Safety and Effectiveness of Sodium-Glucose Co-transporter 2 Inhibitors on Glycemic Control in Patients with Type 2 Diabetes Mellitus Fasting during Ramadan: A Review

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ABSTRACT: This review evaluates the current evidence on the safety and efficacy of sodium-glucose cotransporter 2 (SGLT2) inhibitors for patients with type 2 diabetes mellitus (T2DM) fasting during Ramadan. All studies included in the review were conducted in Asia and the Middle East. Overall, the evidence suggests that SGLT2 inhibitors are a safe and effective treatment option for most T2DM patients fasting during Ramadan. The average incidence of symptomatic hypoglycemia is 12.5%, but ranges from 0.7% to 27%, depending on the study population and concomitant use of other medications. The risk of hypoglycemia is increased when SGLT2 inhibitors are used in combination with insulin and/or sulfonylureas. Therefore, patients taking SGLT2 inhibitors in combination with insulin and/or sulfonylureas can take steps to mitigate this risk, such as having their insulin and/or sulfonylurea doses adjusted and being closely monitored for hypoglycemia. Patients taking SGLT2 inhibitors may be at increased risk of dehydration. To mitigate the risk of dehydration, patients should be advised to consume adequate fluids during the fast-breaking hours. Further research is warranted to validate these findings and extend their applicability to high-risk populations and other regions of the world.

PLAIN LANGUAGE SUMMARY

Safety and effectiveness of sodium-glucose co-transporter 2 inhibitors on glycemic control in patients with type 2 diabetes mellitus fasting during Ramadan: a review

This review delves into the existing evidence regarding the safety and efficacy of sodium-glucose co-transporter 2 (SGLT2) inhibitors for patients with type 2 diabetes mellitus (T2DM) who observe Ramadan fasting. The studies reviewed were conducted exclusively in Asia and the Middle East. Overall, the gathered evidence suggests that SGLT2 inhibitors constitute a safe and effective treatment option for most T2DM patients fasting during Ramadan. While a slightly elevated risk of dehydration compared to other medications may exist, this is generally well-tolerated. To mitigate the risk of dehydration, patients should be advised to consume adequate fluids during the fast-breaking hours. However, further research is warranted to validate these findings and extend their applicability to high-risk populations and other world regions.

KEYWORDS: SGLT2 inhibitors, Ramadan, fasting

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Introduction

Ramadan is the holy month celebrated by Muslims around the world each lunar year. During Ramadan, Muslims fast from sunrise to sunset, withholding water and food intake for about 15 to 20 hours a day for about 29 to 30 days—millions of Muslims with diabetes mellitus worldwide fast during this month. The EPIDIAR and CREED studies showed that patients with type 2 diabetes mellitus (T2DM) who fasted during the month of Ramadan were at 7.5 times higher risk of developing hypoglycemia and 5 times higher risk of hyperglycemia.[1,2] While fasting can provide metabolic benefits such as weight loss and reduced insulin resistance, transitioning from a traditional 3-meal diet to 1 or 2 meals or excessive consumption after breaking the fast can disrupt glycemic control. Medications commonly prescribed for diabetes management, particularly those that can induce hypoglycemia, like insulin and sulfonylurea, may pose significant risks for patients during fasting periods. Therefore, considerable care is taken to harmonize diabetes treatment with the expected fasting state, and healthcare providers begin preparing their patients months in advance to ensure their safety.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new class of oral antidiabetic medications effective as monotherapy and add-on therapy for T2DM. In addition to lowering blood glucose, SGLT2 inhibitors offer many other benefits for patients with T2DM, including weight loss, blood pressure reduction, and improved cardiovascular and renal outcomes.[3]

SGLT2 inhibitors increase glucose excretion in the urine (glucosuria) and lower the renal glucose threshold for glucosuria to as low as 40 mg/dL.[4] However, uncontrolled diabetic

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patients taking SGLT2 inhibitors may experience excessive fluid loss, dehydration, and hypotension, especially if they are unable to drink due to fasting or are taking concurrent diuretics.[5] SGLT2 inhibitors can also be associated with an increased risk of hypoglycemia in patients treated with insulin or sulfonylureas.[6] Additionally, SGLT2 inhibitors can increase the risk of diabetic ketoacidosis (DKA).[7,8]

A recent consensus statement concluded that SGLT2 inhibitors usage during Ramadan should adhere to the standard safety and prescribing measures outlined by each drug's Summary of Product Characteristics. It is generally advisable to avoid SGLT2 inhibitors in elderly individuals, patients taking loop diuretics, and individuals with impaired renal function.[9] Over the past few years, numerous studies have investigated the use of SGLT2 inhibitors during Ramadan. This review examines the current evidence on the safety and effectiveness of SGLT2 inhibitors in fasting patients with T2DM.

Methods

We conducted a literature search of the PubMed and Cochrane databases from January 2015 to September 2023 using the terms "Ramadan" and "SGLT2 inhibitors." Our focus was on safety outcomes during Ramadan, including symptomatic hypoglycemia, symptomatic hyperglycemia, ketonemia and diabetic ketoacidosis (DKA), volume depletion reported as dehydration or postural hypotension, change in estimated glomerular filtration rate (eGFR), urinary tract infections (UTI), and genital infections. We also examined the effectiveness outcome of glycemic control during Ramadan. We calculated each outcome's average rate by weighting each relevant study's results according to its sample size.

In addition, we reported on the rates of symptomatic hypoglycemia, volume depletion, and glycemic control associated with SGLT2 inhibitors versus active comparators during Ramadan in studies that assessed these outcomes. The categorical outcomes between SGLT2 inhibitors and active comparators were compared using the chi-square or Fisher's exact test, as appropriate.

Results

This review analyzed 11 articles that met our criteria.[10-20] These articles were mainly prospective observational cohort studies conducted in various countries and published between February 2016 and April 2023 (Table 1). All studies were conducted during spring and early summer in Asia and the Middle East, where some countries are hot and dry while others are warm, humid, and tropical. The total number of study participants was 1416, with a mean age of 52.2 ± 4.5 years. 50.5% of the participants were female, and 8 studies reported BMI, with a mean BMI of approximately 30.0 ± 2.8 kg/m^2. The percentage of patients using medications that increase the risk of hypoglycemia, such as insulin or sulfonylureas, varied among studies. Seven studies included patients treated with insulin or sulfonylureas.[12-15,18-20]

During Ramadan, the outcomes that were examined in association with the treatment of SGLT2 inhibitors are as follows:

Symptomatic hypoglycemia

Ten studies reported the occurrence of symptomatic hypoglycemia in a total of 1244 patients.[10-14,16-20] The incidence ranged from 0.7% to 27%, with an average rate of 12.5 ± 8.3%. Of the 10 studies, only 1 case of severe hypoglycemia (defined as requiring assistance from another person for recovery[21]) was reported in a study of 417 patients.[12] Notably, the incidence of symptomatic hypoglycemia was significantly lower in studies in which SGLT2 inhibitor-treated patients did not receive insulin or sulfonylureas (3.2% in 538 patients)[10,11,16,17] compared to studies in which some of the SGLT2 inhibitor-treated patients did receive such agents (21.5% in 706 patients).[12-14,18-20]

The timing of hypoglycemic events during Ramadan was reported in only 1 study, with 85% occurring during daylight hours while participants were fasting before the Iftar meal.[12]

Symptomatic hyperglycemia

Only 3 studies (including only 203 patients) reported symptomatic hyperglycemia, with an incidence rate ranging from 0% to 31%, with an average rate of 13.2 ± 6.4%.[16,18,20]

Ketonemia and DKA incidence

Two studies measured beta-hydroxybutyrate levels before and during Ramadan.[13,19] Patients on SGLT2 inhibitors had slightly higher levels than the control group, but there was no significant difference between pre-and during Ramadan measurements. Diabetic ketoacidosis cases were not reported in either study.

Volume depletion (dehydration or postural hypotension)

Nine studies with a total of 950 patients reported the incidence of symptomatic volume depletion.[10,11,13,15-20] The occurrence rate of symptomatic volume depletion in patients treated with SGLT2 inhibitors ranged from 2.6% to 29%, with a mean incidence rate of 11.1 ± 1.6%.

Changes in eGFR

Seven studies reported baseline and follow-up eGFR values for 725 patients.[11,13,14,17-20] The change in eGFR was calculated by comparing the measurement before the month of Ramadan with the measurement during or within 8 weeks of Ramadan fasting. The mean baseline eGFR was 88.1 ± 9.2 *ml/min/1.73 m*^{2}. The changes in eGFR ranged from −6.5 to +5.0 ml/min/1.73 m^2 with an average reduction of −1.0 ± 0.4 ml/min/1.73 m^2.

Table 1. Characteristics and outcomes of patients with T2DM treated with SGLT2 inhibitors in studies conducted during Ramadan.

ARTICLE	COUNTRY	STUDY DESIGN	SGLT2I USED	NUMBER OF PATIENTS (N)	MEAN AGE (YR)	FEMALES (%)	MEAN BMI (KG/M²)	SUTREATMENT (%)	INSULIN TREATMENT (%)	MEAN HBA1C AT BASELINE (%)	HBA1C CHANGE (%)	PATIENTS WITH SYMPTOMATIC HYPOGLYCEMIA (%)	PATIENTS WITH SYMPTOMATIC HYPERGLYCEMIA (%)	MEAN EGFR AT BASELINE (*ML/MIN/1.73 M²*)) (SD)	MEAN EGFR CHANGE (*ML/MIN/1.73 M²*)	PATIENTS WITH SYMPTOMATIC VOLUME DEPLETION (%)	PATIENTS WITH UTI (%)	PATIENTS WITH GENITAL INFECTIONS (%)
Wan Seman et al[10]	Malaysia	ROPS	DAPA	58	53	39.7	29.9	0	0	7.70	−0.05	3.4	NA	NA	NA	13.8	10.3	5.2
Hassanein et al[11]	Lebanon, Kuwait, UAE	POCS	CANA	162	52.3	38.3	30.7	0	0	7.30	−0.40	3.7	NA	89.9 (19.6)	−1.2	9.3	0.6	0
Bashier et al[12]	UAE	POCS	CANA or DAPA	417	54	58.5	NA	46	45.8	8.30	−0.50	27	NA	NA	NA	NA	NA	NA
Shao et al[13]	Singapore	POCS	CANA or EMPA	33	49.9	45.7	33.4	37.1	71.4	9.30	NA	15.4	NA	91.2 (21.8)	−6	0	NA	NA
Abdelgadir et al[14]	UAE	PIS	CANA	49	57.5	65.2	NA	44.8	100	7.95	−0.35	16.3	NA	100.5 (21.4)	−1.5	NA	NA	NA
Gameil et al[15]	Egypt	POCS	EMPA or DAPA	172	52.5	34.9	32.1	76.2	5.8	8.0	NA	NA	NA	NA	NA	29	NA	NA
Ahmed et al[16]	Pakistan	POCS	EMPA	44	44.7	45.5	36.5	0	0	7.20	−0.30	15.9	6.8	NA	NA	11.1	0	0
Pathan et al[17]	Bangladesh	POCS	EMPA	274	49	51	27.3	0	0	8.40	−0.50	0.7	NA	79.3 (21.2)	+0.2	2.6	2.1	NA
Sheikh et al[18]	Pakistan	POCS	EMPA or DAPA	82	52.2	47.6	NA	29.3	40.2	7.90	−0.20	7.3	0	94.3 (37.6)	−6.5	4.8	NA	NA
Goh et al[19]	Malaysia	POCS	EMPA	48	48 (43.5-56.5)*	75	29.9(26-36.4)*	22.9	62.6	8.40 (7.25-9.85)*	NA	19.1	NA	94.1 (71.7-113.2)*	−3**	0	0	0
Samkari et al[20]	Saudi Arabia	POCS	EMPA	77	56 (51-62)*	57	28.8 (25.5-31.6)*	74	0	7.80 (7.10-8.77)*	NA	16.0	31.0	96 (86-105)*	+5**	16.0	NA	NA

Abbreviations: CANA, canagliflozin; DAPA, dapagliflozin; EMPA, empagliflozin, NA, not applicable; PIS, prospective interventional study; POCS, prospective observational cohort study; ROPS, randomized open-label parallel-group study; SU, Sulfonylurea.
*Median value (interquartile range).
**Change in median eGFR values 2weeks before and 2weeks after Ramadan.

UTI and genital infections

Five studies with 586 patients examined the incidence of UTI, with an overall rate ranging from 0% to 10.3% and an average incidence rate of 2.2 ± 0.5%.[10,11,16,17,19] Four studies with 312 patients reported genital infections, with an incidence ranging from 0% to 5.2% and an average incidence of 1.6 ± 0.8%.[10,11,16,19]

HbA1c changes

Baseline HbA1c values were reported in all studies, with a mean HbA1c of 8.1 ± 0.7%.[10-20] Seven studies, including 1086 patients, reported changes in HbA1c during or within 8 weeks of Ramadan fasting, with a range of 0.05% to 0.5% and an average reduction of 0.40 ± 0.1%.[10-12,14,16-18]

Outcomes of SGLT2 inhibitors versus active comparators during Ramadan

SGLT2 inhibitors versus sulfonylureas. Two studies, Wan Seman et al[10] and Hassanein et al[11] compared 220 patients treated with SGLT2 inhibitors (dapagliflozin and canagliflozin, respectively) to 211 patients treated with sulfonylureas. Both studies found that switching from sulfonylureas to SGLT2 inhibitors (dapagliflozin and canagliflozin, respectively) was associated with a lower risk of symptomatic hypoglycemia during Ramadan (19.2% vs 3.4% and 10.7% vs 3.7%, $P = .008$ and $P = .003$ respectively) while maintaining similar glycemic efficacy. However, SGLT2 inhibitors were associated with numerically more episodes of symptomatic volume depletion (13.8% vs 5.8% and 9.3% vs 3.8%, $P = .21$ and $P = .07$ respectively), although these events were generally well-tolerated and in the majority of cases did not lead to breaking of the fast or discontinuation of treatment. Overall, both studies concluded that SGLT2 inhibitors could be considered a safe and effective alternative to sulfonylureas for preventing hypoglycemia during Ramadan.

However, a direct comparison of hypoglycemia rates between sulfonylureas alone and sulfonylureas combined with SGLT2 inhibitors during Ramadan is currently unavailable. Therefore, the impact of adding SGLT2 inhibitors on hypoglycemia risk relative to sulfonylurea monotherapy remains unclear.

SGLT2 inhibitors versus DPP4 inhibitors. Two studies, Ahmed et al[16] and Pathan et al[17] compared the use of empagliflozin (in 318 patients) to DPP4 inhibitors (in 307 patients) during Ramadan and found no increase in the rate of symptomatic hypoglycemia (15.9% vs 15.9% and 0.7% vs 0.4%, respectively; $P = 1$ and $P = .27$).

In Ahmed et al,[16] HbA1c also improved after using empagliflozin before and after Ramadan (7.2 ± 0.8% vs 6.9 ± 0.9% for metformin and empagliflozin and 7.8 ± 1.5% vs 7.6 ± 1.6% for metformin and sitagliptin). Pathan et al[17] also found that the reduction in HbA1c was more significant with empagliflozin than with a DPP4 inhibitor (−0.49% vs −0.12%; $P < .001$).

In both studies, there was no statistically significant difference in the rates of symptomatic volume depletion between the groups taking empagliflozin and DPP4 inhibitors (11.1% vs 7.6% and 2.6% vs 1.8%; $P = .53$ and $P = .55$, respectively). Both studies concluded that SGLT2 inhibitors are just as safe and well-tolerated as DPP4 inhibitors in people with T2DM who are fasting during Ramadan.

Discussion

The use of SGLT2 inhibitors during Ramadan has been a topic of concern. This review included 11 studies that assessed the safety and effectiveness of SGLT2 inhibitors in patients with T2DM during Ramadan.

Most studies found that SGLT2 inhibitors were associated with satisfactory glycemic control and an average reduction in HbA1c of 0.4%. The average incidence of symptomatic hypoglycemia in patients treated with SGLT2 inhibitors during Ramadan is 12.5%, but can range from 0.7% to 27%, depending on the study population and the concomitant use of other medications. The risk of hypoglycemia is increased when SGLT2 inhibitors are used in combination with insulin and/or sulfonylureas.

There was a small and non-significant decrease in eGFR in some patients treated with SGLT2 inhibitors, but no cases of acute kidney injury were reported. Two studies measured beta-hydroxybutyrate levels and found that it was higher in patients treated with SGLT2 inhibitors than in patients treated with other oral hypoglycemic agents, both before and during Ramadan. However, no cases of clinical DKA were reported in any of the studies. In addition, the risk of UTI and genital infection was relatively low.

SGLT2 inhibitors may increase the risk of symptomatic volume depletion due to their osmotic diuresis effect. However, studies have shown conflicting results, with the risk ranging from 2.6% to 29%. This variability may be due to the different definitions of symptomatic hypovolemia, which include a wide range of signs and symptoms such as postural dizziness or hypotension, intense thirst, nausea, headache, vertigo, syncope, or presyncope. Two critical active-comparator studies found that SGLT2 inhibitors were associated with numerically more episodes of symptomatic volume depletion compared with sulfonylurea. However, these events were generally well-tolerated and, in most cases, did not lead to the breaking of the fast or discontinuation of treatment.[10,11]

The studies included in this review have several limitations. These include variation in study designs, small sample sizes, exclusion of high-risk patients, such as those with a recent history of severe hypoglycemia before Ramadan, renal impairment, or age over 65, and restriction to the Middle East and Asia.

Conclusion

The studies suggest that SGLT2 inhibitors are safe and effective for most people with type 2 diabetes who are fasting during Ramadan. However, patients who are taking SGLT2

inhibitors in combination with insulin and/or sulfonylureas should have their insulin and/or sulfonylureas doses adjusted to prevent hypoglycemia, and they should be closely monitored for hypoglycemia. It is generally recommended to break the fast if blood glucose is <70 mg/dL or >300 mg/dL. Fasting during illness (sick days) is also not advised.[22]

SGLT2 inhibitors may be associated with a higher risk of symptomatic volume depletion or dehydration than other antidiabetic medications. While these events were generally well-tolerated, caution should be exercised in patients at high risk for dehydration, such as the elderly and those taking loop diuretics.[23] Patients taking SGLT2 inhibitors during Ramadan should be advised to drink adequate fluids during the fast-breaking hours to reduce the risk of dehydration. More studies are needed to confirm these findings and apply them to other parts of the world and high-risk populations.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Afif Nakhleh: Conceptualization; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing. **Jomana Mazareeb:** Writing – review & editing. **Said Darawshi:** Writing – review & editing. **Amin Masri:** Writing – review & editing. **Naim Shehadeh:** Writing – review & editing.

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