cardiorenal protection in patients with diabetes and without diabetes. There is consistent evidence that these agents increase the risk of genitourinary infections and dehydration, but randomized controlled trials have not included patients from the Middle East.

OBJECTIVES: Determine the efficacy and safety of empagliflozin, specifically whether the genitourinary infection risk differs in our population and whether there is an increased risk of dehydration, ketoacidosis, hypoglycemia, and hospitalization with fasting.

DESIGN: Retrospective review of medical records.

SETTINGS: Department of medicine at tertiary care center.

PATIENTS AND METHODS: We reviewed the electronic records of patients with type 2 diabetes who took empagliflozin from 1 December 2018 to 30 November 2019. We collected safety and efficacy data for 12 months from the initiation of treatment.

MAIN OUTCOMES MEASURES: Glycemic and weight loss efficacy, risk of hospitalization due to hypoglycemia, dehydration, and genitourinary infections.

SAMPLE SIZE: 637 patients.

RESULTS: We observed an improvement in glycated hemoglobin, a 4.2% weight loss, improved left ventricular function, stable serum creatinine, and reduced albuminuria. Our patients did not have an increased risk of genitourinary infections, hypoglycemia, dehydration, ketoacidosis, or hospitalizations. Fasting did not increase the incidence of adverse events.

CONCLUSIONS: Empagliflozin is safe and effective in our local population. We hypothesize that glycosuria induced by empagliflozin is not the sole contributor to the increased risk of genitourinary infections. Local hygiene and circumcision might reduce this risk. Empagliflozin can be used safely during fasting.

LIMITATIONS: Retrospective design.

CONFLICT OF INTEREST: None.

The kidneys filter nearly 180 grams of glucose daily and then virtually reabsorb all of this glucose. This reabsorption occurs with the help of the sodium-glucose cotransporter 1 (SGLT1) and sodium-glucose cotransporter 2 (SGLT2) receptors located in the proximal convoluted tubules in the nephron. The SGLT2 receptors reabsorb approximately 90% of the filtered glucose in a healthy person. The remaining glucose reabsorption occurs through the SGLT1 receptors. As a result, urine remains nearly free of any glucose. Therefore, these receptors and the kidneys provide a unique means to control blood glucose in patients with diabetes, working independently of insulin secretion and the pancreas.

SGLT2 inhibitor drugs target and block these receptors leading to a significant reduction in glucose reabsorption in the nephron. This phenomenon leads to glycosuria, a net loss of calories, osmotic diuresis, improvement in diabetes, and simultaneously conferring a blood pressure-lowering effect and moderate weight loss. Due to their non-insulin-based mechanism of action, these agents minimize any risk of hypoglycemia.

The FDA approved the first SGLT2 inhibitor canagliflozin in 2013,¹ followed by further approval of dapagliflozin, empagliflozin,² and others in this class to treat patients with type 2 diabetes. Interest in using these agents has grown considerably recently as studies have shown that these agents provide cardiorenal protection in patients with type 2 diabetes, reducing the risk of complications of diabetes.³⁻⁷ Further, emerging evidence has shown that these cardiac benefits are seen in patients regardless of the presence or absence of diabetes.⁸⁻¹⁰ These trials have consistently demonstrated a significantly increased risk of mycotic genital tract infections as a class effect. Moreover, urinary tract infections have been higher (but not statistically significantly higher) in patients treated with this class of drugs. This increased risk of infections is related to glycosuria.

Recruitment for these trials lacked any representation from our region. There are, however, some observational studies on SGLT2 inhibitors from Saudi Arabia^{11,12} and the United Arab Emirates.¹³ We, therefore, conducted this “real-world” safety and efficacy study on the use of SGLT2 inhibitor drug empagliflozin (Jardiance, Boehringer Ingelheim and Eli Lilly), empagliflozin/metformin (Synjardy, Boehringer Ingelheim and Eli Lilly). Empagliflozin is the only available SGLT2 inhibitor in our hospital.

There is a specific consideration for our region and patients. Most of the population in the Middle East is Muslim by religion, and most males undergo circumcision at birth or an early age. Moreover, thorough water-

based cleaning of private body parts is our region's most typical method of hygiene. It is crucial to understand if these factors can alter the risk of genitourinary infection or if this risk is exclusively related to glycosuria that these agents induce. These drugs lead to osmotic diuresis of approximately 300-350 mL of extra urine volume per 24 hours. The patients pass more urine each time they void rather than having increased urinary urgency. Under normal circumstances, this is of no adverse consequence. However, the local population observes fasting during Ramadan; some people fast on random days during the rest of the year. Additionally, our region has very low humidity and records very high temperatures, particularly during the long summer. These factors can increase the risk of dehydration, renal impairment, and ketosis in the context of volume loss due to these drugs.

PATIENTS AND METHODS

Our study included all patients aged 18 years and over with or without type 2 diabetes who had received the SGLT2 inhibitor empagliflozin either as a single agent (Jardiance) or in combination with metformin (Synjardy) for four months or more. We excluded patients not taking empagliflozin. We identified patients from the pharmacy records. Empagliflozin was available at our institution in December 2018. We, therefore, included all patients who received the drugs from 1 December 2018 to 30 November 2019. We collected data for 12 months from the initiation of treatment. We anonymized and collected the data using research electronic data capture (REDCap) software and maintained patient confidentiality per institutional policy. The hospital research committee approved the project.

We used Stata version 17.0 software to perform statistical analyses. 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.

RESULTS

We identified 637 patients taking empagliflozin (Jardiance/Synjardy) from the hospital pharmacy records. Of the 637, 46% were males, and 54% were females, with a median age of 62 years (**Table 1**). Nearly all patients had type 2 diabetes (99.7%) of varying duration. Most patients were taking other oral diabetes agents with or without insulin. HbA1c was reduced slightly during the treatment with empagliflozin (**Figure 1**). **Figure 2** shows median body weight was reduced by 3.6 kilograms during treatment with empagliflozin,

Table 1. Baseline characteristics of all patients (n=637).

Age (years)	62 (56-69)
Male	292 (45.8)
Female	345 (54.2)
Weight (kg) (n=597)	84 (75-97.6)
Body mass index (kg/m ²) (n=597)	
Under 20	02 (0.3)
20 to 24.99	40 (6.7)
25 to 29.9	180 (30.1)
30 to 34.9	174 (29.1)
35 to 39.9	116 (19.4)
40 and over	85 (14.2)
Blood pressure (n=614)	
Systolic	131 (119-140)
Diastolic	75 (68-82)
Duration of diabetes	
Less than 5 years	11 (1.7)
5 up to 10 years	111 (17.5)
More than 10 years	328 (51.6)
Unknown	185 (29.1)
Hemoglobin A1C (%) (n=636)	
Less than 6	1.4
6-6.9	4.9
7-7.9	16.2
8-8.9	28.9
9-9.9	21.2
10 and over	22.2
Not checked	5.2
Hemoglobin A1C (%) (n=461)	8.4 (7.7-9.1)
Serum creatinine (n=593) (μmol/L)	69 (55-83)
Glomerular filtration rate (mL/min/1.73m ²) (n=592)	
30 to 44	20 (3.4)
45 to 59	26 (4.4)
60 or more	546 (92.2)
Urine albumin-creatinine ratio (n=637)	
<3 mg/mol	156 (24.5)
3 mg/mol to 30 mg/mol	108 (16.9)
> 30 mg/mol	28 (4.4)

Table 1 (cont). Baseline characteristics of all patients. (n=637).

Not done	345 (54.2)
Established cardiovascular disease (n=175) ^a	
Coronary artery disease	149 (85.1)
Cerebrovascular disease	16 (9.1)
Heart failure	34 (19.4)
Baseline echocardiogram available in preceding 12 months (n=145)	
Left ventricular ejection fraction	
≤40	25 (17.2)
>40	120 (82.8)

Data are n (%) or median (interquartile range, 25th-75th percentile). ^a24 patients had more than one cardiovascular disease.

representing a weight loss of 4.2% of the overall body weight. Weight loss benefit was evident at the first follow-up visit and continued throughout the treatment period. Changes in blood pressure were of no clinical significance but varied somewhat (**Figure 3**). Median serum creatinine levels increased during treatment, as expected, by 1 μmol/L from baseline due to its unique mechanism of action on SGLT2 receptors on the nephrons causing osmotic diuresis (**Figure 4**). The change in urine albumin to creatinine ratio from baseline signified an improvement in micro- and macroalbuminuria (**Figure 5**). 17.24% of patients had an ejection fraction of less than 40% at baseline, while only 13.33% of patients had an ejection fraction of less than 40% during follow up, signifying improvement in cardiac function on treatment (**Figure 6**). The frequency of adverse events noted with the treatment was reassuring in that the drug was tolerated well with very few side effects, even during fasting (**Table 2**).

DISCUSSION

Our results show less improvement in glycemic efficacy than for empagliflozin 10 mg and 25 mg seen in a randomized, placebo-controlled trial.¹⁴ Adherence to strict diet and lifestyle protocols, regular clinic follow-ups, and enhanced motivation during the trials can explain this variation in HbA1c. In contrast, compliance with treatment for any chronic condition, such as diabetes, is a challenge in real life.

The enhanced weight loss in patients in our study was superior to the mean weight loss observed in a randomized placebo-controlled trial with 10 mg and 25 mg doses of empagliflozin (from 2.16 kg [1.76 kg placebo

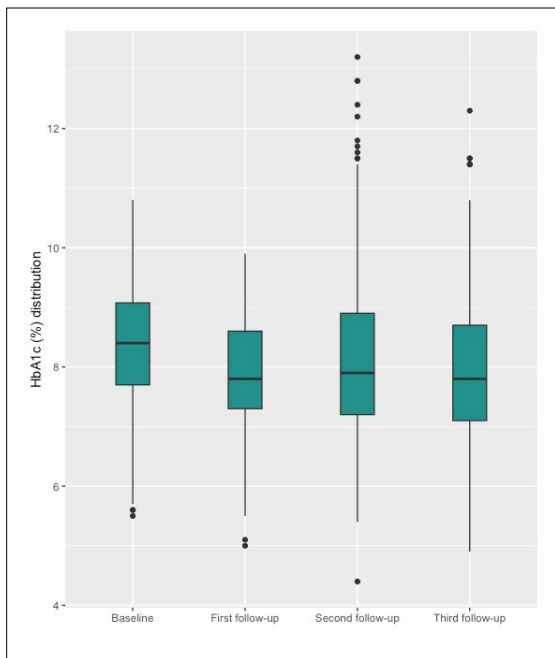


Figure 1. Change in hemoglobin A1c (HbA1c) from baseline to follow up times (median, 25th-75th percentile, outliers).

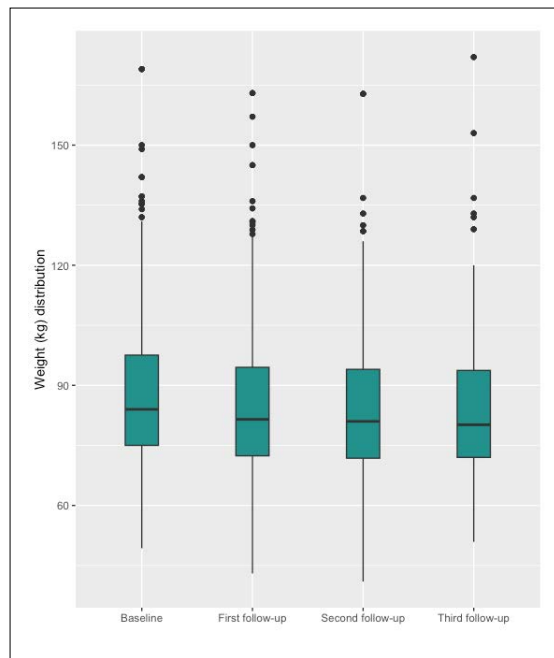


Figure 2. Change in body weight from baseline to follow up times (median, 25th-75th percentile, outliers) (not done=42 at baseline; 406 at third visit).

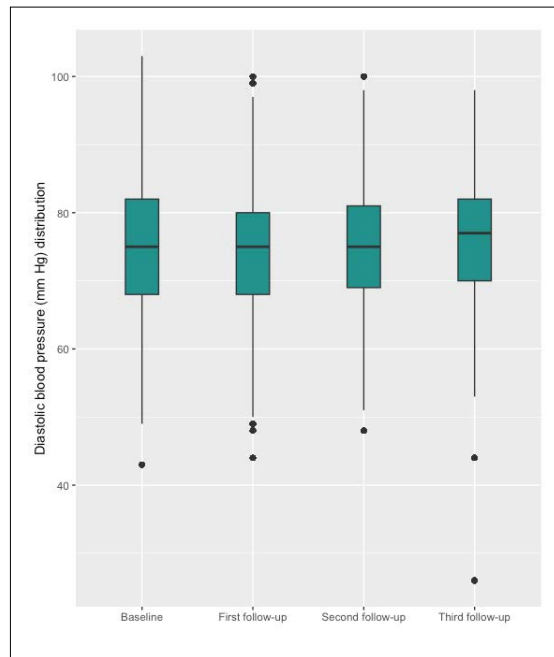
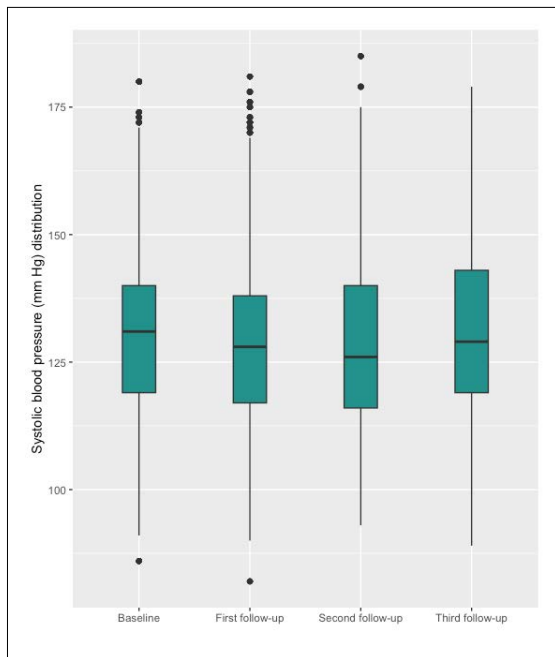


Figure 3. Change in systolic blood pressure (left) and diastolic blood pressure (right) from baseline to follow up times (median, 25th-75th percentile, outliers) (not done=25 at baseline, 381 at third visit for both measurements).

adjusted] and 2.39 kg [1.99 placebo adjusted], respectively).¹⁴ This weight loss efficacy could be due to the concomitant use of drugs such as glucagon-like peptide-1 (GLP-1) analogs with weight loss benefits and the reluctance to use weight-enhancing anti-diabetic medication such as insulin in our community. We ob-

served a mean change in eGFR from baseline by - 0.75 mL/min/1.73m², comparable to the change in the randomized trial.¹⁴

The Middle East regularly witnesses temperatures reaching 50 degrees Celsius (122 degrees Fahrenheit) during most of the year. Additionally, most people fast during the holy month of Ramadan. Furthermore, many people fast randomly during the entire year, following either Islamic traditions or trying to achieve the medical benefits of intermittent fasting.¹⁵ These extreme weather conditions and fasting can make people more prone to dehydration and ketosis, which can worsen when taking the SGLT2 inhibitors. Since our region had very little recruitment for the trials, our real-world evidence confirms that the use of empagliflozin is not associated with an increased risk of hospitalization due to dehydration and diabetic ketoacidosis during normal circumstances and fasting.

All trials on SGLT2 inhibitors reported an increased risk of genitourinary infection. The heightened risk is due to the drug's mode of action, which leads to glycosuria.^{1,2} Our study population did not witness an increased risk of genitourinary infection. Based on our results, we postulate that glycosuria is not the sole contributor to the increased risk of such infections.

Most males in the Middle East undergo circumcision at birth or during early childhood. Additionally, after using the toilet, it is a common practice to wash the body parts with ample water rather than the dry hygiene method with toilet paper used in other parts of the world. We feel that water-based hygiene practices and circumcision might reduce the risk of such infection, as observed in our study population.¹⁶ Randomized studies are required to confirm this hypothesis.

Hypoglycemia is always a cause of concern for patients and physicians. SGLT2 inhibitors do not increase the risk of hypoglycemia, mainly when not used together with insulin or insulin secretagogues due to the insulin-independent mode of action. Our data replicate these findings in the real world. Furthermore, our results provide valuable information on the hypoglycemic safety of empagliflozin when used during fasting in the month of Ramadan, which is consoling.

Our results provide evidence from real life that the changes in the renal parameters, such as eGFR and serum creatinine, are of small magnitude, and more importantly, remain stable during treatment. The metabolic efficacy parameters such as HbA1c, change in body weight, and surrogate cardiac markers such as left ventricular ejection fraction all show improvement with empagliflozin.

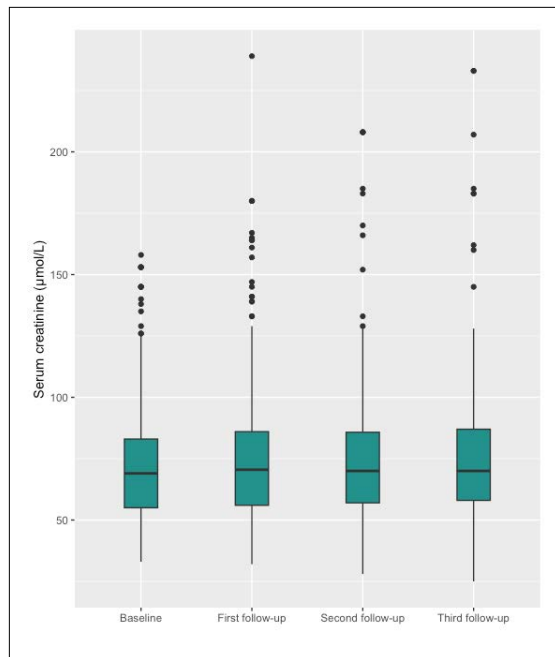


Figure 4. Change in serum creatinine from baseline to follow up times (median, 25th-75th percentile, outliers) (not done=46 at baseline, 337 at third visit).

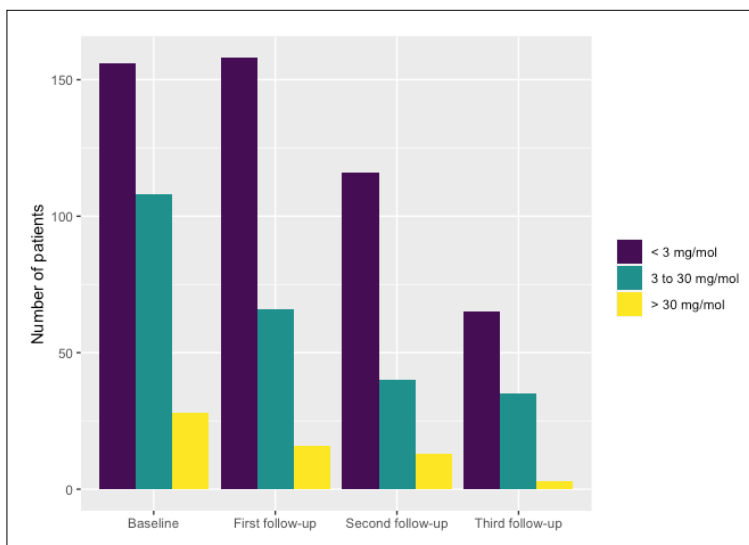


Figure 5. Change in urine albumin to urine creatinine ratio from baseline to follow up times for available data (not done at baseline and each follow up: 350, 402, 473, 539, respectively).

The study draws strength from the availability of results from the local population in real life. Our population has different hygiene practices, observes fasting randomly and during Ramadan, and face extreme weather conditions compared with the patient population studied during the empagliflozin trials. Therefore, our study adds valuable safety information when empagliflozin is used in patients with such lifestyles and circumstances.

Our study has its limitations including the retrospective design and the short-to-medium term follow-up period. Factors other than just the drug itself might influence the results. These factors include a positive change in diet and lifestyle. Concomitant use of drugs that can affect the HbA1c, weight & blood pressure can influence the results. One such example is the use of GLP-1 analogs. The patients might have pre-existing conditions that enhance the risk of genitourinary infection. These include a prior history of urinary bladder pathology, use of urine catheter, history of renal calculi, immune disorder, or concomitant use of immunosuppressive drugs. The clinician might not record safety endpoints during documentation, or the patient might forget to inform the clinician if they had any side effects and required care outside our institution. Likewise, the exact number of days the patient observed fasting during Ramadan while taking the study drug is unknown. As an observational study, the

follow-up appointments were not strictly at specific times. We, therefore, collected data based on their first three follow-ups. We conclude that empagliflozin is safe and effective in our local Saudi population, in severe weather conditions and during fasting.

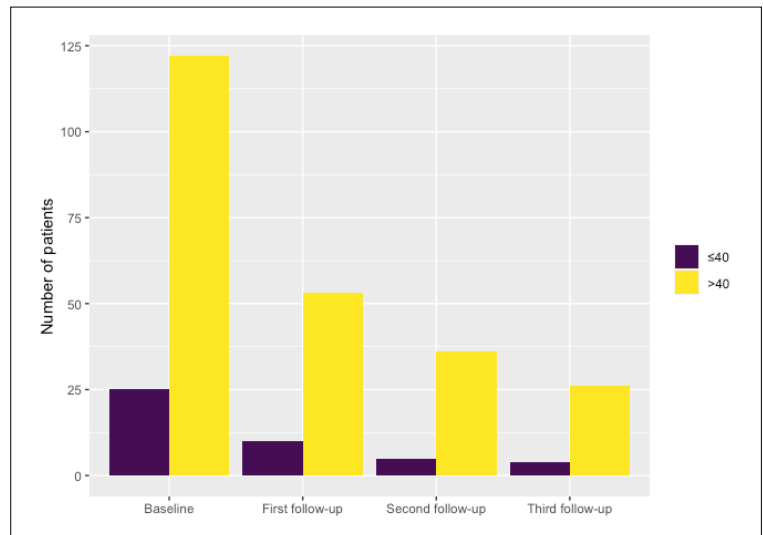


Figure 6. Change in left ventricular ejection fraction (%) from baseline to follow up times for available data (not done at baseline and each follow up: 495, 579, 601, 612, respectively).

Table 2. Adverse events.

Adverse events	First follow up (n=628)	Second follow up (n=459)	Third follow up (n=305)
Genitourinary infection	7	8	6
Required antibiotics	5	5	4
Required hospital visit/hospitalization solely for infection	3	0	1
Totally stopped empagliflozin	2	0	0
Temporary held and restarted	1	0	1
Diabetic ketoacidosis (DKA) ^a	3	1	1
Totally stopped empagliflozin	1	1	1
Temporary held and restarted	2	0	0
Hospitalization for dehydration/acute kidney injury (AKI) ^b	8	0	0
Totally stopped Empagliflozin	2	0	0
Temporary held and restarted	6	0	0
Hospital visit/hospitalization for hypoglycemia ^c	0	1	2

^a1 patient had DKA during Ramadan; ^b1 patient had AKI during Ramadan; ^c1 patient had hospitalization for hypoglycemia during Ramadan.

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