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Original article

Safety and tolerability of Empagliflozin use during the holy month of Ramadan by fasting patients with type 2 diabetes: A prospective cohort study

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) patients are exposed to a 7.5 times higher risk of hypoglycemia while fasting during Ramadan. Relevant diabetes guidelines prioritize the use of SGLT2 inhibitors over other classes. There is a great need to enrich data on their safe and effective use by fasting patients at greater risk of hypoglycemia. Therefore, this study aims to assess the safety and tolerability of Empagliflozin in T2DM Muslim patients during Ramadan.

Methodology: A prospective cohort study was conducted for adult Muslim T2DM patients. Patients who met the inclusion criteria were categorized into two sub-cohorts based on Empagliflozin use during Ramadan (Control versus Empagliflozin). The primary outcomes were the incidence of hypoglycemia symptoms and confirmed hypoglycemia. Other outcomes were secondary. All patients were followed up to eight weeks post-Ramadan. A propensity score (PS) matching and Risk Ratio (RR) were used to report the outcomes.

Results: Among 1104 patients with T2DM who were screened, 220 patients were included, and Empagliflozin was given to 89 patients as an add-on to OHDs. After matching with PS (1:1 ratio), the two groups were comparable. The use of other OHDs, such as sulfonylurea, DPP4 inhibitors, and

Abbreviations: WHO, World Health Organization; DM, Diabetes mellitus; T2DM, Type 2 diabetes mellitus; DKA, Diabetes ketoacidosis; HbA1c, Glycated hemoglobin; HE, Hypoglycemic events; IDF, International Diabetes Federation; DAR, Diabetes and Ramadan International Alliance; FPG, Fasting plasma glucose; RCT, Randomized clinical trial; SU, Sulfonylurea; GLP1RA, Glucagon-like peptide-1 receptor agonist; SGLT-2I, Sodium-glucose co-transport 2 inhibitor; DDP-4, Dipeptidyl transferase 4 inhibitor; P, Value probability of chance; N, Number of individuals; CI, Confidence interval; CDC, Centers for Disease Control and Prevention; CVD, Cardiovascular disease; CKD, Chronic kidney disease; UTI, Urinary Tract Infection.

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Biguanides, was not statistically different between the two groups. The risk of hypoglycemia symptoms during Ramadan was lower in patients who received Empagliflozin than in the control group (RR 0.48 CI 0.26, 0.89; p-value = 0.02). Additionally, the risk of confirmed hypoglycemia was not statistically significant between the two groups (RR 1.09 CI 0.37, 3.22; p-value = 0.89).

Conclusion: Empagliflozin use during Ramadan fasting was associated with a lower risk of hypoglycemia symptoms and higher tolerability. Further randomized control trials are required to confirm these findings.

1. Background

According to the International Diabetes Federation, approximately 116 million Muslims live with Diabetes Mellitus, and most of them fast during the holy month of Ramadan. (Cho et al., 2017) Although the Islamic religion permits those who are sick or old to break their fast, most patients with chronic diseases (such as diabetes) elect to fast despite the risks associated with their practice.(International Diabetes Federation, 2021) Therefore, healthcare practitioners must respect the patient's will in fasting despite health risks associated with their practice, and instead focus on ways to manage the patient's diabetes oral anticoagulants as well as educate them on ways to avoid hyper- or hypoglycemia.

As per the population-based Epidemiology of Diabetes and Ramadan (EPIDIAR) and CREED studies, the risk of hypoglycemia and hyperglycemia is increased up to 7.5 and 5 times respectively among type 2 diabetes mellitus (T2DM) patients who are fasting during Ramadan.(Salti et al., 2004) Consequently, risk categorization and educational programs have been recommended by American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) to start three months prior to fasting. (Babineaux et al., 2015).

Many observational and randomized controlled studies have assessed the safety and risks associated with the use of several antidiabetic classes by patients who fast during Ramadan, particularly hypoglycemia risk. These studies concluded that DPP4 inhibitors and metformin are generally safe however (El Mouhayyar et al., 2020), sulfonylurea was associated with serious consequences of hypoglycemia. (Aravind et al., 2011) Generally, other oral antidiabetic medications are safe except that the risk of hypoglycemia cannot be eliminated with patients who take multiple agents. (Tsang, 2012).

There is currently a growing interest in the use of the oral antidiabetic agent class of Sodium-Glucose Co-transporter 2 inhibitor (SGLT-2i) ever since Canagliflozin -the first of this class- was granted FDA approval in 2013 for the management of patients with type 2 diabetes mellitus (Lavalle-González et al., 2013) followed by Dapagliflozin and Empagliflozin. (Neal et al., 2017; Wanner et al., 2016; Zinman et al., 2015).

Relevant diabetes guidelines, such as those of the 2023 American Diabetes Association (ADA), prioritize the use of SGLT2i's over other classes particularly for reducing atherosclerotic cardiovascular risk, slowing chronic kidney disease progression as well as decreasing heart failure exacerbation in patients with preserved and reduced ejection fraction. (Elsayed et al., 2023).

SGLT2i regulates blood glucose by lowering renal glucose reabsorption, which leads to increased glucose excretion in the urine. Although this mechanism is associated with a low risk of hypoglycemia, mild osmotic diuresis increases the risk of volume–depletion and dehydration. ("Boehringer Ingelheim Pharmaceuticals. Jardiance (empagliflozin) tablets; prescribing information," n.d.) A previous study reported that 27% (n = 417) of the patients taking SGLT-2i during Ramadan experienced symptoms of hypoglycemia. Of these, 38 patients had to break their fast. (Bashier et al., 2018) Furthermore, another study documented volume depletion events in patients receiving Canagliflozin including dehydration (86.3%), postural dizziness (6%), and hypotension (2%). (Hassanein et al., 2017).

There is a pressing need to enrich data on SGLT2i use during Ramadan by fasting patients, in order to ensure the safety of using this class by Muslims worldwide. Current literature discusses them as a class, and most studies included either Canagliflozin or Dapagliflozin. Only one study discussed Empagliflozin use in Ramadan by fasting Muslims and was conducted in Bangladesh however the study excluded patients on insulin secretagogues which is commonly prescribed with SGLT2i. (Pathan et al., 2022) Therefore, this study aimed to assess the safety and tolerability of Empagliflozin along with other oral hypoglycemic agents in patients with type 2 diabetes mellitus among Muslim patients who fast during Ramadan.

2. Methods

2.1. Study design

A prospective cohort study for adult Muslim patients with type 2 Diabetes Mellitus who are following at Al-Noor Specialist Hospital located in Makkah, Saudi Arabia. All outpatients who were followed at Al-Noor Endocrine and Diabetic Center were screened for eligibility using electronic medical records between 01/01/1443 (09/08/2021) and 28/06/1443 (31/01/2022). Eligible patients were categorized into two sub-cohorts based on Empagliflozin use during the holy month of Ramadan (Control versus Empagliflozin). The control group used Oral Hypoglycemic Medications (OHDs), including Metformin (500–2000 mg/day); Sulfonylureas (i.e., Glimepiride (1–6 mg/day), Gliclazide MR (30–120 mg/day)); or Dipeptidyl Peptidase 4 (DPP-4) inhibitors (i.e., Sitagliptin(100 mg/-day) or Linagliptin(5 mg/day)). In comparison, the active group received Empagliflozin 10 mg/day in addition to OHDs. All patients were followed up to eight weeks post Ramadan. Informed verbal consent was obtained from the patient before the enrollment in the study. The study protocol was approved by the institutional review board (IRB) of Makkah health affairs (Ref. #: H-02-K-076–0222-669).

2.2. Study participants

We assessed the eligibility of all patients with T2DM aged 18–70 years and following at Endocrine and Diabetic Center - Alnoor Specialist Hospital. Patients were excluded if known to have chronic kidney disease (CKD); estimated glomerular filtration rate (eGFR) less than 60 ml/min; dementia, heart failure; stroke/transient ischemic attacks; coronary artery disease; peripheral arterial diseases (PAD); uncontrolled DM with recurrent hypoglycemic or hyperglycemic episodes in the prior three months. Moreover, patients using injectable antidiabetic therapy (e.g., insulin or

glucagon-like peptide-1 (GLP-1) agonists), pregnant women, and patients known to have disabilities or language barriers were also excluded from the study (Fig. 1).

2.3. Study protocol and procedure

Before initiating the study, the research teams and investigators secured all necessary official permissions from eligible patients. A virtual education meeting was held three weeks before Ramadan for all eligible patients to educate them about the appropriate nutritional and therapeutic options. The signs and symptoms of hypoglycemia/hyperglycemia, dehydration, severe body fluid loss, and the appropriate quick action for each condition were discussed. Both groups received the same educational materials and followed the endocrine and diabetic center's protocol. Patients underwent a pre-Ramadan assessment two weeks before Ramadan to investigate and evaluate their medications. Two weeks after Ramadan, the patients answered the structured and validated questionnaire via a virtual interview[15]. Additionally, we requested laboratory tests (i.e., serum creatinine, eGFR, HbA1C) for patients six to eight weeks post-Ramadan.

2.4. Outcomes

This study aimed to assess the safety and tolerability of Empagliflozin use among Muslim patients with T2DM who fast during Ramadan. The primary outcomes were the incidence of hypoglycemia symptoms and confirmed hypoglycemia. Other outcomes, such as hyperglycemia symptoms, confirmed hyperglycemia, volume depletion, severe dehydration, hospital admission, fasting break, and laboratory follow-up tests were considered secondary.

2.5. Outcomes definition

- Hypoglycemia symptoms are defined as palpitation, anxiety, sweating, hunger, paresthesia weakness, drowsiness, confusion, dizziness, seizure, and coma.
- Hyperglycemia symptoms are defined as thirst, polyuria, weight loss, and blurry vision.
- Confirmed hypoglycemia is defined as a measured blood glucose level $\leq$ 70 mg/dL (3.9 mmol/L).
- Confirmed hyperglycemia is defined as a measured random blood glucose level of 200 mg/dL (11.1 mmol/L) or higher.
- Confirmed hypotension is defined as a blood pressure reading of less than 90/60 mmhg.
- Severe dehydration symptoms are defined as extreme and unusual thirst.
- Volume depletion symptoms are defined as lassitude, easy fatigability, thirst, muscle cramps, and postural dizziness.

2.6. Study setting

The study was carried out at the outpatient clinics of the Endocrine and Diabetic center at Al-Noor Specialist Hospital. It is

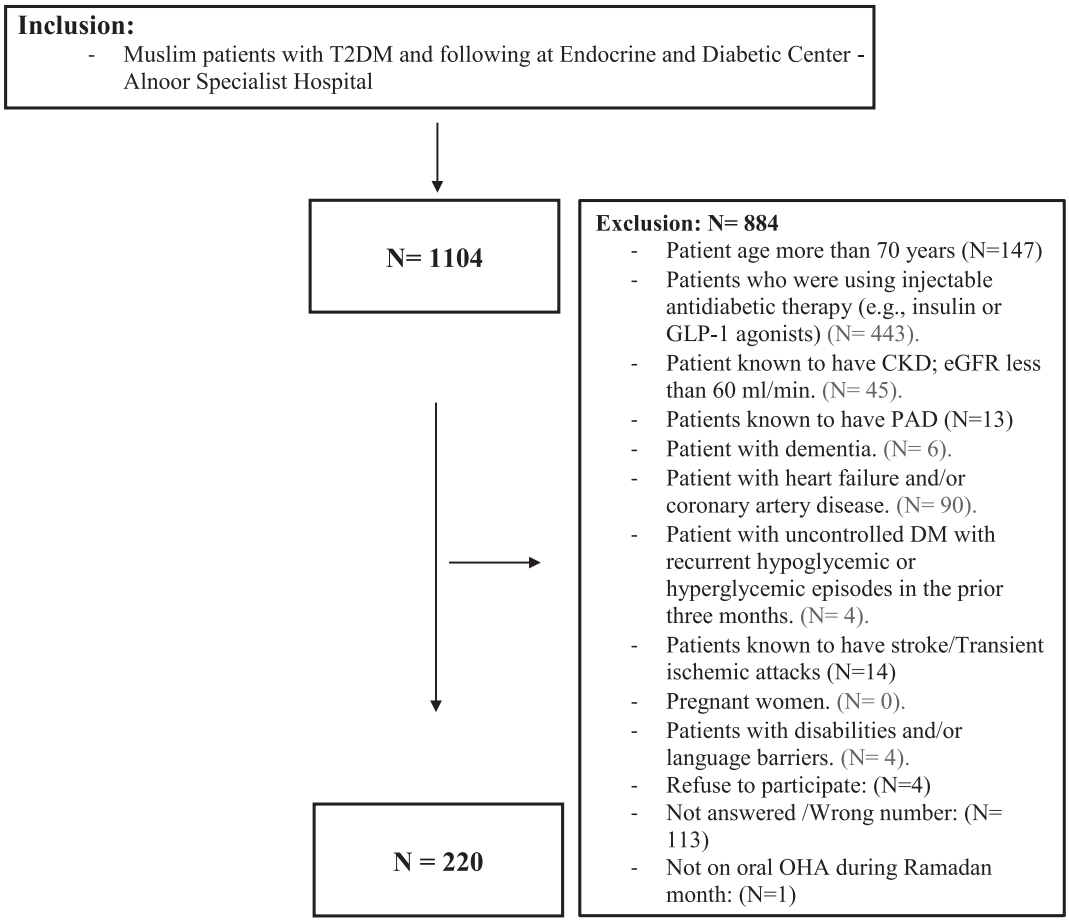

Fig. 1. Flow diagram showing patients recruited with T2DM. T2DM = Type 2 Diabetes Mellitus, OHA = Oral Hypoglycemic Agents Glucagon-like peptide-1 agonist = GLP-1 agonists Chronic kidney disease = CKD.

a tertiary-care referral hospital with bed capacity of 500 beds in Makkah, Saudi Arabia.

2.7. Data collection

Variables and data were collected from the electronic database and medical records using an Excel sheet. We collected demographic data (e.g., age, gender, BMI), comorbidities, laboratory tests such as baseline HbA1C, serum creatinine, and eGFR pre and post Ramadan. In addition, we gathered clinical information such as the duration of diabetes, antidiabetic medications, and detailed medical/surgical history. A validated questionnaire was used to assess the clinical outcomes during Ramadan[15]. (Supplementary File 1). To ensure accuracy, two independent investigators tested the data.

2.8. Statistical analysis

Based on the data distribution using a statistical test (the Shapiro-Wilk test) and graphical representation (i.e., histograms and Q-Q plots), continuous data were reported as median with interquartile range (IQR). Non-normally distributed continuous variables were compared using the Mann-Whitney *U* test. At the same time, categorical variables were reported as crude numbers with percentages and compared using either Chi-square or Fisher exact test, as appropriate.

A propensity score (PS) analysis using greedy nearest-neighbor matching (1:1 ratio) was utilized based on the patient's serum creatinine, HbA1C, hypothyroidism as comorbidity, Metformin, Sulfonylurea and, DPP4 Inhibitor use. Those factors were selected for their possible association with the study outcomes. One empagliflozin-treated patient was matched with one control patient, resulting in the smallest within-pair difference among all available pairs of treated patients. Patients were matched only if the difference in the logits of the propensity scores for pairs of patients from the two groups was less than or equal to 0.5 times the pooled estimate of the standard deviation (SD).

Binomial regression analysis was performed for this cohort's primary and secondary outcomes and reported using the Risk Ratio (RR). Regression analysis was performed with the PS score as one of the model's covariates. The Hosmer-Lemeshow goodness-of-fit test was used to evaluate model fit. A *p*-value of less than 0.05 was considered statistically significant. All statistical analysis were performed using STATA version 17.

3. Results

Among 1104 patients with T2DM who were screened, a total of 220 patients were included based on the eligibility criteria (Fig. 1). Empagliflozin was given to 89 patients as an add-on to OHDs, while 131 patients received only OHDs. Table 1 shows the patients' baseline characteristics before and after propensity score matching between the two sub-cohorts. Prior to PS matching, concomitant Sulfonylurea use, the HbA1C, and serum creatinine two weeks before Ramadan were higher in patients who received Empagliflozin than in the control group. The prevalence of hypothyroidism and the concomitant use of Metformin and DPP4 inhibitors were lower among patients who received Empagliflozin compared with the control group. After matching with PS (1:1 ratio) based on the predefined criteria, the two groups were comparable (Table 1). The use of other OHDs such as sulfonylurea (74% vs. 71%; p-value = 0.72), DPP4 inhibitors (86% vs. 90%; p-value = 0.46), and Biguanides (90% vs. 91%; p-value = 0.79) was not statistically different between the two groups. Most of the patients in the empagliflozin group received four concomitant OHDs compared with the control group (56.0% vs. 0.0%). In comparison, 62.0% of the patients in the control group used three concomitant OHDs compared with 34.0% in the empagliflozin group.

3.1. Hypoglycemia during Ramadan

Table 2 shows the primary and secondary outcomes during the holly month. In crude analysis, patients with T2DM who received Empagliflozin have a lower incidence of hypoglycemia symptoms during Ramadan compared with the control group (16% vs. 32%; p-value = 0.01). Moreover, binomial regression analysis showed a lower risk of hypoglycemia symptoms in the Empagliflozin group (RR 0.48 CI 0.26, 0.89; p-value = 0.02).

Among patients with hypoglycemia symptoms, 67% of those who received Empagliflozin checked their BSL compared with 60% in the control group (67% vs. 60%; p-value = 0.70). Meanwhile, only four patients in the Empagliflozin group reported confirmed hypoglycemia compared to six in the control group (RR 1.09 CI 0.37, 3.22; p-value = 0.89). Of the four patients in the Empagliflozin group, three patients (75%) were also taking Sulfonylurea, while among the six patients in the control group, five patients (83.3%) were taking Sulfonylurea. Although, a statistically significant fasting break during Ramadan was observed in seven patients in the control group compared to non patients in the Empagliflozin group (p-value = 0.01).

3.2. Hyperglycemia during Ramadan

Patients in the Empagliflozin group developed fewer symptoms of hyperglycemia compared to the control group; however, the difference was not statistically significant in the crude analysis as well in regression analysis (31% vs. 40%; p-value = 0.24 and RR 0.75 CI 0.50, 1.16; p-value = 0.20, respectively). Among those who checked their BSL, the risk of confirmed hyperglycemia was higher but not statistically significant in patients who received Empagliflozin than in the control group (RR 1.36 CI 0.79, 2.32; p-value = 0.26) (Table 2).

3.3. Dehydration and volume depletion during Ramadan

Symptomatic volume depletion occurred in fifteen patients (19%) in the Empagliflozin group compared with twenty-two patients (29%) in the control group, which was not statistically significant (RR 0.67 CI 0.38, 1.19; p-value = 0.18). In addition, the severe dehydration symptoms were comparable between the two groups (RR 1.15 CI 0.41, 3.19; p-value = 0.79). Only one patient in the control group had confirmed hypotension; however, it was not statistically significant (1.2% vs. 0%; p-value = 1.0). (Table 2).

3.4. Follow-up and other outcomes

Two-week laboratory results post Ramadan follow-up showed that the fasting blood glucose was not statistically different between the two groups (beta coefficient 18.5; CI −10.73, 47.88; p-value = 0.17, respectively). Moreover, the serum creatinine and eGFR were comparable between the two groups (beta coefficient −0.82 CI −7.10, 5.42; p-value = 0.78 and beta coefficient 0.52 CI −4.95, 6.00; p-value = 0.85, respectively). (Table 2).

4. Discussion

Most diabetic Muslim patients prefer to fast during Ramadan, even against medical advice and high risk.(Hassanein et al., 2022) To safely fast during Ramadan, people with diabetes and healthcare professionals (HCPs) need to engage in a shared process in

Table 1
Baseline characteristic before and after propensity score matching.

	Before propensity score (PS)			After propensity score (PS)		
	Control (N = 131)	Empagliflozin (N = 89)	P-value	Control (N = 77)	Empagliflozin (N = 77)	P-value
Demographic Data						
Age (Years), Median (IQR)	55 (47–64)	56 (51–62)	0.70	52 (47–64)	56 (51–62)	0.66
Gender (Male), n (%)	73 (55.7%)	40 (44.9%)	0.12	35 (45%)	33 (43%)	0.75
BMI, Median (IQR)	29.60 (26.00–34.30)	28.50 (24.90–31.60)	0.12	29.30 (25.90–32.80)	28.80 (25.50–31.60)	0.69
Duration of T2DM, Median (IQR)	7.50 (5.00–15.00)	9.00 (5.00–15.00)	0.59	7.00 (5.00–15.00)	9.00 (5.00–15.00)	0.69
Two-weeks before Ramadan						
HbA1C, Median (IQR)	7.29 (6.56–8.30)	7.80 (7.00–8.80)	0.009	7.50 (6.70–8.33)	7.80 (7.10–8.77)	0.21
Serum creatinine, Median (IQR)	69 (57–80)	72 (64–85)	0.048	69 (61–87)	72 (64–84)	0.56
eGFR, Median (IQR)	97 (84–106)	94 (84–105)	0.35	96 (84–106)	96 (86–105)	0.92
Comorbidity, n (%)						
Hypothyroidism	32 (24.4%)	11 (12.4%)	0.027	9 (12%)	9 (12%)	1.00
Hypertension	53 (40.5%)	45 (50.6%)	0.14	29 (38%)	38 (49%)	0.14
Concomitant Oral Antidiabetic Medications (s) use, n (%)						
Biguanide (i.e., Metformin)	123 (93.9%)	77 (86.5%)	0.062	70 (91%)	69 (90%)	0.79
Sulfonylurea	73 (55.7%)	64 (71.9%)	0.015	55 (71%)	57 (74%)	0.72
DPP4 inhibitor	122 (93.1%)	70 (78.7%)	0.002	69 (90%)	66 (86%)	0.46

Table 2
Outcomes after Propensity Score matching.

Outcome (s)	Number of outcomes/Total number of patients			Risk Ratio (RR) (95%CI)	P-value
	Control	Empagliflozin	P-value		
Hypoglycemia during Ramadan					
Hypoglycemia Symptoms, n (%)	25/77 (32%)	12/77 (16%)	0.01 ^^	0.48 (0.26, 0.89)	0.02
BSL checked, n (%)	15/25 (60%)	8/12 (67%)	0.70 ^^	1.15 (0.68, 1.93)	0.54
Confirmed hypoglycemia, n (%)	6/15 (40%)	4/8 (50%)	0.64 ^^	1.09 (0.37, 3.22)	0.89
Fasting break, n (%)	7/17 (41%)	0 (0%)	0.01^^	NC	NC
Hyperglycemia during Ramadan					
Hyperglycemia Symptoms, n (%)	31/77 (40%)	24/77 (31%)	0.24 ^^	0.75 (0.50, 1.16)	0.20
BSL checked, n (%)	16/31 (52%)	12/25 (48%)	0.79 ^^	0.90 (0.54, 1.51)	0.70
Confirmed hyperglycemia, n (%)	11/17 (65%)	10/12 (83%)	0.27 ^^	1.36 (0.79, 2.32)	0.26
Volume depletion/Severe Dehydration during the holly month					
Volume depletion symptoms, n (%)	22/77 (29%)	15/77 (19%)	0.19 ^^	0.67 (0.38, 1.19)	0.18
Severe dehydration symptoms, n (%)	6/75 (8%)	8/75 (10.6%)	0.58 ^^	1.15 (0.41, 3.19)	0.79
Confirmed hypotension, n (%)	1/77 (1.2%)	0 (0%)	1.00 ^*	NC	NC
Other outcomes					
Hospital admission, n (%)	0 (0%)	1 (1%)	1.00 ^*	NC	NC
				beta coefficient (Estimates) (95% CI)	**P-value S***
Two-weeks post Ramadan					
Serum creatinine (umol/l), Median (Q1,Q3)	72.35 (63.45–91.00)	77.00 (61.50–88.10)	0.87 ^	−0.82 (-7.10, 5.42)	0.78
eGFR, Median (Q1,Q3)	95.0 (83.0–108.0)	101.0 (82.5–105.5)	0.75 ^	0.52 (-4.95, 6.00)	0.85
Fasting Blood Glucose (FBG) (mmol/l), Median (Q1, Q3)	122.40 (96.30–151.00)	136.80 (127.80–148.00)	0.16 ^	18.5 (-10.73, 47.88)	0.17

^ Wilcoxon rank sum test is used to calculate the P-value.
^^ Chi-square test/ ^* is used to calculate the P-value.
$* Generalized linear model is used to calculate estimates and p-value.

which the guidance provided uses the best available evidence. Most applicable guidance on the management of diabetes during Ramadan relies on expert opinions rather than medical evidence. (Hassanein et al., 2022).

The prevalence of many new oral antidiabetic medications may bring us closer to safe diabetes management while fasting. However, some safety issues related to the use of SGLT2i during Ramadan have been raised. For example, susceptible patients have an increased risk of dehydration and hypoglycemia, which may be an especially relevant issue during Ramadan. Several experts in diabetes have reevaluated the current recommendations for the use of SGLT2i during Ramadan fasting based on studies focused on Canagliflozin and Dapagliflozin; however, few studies have examined the use of Empagliflozin in this context. (Ahmed et al., 2022; Bashier et al., 2018; Goh et al., 2023; Hassanein et al., 2022, 2017; Pathan et al., 2022; Shao et al., 2018).

In the present study, Empagliflozin was associated with a lower incidence of hypoglycemia compared to other oral antidiabetic agents. This finding is in line with those of Wan et al.'s (2016) randomized, open-label, two-arm parallel group study in Malaysia, which compared the effects of Dapagliflozin and sulfonylurea on patients with at least one episode of hypoglycemia during Ramadan and assessed the safety of Dapagliflozin use during Ramadan. (Steiner, 2016) The results showed that SU individuals with any reported event of hypoglycemia were 6.9% in the SGLT2i and 28.8% in the control group (p = 0.002).(Shao et al., 2018) The present study's findings suggest that symptomatic and confirmed hypoglycemic incidences are seen more often in patients using

Empagliflozin along with sulfonylurea (83.33% and 75.5%, respectively). The results showed that 3.7% of the SGLT2i group had symptomatic events of hypoglycemia compared to 13.2% of the SU group (adjusted odds ratio = 0.27, (95% CI 0.10–0.72), $p = 0.009$). Meanwhile, Bashier et al. (2018) conducted a retrospective observational study in the UAE to explore the safety of SGLT2i use and found that the use of insulin in combination with SGLT2i increased the risk of hypoglycemia during Ramadan.(Bashier et al., 2018).

Furthermore, none of the participants using Empagliflozin had to break their fast; seven in the control group had to do so. This is of concern since four in the Empagliflozin group had confirmed hypoglycemia readings and yet decided to continue their fast. This is in line with previous studies that emphasized fasting against medical advice and thus needs to be further reinforced and analyzed. (International Diabetes Federation, 2021).

Our study revealed no difference between the study groups in terms of the occurrence of confirmed episodes of hypotension. In contrast, Wan et al. reported postural hypotension in 13.8% of the Empagliflozin group and 3.8% of the non-empagliflozin group; however, this difference was not statistically significant ($p = 0.210$). (Steiner, 2016) Shao et al. (2018) who conducted a prospective, observational, controlled cohort study in Singapore to compare SU, insulin, and SGLT2i reported no differences between the groups or cases of severe hypoglycemia. (Shao et al., 2018) Although a decrease in systolic blood pressure was reported in both groups, it was not statistically significant. (Shao et al., 2018) Similarly, Abdelgadir et al. (2019) conducted a prospective controlled study in the UAE to compare SU and other oral hypoglycemic agents (OHAs) (except insulin) among individuals not using SGLT2i for hypoglycemic events measured using flash glucose monitoring systems. In terms of systolic blood pressure, no adverse events or statistically significant changes were reported. (Abdelgadir et al., 2019).

The use of Empagliflozin increased the risk of severe dehydration (Cho et al., 2017; International Diabetes Federation, 2021) and severe fluid loss; however, this finding was not statistically significant. In addition, the risk of developing symptoms of volume depletion was lower with Empagliflozin usage; however, this finding was not statistically significant either. Symptoms of volume depletion can be linked to patient-related factors, such as not being properly hydrated the day before or having a heavy meal the night before. Other factors could be linked to the study location, which was conducted in Saudi Arabia, a known country for its hot climate that could have accentuated volume depletion symptoms. (Alluqmani et al., 2019) Meanwhile, a study in the UAE found hypovolemia in 16.1% of the SGLT2i group and 5% of the SU group. The adjusted odds ratio for SGLT2i against SU was 3.5 ((95% CI 1.3–9.2), $p = 0.011$), which was statistically significant. (Hassanein et al., 2017).

Empagliflozin had no effect on eGFR mean baseline levels after Ramadan. In 2018, a single-center prospective observational controlled cohort study concluded that patients from the treatment and control groups had a similar statistically significant reduction in eGFR from baseline to after Ramadan. (Shao et al., 2018) Furthermore, patients from the treatment and control groups showed a slight increase in mean creatinine levels from baseline to after Ramadan. Meanwhile, in a trial conducted in 2016, the serum creatinine level doubled in 70 of the 4,645 patients (1.5%) in the Empagliflozin group and 60 of the 2,323 patients (2.6%) in the placebo group. (Wanner et al., 2016).

This study is limited by the inclusion of one center, involving one city in Saudi Arabia with a fasting average of 14 hours. It is also limited by the cultures and norms that are very different from one country to another, with different Ramadan dishes that can influence the results of this study. Moreover, 40.5% and 50.6% had hypertension in both the control and Empagliflozin groups respectively. However, we were not able to identify whether our patients were on thiazide diuretics as part of their blood pressure regimen, which may have increased dehydration risk in both groups. Lastly, although the included patients were restricted to a dose of 10 mg, unifying the dose might minimize potential confounding factors. Future studies should investigate the risk of using both SGLT2i and HCTZ, particularly in patients with diabetes mellitus, with or without heart failure. Finally, follow-up was conducted virtually which may have affected self-reporting symptoms.

5. Conclusion

Empagliflozin use during Ramadan fasting was associated with a lower risk of hypoglycemia symptoms and higher tolerability. Further randomized control trials are required to confirm these findings, particularly in patients with multiple comorbidities and above the age of 65 who may be at increased risk of both hypoglycemia and hypovolemia. Overall, these findings provide valuable insights into the use of Empagliflozin in T2DM patients during Ramadan and may have important implications for the management of T2DM during this period.

Author contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; they took part in drafting, revising, or critically reviewing the article; they gave final approval of the version to be published; they agreed on the journal to which the article had been submitted; and they agreed to be accountable for all aspects of the work.

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Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical considerations

The study protocol was approved by the institutional review board (IRB) of Makkah Health Affairs (approval number: H-02-K-076–0222-669). The study's objectives, methodology, outcome, possible dangers, and withdrawal protocol were explained to all participants. Furthermore, participation was voluntary and did not involve any rewardable benefits. All patients had enough time and the right to participate in the study. Verbal consent was obtained from all participants.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Abdelgadir, E., Rashid, F., Bashier, A., Al Saeed, M., Khalifa, A., Alawadi, F., Hassanein, M., 2019. Use of flash glucose monitoring system in assessing safety of the SGLT2 inhibitors during Ramadan fasting in high risk insulin treated patients with type 2 diabetes. Diabetes Metab. Syndr. Clin. Res. Rev. 13, 2927–2932. https://doi.org/10.1016/j.dsx.2019.07.055.

Ahmed, I., Raja, U.Y., Wahab, M.U., Rehman, T., Ishtiaq, O., Aamir, A.H., Ghaffar, T., Raza, A., Kumar, S., Sherin, A., Masood, F., Randhawa, F.A., Asghar, A., Khan, S., 2022. Efficacy and safety of combination of empagliflozin and metformin with combination of sitagliptin and metformin during Ramadan: an observational study. BMC Endocr. Disord. 22, 1–7. https://doi.org/10.1186/s12902-022-01168-3.

Aravind, S.R., Tayeb, K.A., Ismail, S.B., Shehadeh, N., Kaddaha, G., Liu, R., Balshaw, R., Lesnikova, N., Heisel, O., Girman, C.J., Musser, B.J., Davies, M.J., Katzeff, H.L., Engel, S.S., Radican, L., 2011. Hypoglycaemia in sulphonylurea-treated subjects with type 2 diabetes undergoing Ramadan fasting: A five-country observational study. Curr. Med. Res. Opin. 27, 1237–1242. https://doi.org/10.1185/03007995.2011.578245.

Babineaux, S.M., Toaima, D., Boye, K.S., Zagar, A., Tahbaz, A., Jabbar, A., Hassanein, M., 2015. Multi-country retrospective observational study of the management and outcomes of patients with Type 2 diabetes during Ramadan in 2010 (CREED). Diabet. Med. 32, 819–828. https://doi.org/10.1111/dme.12685.

Bashier, A., Khalifa, A.A., Abdelgadir, E.I., Al Saeed, M.A., Al Qaysi, A.A., Ali Bayati, M. B., Alemadi, B., Bachet, F., Alawadi, F., Hassanein, M., 2018. Safety of sodium-glucose cotransporter 2 inhibitors (SGLT2-I) during the month of ramadan in muslim patients with type 2 diabetes. Oman Med. J. 33, 104–110. https://doi.org/10.5001/omj.2018.21.

Boehringer Ingelheim Pharmaceuticals. Jardiance (empagliflozin) tablets; prescribing information [WWW Document], n.d. URL https://www.boehringer-ingelheim.com/us/press-release/fda-approves-jardiance-empagliflozin-tablets-adults-type-2-diabetes (accessed 3.2.23).

Cho, N., Kirigia, J., Ogurstova, K., Reja, A., 2017. IDF Diabetes Atlas, tenth edition [WWW Document]. URL http://www.diabetesatlas.org (accessed 3.2.23).

El Mouhayyar, C., Riachy, R., Khalil, A.B., Eid, A., Azar, S., 2020. SGLT2 Inhibitors, GLP-1 agonists, and DPP-4 inhibitors in diabetes and microvascular complications: a review. Int. J. Endocrinol. 2020. https://doi.org/10.1155/2020/1762164.

Elsayed, N.A., Aleppo, G., Aroda, V.R., Bannuru, R.R., Brown, F.M., Bruemmer, D., Collins, B.S., Hilliard, M.E., Isaacs, D., Johnson, E.L., Kahan, S., Khunti, K., Leon, J., Lyons, S.K., Perry, M.L., Prahalad, P., Pratley, R.E., Seley, J.J., Stanton, R.C., Gabbay, R.A., 2023. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023. Diabetes Care 46, S140–S157. https://doi.org/10.2337/dc23-S009.

Goh, K.G., Zakaria, M.H., Raja Azwan, R.N., Bhajan Singh, K.K., Badrul Hisham, M.H., Hussein, Z., 2023. Effect of empagliflozin in patients with type 2 diabetes during Ramadan on volume status, ketonaemia, and hypoglycaemia. Diabetes Metab. Syndr. Clin. Res. Rev. 17. https://doi.org/10.1016/j.dsx.2022.102680.

Hassanein, M., Afandi, B., Yakoob Ahmedani, M., Mohammad Alamoudi, R., Alawadi, F., Bajaj, H.S., Basit, A., Bennakhi, A., El Sayed, A.A., Hamdy, O., Hanif, W., Jabbar, A., Kleinebreil, L., Lessan, N., Shaltout, I., Mohamad Wan Bebakar, W., Abdelgadir, E., Abdo, S., Al Ozairi, E., Al Saleh, Y., Alarouj, M., Ali, T., Ali Almadani, A., Helmy Assaad-Khalil, S., Bashier, A.M.K., Arifi Beshyah, S., Buyukbese, M.A., Ahmad Chowdhury, T., Norou Diop, S., Samir Elbarbary, N., Elhadd, T.A., Eliana, F., Ezzat Faris, M.A.I., Hafidh, K., Hussein, Z., Iraqi, H., Kaplan, W., Khan, T.S., Khunti, K., Maher, S., Malek, R., Malik, R.A., Mohamed, M., Sayed Kamel Mohamed, M., Ahmed Mohamed, N., Pathan, S., Rashid, F., Sahay, R.K., Taha Salih, B., Sandid, M.A., Shaikh, S., Slim, I., Tayeb, K., Mohd Yusof, B.N., Binte Zainudin, S., 2022. Diabetes and Ramadan: Practical guidelines 2021. Diabetes Res. Clin. Pract. 185. https://doi.org/10.1016/j.diabres.2021.109185.

Hassanein, M., Echtay, A., Hassoun, A., Alarouj, M., Afandi, B., Poladian, R., Bennakhi, A., Nazar, M., Bergmans, P., Keim, S., Hamilton, G., Azar, S.T., 2017. Tolerability of canagliflozin in patients with type 2 diabetes mellitus fasting during Ramadan: Results of the Canagliflozin in Ramadan Tolerance Observational Study (CRATOS). Int. J. Clin. Pract. 71. https://doi.org/10.1111/ijcp.12991.

International Diabetes Federation, 2021. Diabetes and Ramadan Diabetes and Ramadan International Diabetes Federation (IDF), in collaboration with the Diabetes and Ramadan (DAR) International Alliance [WWW Document]. URL http://www.idf.org/sites/default/files/IDF-DAR-Practical-Guidelines-Final-Low.pdf. (accessed 2.20.23).

Lavalle-González, F.J., Januszewicz, A., Davidson, J., Tong, C., Qiu, R., Canovatchel, W., Meininger, G., 2013. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Diabetologia 56, 2582–2592. https://doi.org/10.1007/s00125-013-3039-1.

Neal, B., Perkovic, V., Mahaffey, K.W., de Zeeuw, D., Fulcher, G., Erondu, N., Shaw, W., Law, G., Desai, M., Matthews, D.R., 2017. Canagliflozin and cardiovascular and renal events in Type 2 Diabetes. N. Engl. J. Med. 377, 644–657. https://doi.org/10.1056/nejmoa1611925.

Pathan, M.F., Akter, N., Selim, S., Saifuddin, M., Qureshi, N.K., Kamrul-Hasan, A., Hannan, M.A., Ahmed, M.A.U., Mustari, M., Chakraborty, A.K., 2022. Efficacy and safety of Empagliflozin in patients with Type 2 Diabetes mellitus fasting during Ramadan: a real-world study from Bangladesh. Diabetes Metab. Syndr. Obes. Targets Ther. 15, 4011–4021. https://doi.org/10.2147/dmso.s380544.

Salti, I., Bénard, E., Detournay, B., Bianchi-Biscay, M., Le Brigand, C., Voinet, C., Jabbar, A., 2004. A population-based study of diabetes and its characteristics during the fasting month of ramadan in 13 countries: Results of the epidemiology of diabetes and ramadan 1422/2001 (EPIDIAR) study. Diabetes Care 27, 2306–2311. https://doi.org/10.2337/diacare.27.10.2306.

Shao, Y., Lim, G.J., Chua, C.L., Wong, Y.F., Yeoh, E.C.K., Low, S.K.M., Sum, C.F., 2018. The effect of Ramadan fasting and continuing sodium-glucose co-transporter-2 (SGLT2) inhibitor use on ketonemia, blood pressure and renal function in Muslim patients with type 2 diabetes. Diabetes Res. Clin. Pract. 142, 85–91. https://doi.org/10.1016/j.diabres.2018.05.022.

Steiner, S., 2016. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. Zeitschrift fur Gefassmedizin 13, 17–18. https://doi.org/10.1056/nejmoa1504720.

Tsang, M.-W., 2012. The Management of Type 2 Diabetic Patients with Hypoglycaemic Agents. ISRN Endocrinol. 2012, 1–9. https://doi.org/10.5402/2012/478120.

Wanner, C., Inzucchi, S.E., Lachin, J.M., Fitchett, D., von Eynatten, M., Mattheus, M., Johansen, O.E., Woerle, H.J., Broedl, U.C., Zinman, B., 2016. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N. Engl. J. Med. 375, 323–334. https://doi.org/10.1056/nejmoa1515920.

Zinman, B., Wanner, C., Lachin, J.M., Fitchett, D., Bluhmki, E., Hantel, S., Mattheus, M., Devins, T., Johansen, O.E., Woerle, H.J., Broedl, U.C., Inzucchi, S.E., 2015. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N. Engl. J. Med. 373, 2117–2128. https://doi.org/10.1056/NEJMoa1504720.

Alluqmani, W.S., Alotaibi, M.M., Almalki, W.J., Althaqafi, A., Alawi, H.A., Althobiani, F., Albishi, A.A., Madkhali, A.A., Baunes, L.Y., Alhazmi, R.I., Doman, E.M., Alhazmi, A.H., Ali, M., Cheema, E., 2019. Exploring drug-related problems in diabetic patients during ramadan fasting in Saudi Arabia: a mixed-methods study. Int. J. Environ. Res. Public Health 16. https://doi.org/10.3390/ijerph16030499.