



Association between SGLT2 Inhibitors and Diabetic Ketoacidosis among Patients Fasting in Ramadan

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ABSTRACT

Aims: The use of SGLT2 inhibitors during Ramadan may be unsafe (risk of ketoacidosis, postural hypotension and dehydration), specifically during long hours of Ramadan fasting in hot climates. The objective of this study was to determine the main risk factors associated with the increased occurrence of DKA during Ramadan among patients utilizing SGLT2 inhibitors and assess DKA risk during Ramadan.

Methods: This retrospective diagnostic study assessed the role of SGLT2 inhibitors in 99 patients (50 men and 49 women) with declared diabetes mellitus treated with empagliflozin and followed-up in diabetes clinics. The main variables were:

1. Demographic data (age and gender).
2. Number of break days during Ramadan fasting.
3. Comorbidities associated with diabetes.
4. Signs and symptoms of DKA.

Most of the patients (61 subjects) had a 6-10 year diabetes history, and 93 patients continued their regular follow-up. About 93% of the patients were used to Ramadan fasting, whereas only five patients did not fast in Ramadan.

Results: Thirty-one of the fasting patients broke fasting during Ramadan for 1-5 days, and only two patients did so for more than 6 days. Patients exhibited known diabetes mellitus complications, such as hypertension, dyslipidaemia, cardiovascular and other associated diseases. None of the participants showed diabetic ketoacidosis signs and symptoms.

Conclusions: SGLT2 inhibitors are considered an effective antidiabetic agent that can be safely used in patients with diabetes who are fasting in Ramadan.

Keywords: SGLT2 inhibitors; Gliflozin; DKA; Diabetic ketoacidosis; Ramadan; Hypertension; Dyslipidaemia

INTRODUCTION

Fasting during Ramadan is one of the five pillars of Islam and commemorates the time when the Holy Quran was revealed. Ramadan can take place in distinct climate conditions; therefore, Ramadan fasting can occur during very dry and hot weather, and other years it can happen in cold temperatures. Importantly, dry and hot weather could be a risk factor for

fasting among certain individuals who are particularly vulnerable, such as those with poorly controlled diabetes and those with other comorbidities.

Many Muslims have a strong desire to fast during Ramadan regardless of the conditions. This is noted specifically in patients with diabetes mellitus, although there is some guidance available for the management of diabetes during Ramadan based on expert opinion [1].

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The Middle East and North Africa (MENA) and Southeast Asia regions, where Islam predominates, exhibit a high proportion of patients with diabetes who fast in Ramadan [2]. The International Diabetes Federation states that the MENA region is expected to have the highest age-adjusted prevalence of diabetes in adults in 2019, 2030 and 2045 (12.2%, 13.3% and 13.9%, respectively). In Saudi Arabia, diabetes mellitus is present in more than 4 million individuals, i.e. approximately >18% of the total population [3,4].

The Epidemiology of Diabetes and Ramadan (EPIDIAR) study of 2001 found that 42.8% of people with Type 1 Diabetes Mellitus (T1DM) and 78.7% of those with Type 2 Diabetes Mellitus (T2DM) fasted for at least 15 days during Ramadan [5]. More recently, the Diabetes and Ramadan-Middle East and North Africa (DAR-MENA) study revealed that 86% of participants with T2DM fasted for at least 15 days [6]. Most patients with diabetes think that by fasting during Ramadan they will control their blood glucose or at least reduce their body weight. Therefore, it is important that the decision of fasting during Ramadan for all patients with diabetes is made on an individual basis in consultation with the patient's treating physician and considering the severity of the illness and the level of risk involved.

The potential health hazards of fasting in the presence of diabetes include hypoglycaemia, hyperglycaemia, dehydration and acute metabolic complications, such as Diabetic Ketoacidosis (DKA) [7]. The incidence of DKA seems to be higher during Ramadan, as observed in the EPIDIAR and other studies. Conversely, another study found that the DKA rates during Ramadan were similar to those of other months [8]. Furthermore, according to a large population-based retrospective survey conducted across 13 countries, adult individuals with T1DM reported a higher incidence of severe hypoglycaemia and DKA during Ramadan compared with other months of the year [9].

Over the last few years, the use of Sodium-Glucose Co-Transporter 2 (SGLT2) inhibitors has increased, particularly because of their favorable cardiovascular and renal effects [10]. The pharmacological action of SGLT2 inhibitors is exerted via the inhibition of 'glucose re-absorption' in the proximal renal tubules, where 90% of glucose re-absorption occurs [11]. In turn, glucose re-absorption induces osmotic diuresis, which could pose a higher risk of hypovolemia and higher rates of urinary tract infections among patients with diabetes. The Food and Drug Administration published a warning letter stating that SGLT2 inhibitors reportedly induce DKA and acute kidney injury [12,13].

The assessment of the effect of Ramadan fasting and continuing SGLT2 inhibitor use on ketonemia, blood pressure and renal function in Muslim patients with type 2 diabetes showed that SGLT2 inhibitors did not increase ketonemia, the risk of eGFR deterioration or hypoglycaemia [14]. SGLT2 inhibitors were also studied during Ramadan from a viewpoint of inducing a risk of actual occurrence of DKA; it was suggested that the risk of DKA was not increased during Ramadan fasting [15]. Another study suggested increasing the water intake during the non-fasting

hours, which is highly recommended to overcome any of the risk factor(s) associated with SGLT2 inhibitors [16].

The use of SGLT2 inhibitors during Ramadan is associated with various safety concerns, such as the risk of ketoacidosis, postural hypotension and dehydration, especially during long hours of Ramadan fasting in hot climates, as in Riyadh. It should be avoided in specific groups of patients, including those taking diuretics, those with hypotension, patients with renal impairment or elderly patients. The use of SGLT2 inhibitors may also increase the risk of dehydration or ketoacidosis.

This research explored the risk of DKA during Ramadan among patients treated with SGLT2 inhibitors. The primary objective was to assess the safety of SGLT2-I during Ramadan among fasting patients in a real-life scenario by determining the frequency and severity of DKA events, as well as the frequency of dehydration. There is a big debate regarding the use of SGLT2 inhibitors for validating the effects of SGLT2-I on DKA during fasting. Nevertheless, there is a lack of qualified literature about the risk of DKA during Ramadan among patients utilizing SGLT2 inhibitors. Therefore, this study may help diabetologists assess the risk of DKA during Ramadan among patients treated with SGLT2 inhibitors.

Objectives

The objective of this study was to determine the main risk factors associated with the increased occurrence of DKA during Ramadan among patients treated with SGLT2 inhibitors. Our aims were to emphasize the safety of SGLT2 inhibitors and to assess if there is a risk of DKA during Ramadan among patients using SGLT2 inhibitors specifically.

MATERIALS AND METHODS

This research was designed as a retrospective diagnostic study to determine the role of SGLT2 inhibitors in the induction of DKA among patients with diabetes during Ramadan. The participants in this study were patients with established diabetes mellitus who were followed-up in diabetes clinics. The main collected variables were:

- Demographic data, including age and gender.
- Number of break days during Ramadan fasting.
- Comorbidities associated with diabetes.
- Signs and symptoms of DKA.

Inclusion criteria

Patients with any type of diabetes mellitus aged 18-79 years who fasted during Ramadan and utilizing SGLT2 inhibitors.

Exclusion criteria

Age of <18 years old or >79 years, patients not fasting during Ramadan, patient with diabetes not utilizing SGLT2 inhibitors and patients with contraindications for SGLT2-I, such as pregnancy and chronic renal disease with GFR of <45.

Study procedure

This study was conducted at the endocrine department, King Saud Medical City in Riyadh, Saudi Arabia, with a sample size of 99 patients with diabetes utilizing SGLT2 inhibitors.

The study population included patients with diabetes who fasted during Ramadan and utilized an SGLT2 inhibitor (empagliflozin, 10 or 25 mg) and who experienced diabetic acidosis. The patients received a phone call from the investigators to clarify if diabetic ketoacidosis symptoms occurred during their fasting. If any symptoms were reported by any of the participants, a laboratory investigation was performed, including venous blood gases, blood glucose level and urine ketone. Moreover, an appointment was made at the diabetic clinic urgently or they were directed to the nearest urgent care center in primary health or emergency department.

Statistical consideration

Descriptive statistics were calculated regarding the number of patients with diabetes who exhibited signs and symptoms of DKA. Simple correlation coefficients of the patients with DKA who fulfilled all inclusion criteria were obtained using a bivariate correlation analysis, followed by linear regression. The relationship between the dependent and the independent variables was analyzed using the chi-squared test for qualitative variables. Differences were considered significant at $P < 0.05$.

Ethics consideration

Approval of the institutional review board of the KSMC (reference no. H1RI-05-May21-05) was obtained for this study.

RESULTS AND DISCUSSION

This was a retrospective study conducted on 99 patients with diabetes who were receiving empagliflozin therapy (50 men and 49 women). Their average of age was 52 (SD, ± 11.5) years. Most of the patients (61 subjects) had a 6-10-year diabetes history, 27 subjects had a diabetes history for >10 years and only 10 subjects had diabetes for <5 years. Most importantly, 92 patients (93%) were used to Ramadan fasting, whereas only five patients were not used to fasting during Ramadan (Table 1).

This study considered the last readings of glycated hemoglobin (HbA1C); it was found that 25 patients had an HbA1c level $<7\%$; 45 patients had HbA1c of $7\%-9\%$; and 29 patients had a level of $>9\%$. Twenty-one patients suffered a hypoglycaemic attack during Ramadan. The results showed that 31 of the patients who were fasting broke their fast during Ramadan for 1-5 days and only two patients broke their fasting for more than 6 days during Ramadan.

Patients receiving empagliflozin 25 mg (79 subjects) and 10 mg (20 subjects) exhibited diabetes mellitus complications, such as hypertension (66 subjects), dyslipidaemia (79 subjects), cardiovascular diseases (39 subjects), retinopathy (5 subjects) and neuropathy (10 subjects).

None of the 99 patients involved in this study exhibited any of the DKA signs and symptoms, including abdominal pain, nausea, vomiting, excessive thirst, shortness of breath, confusion, fruit-scented breath, weakness or fatigue. Moreover, no ketones were detected in their urine or blood from previous laboratory results.

SGLT2 inhibitors seem to be associated with euglycemic DKA and ketosis, perhaps as a consequence of noninsulin-dependent glucose clearance, hyperglucagonemia and volume depletion [17]. Patients with type 1 or type 2 diabetes who experience nausea, vomiting or malaise or develop metabolic acidosis in the setting of SGLT2 inhibitor therapy should be promptly evaluated for the presence of urine and/or serum ketones. SGLT2 inhibitors were generally well tolerated, no serious side effect or hypoglycemic events have been reported during or after Ramadan, and has better influence on weight reduction over the other hypoglycemic medications [18].

The majority of the participants lived in Riyadh City, which is characterized by hot weather during the summer and prolonged fasting hours in Ramadan; hence, they were at risk of dehydration and volume depletion. Such circumstances mandate a close monitoring of patients, especially those using SGLT2 inhibitors, as these agents can reduce blood glucose levels, body weight and blood pressure as a monotherapy or when used in combination with other antidiabetic agents. This study revealed a controlled blood glucose level during the use of empagliflozin with or without other antidiabetic agents, under the safety margins and without any risk [19,20].

Table 1: Comparative results for female and male fasting Ramadan and while they were receiving SGL2.

		All (n=99)	Female; n=49 (49.5%)	Male; n=50 (50.5%)
Average of Age (\pm SD)		52.01 (11.5)	51.37 (11.4)	52.64 (11.7)
Duration of diabetes	5yrs or less	10 (10.1%)	5 (10.2%)	10.2 (5%)
	6-11 years	62 (62.6%)	32 (65.3%)	65.3 (30%)
	11yrs and more	27 (27.3%)	12 (24.5%)	24.5 (15%)
Regular fasting	No	6 (6.1%)	3 (6.1%)	3 (6%)
	Yes	93 (93.9%)	46 (93.9%)	47 (94%)
HBA1c level	Less than 7	25 (25.3%)	11 (22.4%)	14 (28%)
	07-Sep	45 (45.5%)	22 (44.9%)	23 (46%)
	More than 9	29 (29.3%)	16 (32.7%)	13 (26%)

This study identified 21 cases of hypoglycaemic attacks and 31 patients who broke their fasting during Ramadan for 1-5 days, which was similar to another study reporting a high incidence of hypoglycaemia among patients with diabetes [21]. Hypoglycaemia varies according to the different hypoglycaemic medications in people with T2DM during Ramadan fasting; however, none of the participants in this study exhibited hypoglycaemic attacks during the year, suggesting that these hypoglycaemic attacks were caused by Ramadan rather than medications [22,23].

Obviously, most patients with diabetes have one or more comorbid diseases [24]. This study yielded similar findings in that most of the patients with diabetes had dyslipidaemia, hypertension and Cardiovascular Disease (CVD) [25-27]. This is in addition to the association between DM and its complications, such as neuropathy and retinopathy [28].

Although the risk of DKA has been shown to not be increased during Ramadan among patients with diabetes, this retrospective study focused on the safety profile and the risk of DKA incidence among patients who fasted during Ramadan and used SGLT2 inhibitors combined with insulin or other oral hypoglycaemic agents. All participants in this study had type 2 diabetes managed by empagliflozin (either 25 mg or 10 mg), because the incidence of DKA was 1.02 per 1000 patients receiving SGL2 inhibitor therapy [29,30].

CONCLUSION

All participating patients were compliant with empagliflozin and took it on a daily basis during the fasting days. We evaluated each patient regarding the occurrence of common DKA symptoms, with reassuring results. Moreover, we attempted to include the standard monitoring of blood glucose average readings during this evaluation; we found that some of the patients had average glucose readings between 200-300, and none of them had DKA or other symptoms, such as abdominal pain, vomiting, excessive urination or excessive thirst during Ramadan.

SGLT2 inhibitors are considered an effective antidiabetic agent. Although there is an existing concern about the potential risk of euglycemic diabetic ketoacidosis among patients on SGLT2 inhibitor therapy, this study demonstrated that SGLT2 inhibitors can be safely used in patients with diabetes who are fasting during Ramadan. However, frequent monitoring and follow-up of patients with diabetes using this class of medication is warranted.

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AUTHORSHIP CONTRIBUTION

AR, AG, and AJ, had contributed in research proposal, study design and data collection under the supervision of SA. MA, and FD had analyzed the data and wrote a draft of the manuscript also under the supervision of SA. All authors have read and approved the final manuscript.

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