Efficacy and Safety of Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitor Use during Ramadan Fasting: A Systematic Review

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Abstract

Background Religious intermittent fasting for 30 days during Ramadan may increase the risk of dehydration, hypovolemia, and hypoglycemia. These events may also be encountered when using sodium-glucose cotransporter 2 inhibitors (SGLT2is).

Objectives This article evaluates the safety of the SGLT2 inhibitors in people with type 2 diabetes during Ramadan.

Search Methods We searched PubMed CENTRAL, MEDLINE, and Google Scholar on July 25, 2023 without language restrictions.

Selection Criteria All trials assessing the safety of SGLT2 inhibitors during Ramadan were assessed and summarized into preset points.

Data Extraction Two authors independently extracted and reviewed the retrieved studies. A third author reviewed the merged summary of the two authors and modified the article when necessary.

Results Diabetic ketoacidosis, hospitalization due to diabetes-related problems, and thrombosis were either not significantly related to SGLT2i use or not studied. Estimated glomerular filtration rate (eGFR) dropped significantly in one study; otherwise, it was either not statistically significant or not studied. Hypovolemia and dehydration were significantly increased in one study only.

Keywords
► fasting
► Ramadan
► Ramadan fasting
► safety
► SGLT2i

Conclusion From the available evidence, the use of SGLT2 inhibitors in people with diabetes during Ramadan seems to be safe and well tolerated. Hypovolemia and a drop in eGFR were reported in a few studies, with no reported clinical significance.

Introduction

Most healthy adults will tolerate the religious intermittent fasting during Ramadan. However, it may increase the risk of dehydration, hypovolemia, hypoglycemia, diabetic ketoacidosis (DKA), and hospitalization in people with diabetes mellitus (PwD).[1–3] Some of these consequences may overlap with the expected adverse events of some antidiabetic drugs.

For instance, hypoglycemia typically increases with sulfony-lureas (SU) and insulin, while dehydration and hypovolemia may increase with sodium-glucose cotransporter 2 inhibi-tors (SGLT2i).[4]

The management paradigm of type 2 diabetes mellitus (T2DM) has been steadily evolving over the last one or two decades and more rapidly in the last few years.[5–7] Various options were approved for practitioners' use and more in the industrial pipelines.[8] The cardiometabolic renal benefits beyond glycemic control drove the change in recommenda-tions demonstrated for certain drug classes.[9]

The safety of the hypoglycemic agents in special pop-ulations and special situations, like Ramadan fasting, was demonstrated in several studies.[4] More recently, several studies have been devoted to assessing the safety of rela-tively new hypoglycemic agents, specifically SGLT2i and glucagon-like peptide-1 receptor agonists (GLP-1 RA). How-ever, these studies used different members of these classes and involved varying numbers of subjects under different geographical and socioeconomic circumstances, leading to potentially different conclusions when presented separate-ly. Therefore, we wish in this systematic review to critically evaluate the data on the safety of the SGLT2i during Rama-dan fasting and inform clinical practice of their use during Ramadan fasting.

Methods

The Preferred Reporting Items for Systematic Review and Meta-Analysis was used to conduct a systematic review.[10] The study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with a reference code CRD42023472977.

Objectives

We aimed to assess the safety of the SGLT2i in PwD during Ramadan fasting for people with T2DM fasting during Ram-adan, regardless of the risk category of the studied populations.

Search Methods

We searched PubMed CENTRAL, MEDLINE, and Google Schol-ar on July 25, 2023 without language restrictions.

Selection Criteria

All trials assessing the safety of SGLT2i during Ramadan were assessed. We included randomized controlled trials (RCTs), observational, and retrospective studies. Review articles, systematic reviews, meta-analyses, and clinical guidelines were excluded.

Data Extraction

Two authors independently extracted and reviewed the available studies in the above search engines. No language, year of publication, country or conduct, funding, or study duration restrictions were applied. A third author reviewed

the merged summary of the two authors and modified the article when necessary; the fourth and fifth authors reviewed the final version and concurred on the final article and the conclusions.

Inclusion Criteria

The data evaluation was designed following PICO criteria: Study designs: RCT, observational cross-sectional, retrospec-tive studies; study population: patients on SGLT2i during the month of Ramadan; intervention: SGLT2i; control: individu-als receiving other hypoglycemic agents or placebo; out-come: efficacy and safety of the SGLT2i during Ramadan.

Results

We identified 380 records, of which only 44 met the criteria for further in-depth screening. Based on the preset inclusion and exclusion criteria, we identified 12 articles meeting the criteria of the current review (►Fig. 1). These studies were retrieved, reviewed, and summarized in ►Tables 1–3.[10–21] The studies included one RCT and nine prospective observa-tional studies. In addition, two documents were retrospec-tive studies. Out of the commonly used SGLT2is, dapagliflozin alone was assessed in one study (►Table 1), canagliflozin alone in one study (►Table 1), and empagli-flozin in 8 (►Table 3). While some studies have assessed the SGLT2is in groups (►Table 2). The studied age group extend-ed from 18 to 79. DKA, hospitalization due to DM-related problems, and thrombosis were either not significantly related to SGLT2i use or not studied in some papers. Estimat-ed glomerular filtration rate (eGFR) dropped significantly in one study; otherwise, it was either not statistically signif-icant or not reported in some papers. Also, hypovolemia and
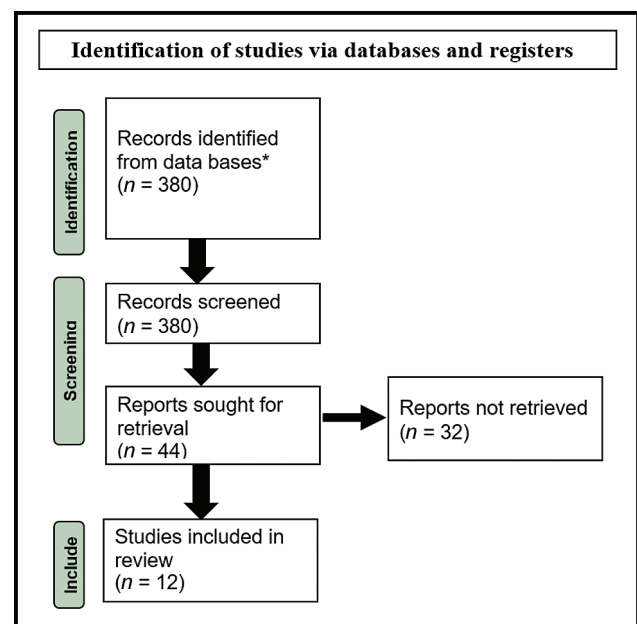
Fig. 1 The data identification and extraction flow chart.

Table 1 Summary of the studies on the efficacy and safety of dapagliflozin or canagliflozin during Ramadan fasting

Authors (year) [Ref]	Population/Risk stratification	SGLT2i used	Study design	HbA1c changes	eGFR changes	Fluid homeostasis	Hypoglycemia	DKA	Thrombosis	Hospitalization
Wan Seman et al (2016)[11]	• 110 patients • Aged 18–65 years • Low risk	Dapagliflozin	Randomized, open-label, two-arm parallel group study	NA — Drop of 0.05% in the SGLT2i group and 0.32% in the controls	NA	Not significant — Dehydration in 13.8 vs. 3.8%; $p = 0.210$ in SGLT2i vs. control group — in SGLT2i VS control group	Significant — Patients with hypoglycemia: 4 (6.9%) vs. 15 (28.8%); $p = 0.002$ in SGLT2i vs. control	Data not available	Data not available	Data not available
Hassanein et al (2017)[10]	• 379 patients • Aged 18–65 years • Mean age • Low/moderate risk	Canagliflozin	Nonrandomized, parallel cohort, prospective, comparative, observational study	NA — Dropped in SGLT2i group by −0.4%, dropped in control group by −0.2%	NA — Dropped in SGLT2i group by −1.2, increased in control group by 3.1	Significant — Hypovolemia in 26 (16.1%) and 8 (5%) in SGLT2i vs. control group, $p = 0.11$	Significant — Hypoglycemia in 6 (3.7%) and 21 (13.2%) in SGLT2i vs. control group, $p = 0.009$	Data not available	Data not available	Data not available

Abbreviations: DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; NA, not available; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

dehydration were significant in one study only (►**Table 1**).[10–21]

Discussion

This is the most comprehensive systematic review of the use of SGLT2i during Ramadan fasting. There were more studies on empagliflozin than dapagliflozin and canagliflozin. DKA, hospitalization due to diabetes-related problems, and thrombosis were either not significantly related to SGLT2i use or not studied. eGFR dropped significantly in a single study; otherwise, it was either not statistically significant or not studied. Hypovolemia and dehydration were significantly increased in one study only. These findings are reassuring about using this class of antidiabetic medications in general.

Several guidelines and consensus statements have been published during the last two decades. However, a few of them included the SGLT2i in the recommendations (since they are relatively new antidiabetic agents and the stance on their safety in Ramadan has yet to be firmly developed). SGLT2i use during Ramadan has first come into the recommendations in International Diabetes Federation/Diabetes and Ramadan Alliance (IDF/DAR) guidelines and two other independent international groups of professionals.[22–24] Then, there was a single study assessing the safety of the SGLT2i during Ramadan,[11] a physician survey,[25] and an expert statement working from first principles.[26]

The IDF/DAR committee advised taking the same dose of pre-Ramadan SGLT2i at Iftar time and drinking plenty of water during the fed state hours. They also advised cautious use in elderly individuals and those with renal impairment, hypotension, and those taking diuretics therapy.[24] Recently, a Canadian consensus statement advised generally continuing the same SGLT2i dose. However, the dose must be adjusted or withheld in people at high risk for volume depletion (age > 75 years, eGFR < 60 mL/min/1.73 m^2, and loop diuretics). However, given the robust cardiovascular (CV) protection data, they recommended the continuation of these agents in patients with established CV disease (CVD).[27] Additionally, the Canadian recommendations advised withholding the SGLT2i in cases of acute vomiting, diarrhea, or orthostatic hypotension and to seek immediate medical attention.[27] Until the latest IDF/DAR guidelines in 2021,[28] five more studies on the safety of SGLT2i during Ramadan were published. The IDF/DAR guideline 2021 recommended no dose adjustment; the benefit outweighs the risk, so initiation at a low dose is warranted up to 2 weeks before fasting starts. In addition, the guidelines recommended increasing fluid intake and raising awareness among patients of all potential side effects.[28] Since the time of the latest IDF/DAR guidelines, more studies on the safety of SGLT2i emerged, which may top up the confidence in this relatively new class of medication during Ramadan. Although professional opinion has evolved more favorably toward more liberal use of the SGLT2i class in people with diabetes during Ramadan fasting,[29,30] a formal evaluation of these studies in a systematic manner is warranted.

Table 2 Summary of the studies on the efficacy and safety of multiple SGLT2is during Ramadan fasting

Authors (year) [Ref]	Population/Risk stratification	SGLT2i used	Study design	HbA1c changes	eGFR changes	Fluid homeostasis	Hypoglycemia	DKA	Thrombosis	Hospitalization
Bashier et al (2018)[12]	• 417 patients • Aged 18–75 years • Mean age 54.0±11.6 • Low to high risk • All patients were on SGLT2i+OHA or insulin	NA	Retrospective, medical records examination + individual phone interview with patients	Significant — HbA1c dropped from 8.3±1.7% before Ramadan to 7.8±1.3% after Ramadan; $p=0.001$	Not significant — Not significant	Not significant — Observed in 39 patients (9.3%) - SGLT2i+insulin (13.1%) vs. SGLT2i+OHA (6.1%), p 0.03	Not significant — Symptomatic: 27% Confirmed: 18.7% More in SGLT2i+insulin (37%) than SGLT2i+OHAs (17%), $p<0.005$	None	None	One patient with hypoglycemia
Shao et al (2018)[13]	• 68 patients • Aged 21–75 years • Mean age 52.2±11.1 years • Low/moderate risk	Canagliflozin, dapagliflozin	Prospective, observational controlled cohort study	NA — NA	Not significant — NA	Not significant — - Mean drop in sitting systolic BP –8.1 vs. –10.4 mm Hg, $p=0.569$, in SGLT2 vs. control group, respectively	Not significant — Less hypoglycemic episodes in SGLT2i group (22.9–15.4%, $p=0.687$) from pre-Ramadan to Ramadan	None -B-hydroxybutyrate were measured = 0.31 vs. 0.24 mmol/L, $p=0.076$ in SGLT2i vs. control group, respectively	Data not available	Two patients, one with stroke and one with gouty arthritis (non-DM related admissions)
Abdelgadir et al (2019) 14	• 95 patients • Aged 18–75 years • Mean age 56.4+9.3 • High risk	Dapagliflozin, empagliflozin, canagliflozin	Prospective, controlled study	Significant — SGLT2i group: 7.95±1.1 before Ramadan to 7.6±1.1% after Ramadan, p 0.028	Not significant — SGLT2i: 100.5±21.4 before Ramadan to 99±16.8 after Ramadan, p 0.97	NA — NA	Not significant — Number of hypoglycemic episodes during Ramadan SGLT2i 3.9±5.1 vs. 3.3±3.8 in controls, p 0.97	None	Data not available	Data not available
Sheikh et al (2023)[15]	• 82 patients • Aged 21–70 years • Mean age: 52.2±9.5 • Low/moderate risk	Dapagliflozin, empagliflozin	Prospective, observational, controlled cohort study	Not Significant — HbA1c dropped from 7.9±2.3 before Ramadan to 7.7±1.2 after Ramadan, $p=0.34$	Significant — eGFR dropped from 94.3±37.6. before Ramadan to 87.8±27.9 after Ramadan, $p \leq 0.001$	NA — Symptomatic dehydration reported in 4 patients (4.8%). No hospitalization for dehydration	Not significant — Hypoglycemia reported in 6 (7.3%) patients receiving SGLT2 inhibitors. All 6 cases confirmed with capillary blood glucose readings. No hospital admission due to severe hypoglycemia	Did not occur	Not studied	Did not occur

Abbreviations: BP, blood pressure; DKA, diabetic ketoacidosis; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; NA, not available; OHA, oral hypoglycemic agent; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Table 3 Summary of the studies on the efficacy and safety of empagliflozin during Ramadan fasting

Authors (year) [Ref]	Population/Risk stratification	SGLT2i used	Study design	HbA1c changes	eGFR changes	Fluid homeostasis	Hypoglycemia	DKA	Thrombosis	Hospitalization
Ahmed et al (2022)[16]	• 132 patients • Mean age 44.7 ± 10.7 • Low risk	Empagliflozin	Prospective, observational controlled study	Not Significant HbA1c dropped from 7.2 ± 0.8 before Ramadan to 6.9 ± 0.9 after Ramadan, $p = 0.027$	NA	Not significant No statistically significant difference in rate of dehydration in DPPv4 group and SGLT2i group (7.6% vs. 11.1%)	Not significant Similar episodes of hypoglycemia (15.9%) in both groups, $p = 1.00$	None in either group	Not studied	Did not occur
Goh et al (2023)[18]	• 98 patients (48 on empagliflozin, and 50 control) • Aged 18–75 • Mean age: 48 (43.5–56.5) in empagliflozin arm, 51.5 (42–58) in control arm Low/moderate/severe risk	Empagliflozin	Single-center prospective cohort study	NA HbA1c = Not assessed	Not significant Dropped by -3.03 in empagliflozin arm, and by -5.46 in control arm; $p = 0.51$	NA Not directly studied	Not significant Patients with hypoglycemia: 19.1% in empagliflozin arm vs. 16% in control arm; $p = 0.68$	None Higher ketone level in empagliflozin (0.17 ± 0.247 mmol/L) vs. (0.13 ± 0.082 mmol/L) in controls; $p = 0.304$	Not studied.	Non-ST-elevation MI in one subject from empagliflozin arm, discharged well
Pathan et al (2022)[17]	• 493 patients • Aged > 18 years • Mean age: 49.0 ± 11.8	Empagliflozin	Multicenter, open-label, two-arm parallel-group study, comparative observational study	Significant HbA1c dropped from 8.4 ± 1.45 before Ramadan to 7.9 ± 1.2 after Ramadan, $p \leq$ 0.001 in SGLT2i group. Drop of 0.49 in SGLT2i group compared to 0.1 in control	Not significant No change in renal function in both groups was observed, p-value of 0.550	Not significant Symptomatic volume depletion in 7 patients (2.6%) vs. 4 (1.8%); p-value: 0.55 in SGLT2i vs. control group	Not significant Patients with hypoglycemia: 2 (0.7%) vs. 1 (0.4%); $p = 0.26$ in SGLT2i vs. control group	Not studied.	Not studied.	No hospitalization occurred in either of the groups
Samkari et al (2023)[19]	• 220 patients (89 on empagliflozin, and 131 control) • Aged 18–70 • Mean age: 56 (51–62) in empagliflozin arm, 55 (47–64) in control arm	Empagliflozin	Single-center prospective cohort study	NA HbA1c = Not assessed	Not significant After fasting was higher in empagliflozin arm (101), and 95 in control arm; $p = 0.85$	Not significant Symptomatic volume depletion in 19% vs. 29% in empagliflozin vs. control group; p-value: 0.18. Only one patient in the control group had confirmed hypotension	Significant (for breaking the fast only) Four patients with confirmed hypoglycemia in empagliflozin arm vs. six in control arm; $p = 0.89$. None of empagliflozin broke their fast, while 7	Did not occur.	Not studied.	One subject from the empagliflozin arm (cause of admission is not mentioned)

Table 3 (*Continued*)

Authors (year) [Ref]	Population/Risk stratification	SGLT2i used	Study design	HbA1c changes	eGFR changes	Fluid homeostasis	Hypoglycemia	DKA	Thrombosis	Hospitalization
	• Low/moderate/severe risk						in the control arm did so, $p = 0.01$			
Ruqaib et.al (2023)[20]	• 99 patients (all of them were on empagliflozin) • Aged 18–79 • Mean age: 50 years for men, 49 years for women	Empagliflozin	Single-center retrospective cohort study	NA / HbA1c = Not assessed	NA / Not assessed	NA / Not assessed	NA / • 21 patients had hypoglycemia during Ramadan • 31 patients broke fast 1–5 times/month • 2 patients broke fast $\geq$ 6 times/month	Did not occur.	Not studied.	Not studied.
Yousuf and Ahmedani (2022)[21]	• 116 patients (58 on empagliflozin + metformin, 58 on SU + metformin) • Aged 18–65 • Mean age: 51.27 ± 9.94 years	Empagliflozin	Single-center case–control observational study	Significant (for SGLT2i group) / HbA1c dropped by 0.5 ± 0.84 after Ramadan, $p \leq 0.0001$ in SGLT2i group. Dropped by 0.26 ± 1.4 SU group, $p = 0.166$	Significant (for SGLT2i group) / eGFR dropped by 4.83 ± 16.62 after Ramadan, $p \leq 0.031$ in SGLT2i group. Dropped by 5.97 ± 24.74 SU group. $p = 0.07$	NA / • Symptomatic volume depletion in 1 (1.7%) vs. 3 (5.17%) in empagliflozin vs. SU -1 patient had postural dizziness and 1 had hypotension in empagliflozin group- zero in SU group	NA / - 5 patients (8.6%) had hypoglycemia during Ramadan in SU group - 1 patient (1.7%) had hypoglycemia in empagliflozin group - 2 patients broke fast $\geq$ 6 times/month	Not studied	Not studied	Not studied

Abbreviations: DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; MI, myocardial infarction; NA, not available; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylureas.

Several studies on the safety of SGLT2i have been published since 2016 (►Table 1).[10–21] Most of the studies had a similar theme of assessing the risk of fasting in people with diabetes (hypoglycemia, dehydration, deterioration in kidney function, DKA, thrombotic events, and hospitalization during the study period).

The first study that assessed the safety of SGLT2i during Ramadan was from Malaysia.[11] Wan Seman et al evaluated the safety of switching SU to SGLT2i in patients with low-risk T2DM. They recruited 110 patients and randomized into SU and dapagliflozin. The study showed a nonsignificant drop in hemoglobin A1c (HbA1c) of 0.05 and 0.32% from baseline in dapagliflozin and SU, respectively. The percentage of patients who developed hypoglycemia was lower in the dapagliflozin group (9.6%) compared to the SU group (28.8%), $p = 0.002$. Dehydration was reported numerically higher in the dapagliflozin group (13.8%) compared to the SU group (3.8%), p 0.21. The kidney function was not a predefined outcome of this study, nor was the DKA, thrombotic events, and hospitalization during the study period. Another international multicenter study evaluated the tolerability of canagliflozin use during Ramadan and recruited 379 patients with low to moderate risk of fasting.[10] In this study, there was a drop in HbA1c in the canagliflozin group compared to SU (0.4 and 0.2%, respectively) and a drop of eGFR in the canagliflozin group compared to SU (−1.2 and +3.1, respectively), neither of those outcomes were tested for statistical significance. The percentage of hypoglycemia was lower in the canagliflozin group compared to the SU group (3.7 and 13.2%, respectively), $p = 0.009$. Hypovolemia was also reported numerically higher in the canagliflozin group, 16.1% versus 5% in the SU group, but it did not reach a statistical significance with a p-value of 0.11.[10] The study did not report any serious adverse events for either group.

A real-world evidence study by Bashier et al[12] evaluated 417 patients on SGLT2i at a background of SU (46%, $n = 192$) and insulin (48.8%, $n = 191$). The HbA1c improved from a mean of $8.3 \pm 1.7\%$ before Ramadan to $7.8 \pm 1.3\%$ after Ramadan; $p = 0.001$. Twenty-seven percent of patients had symptomatic hypoglycemia ($n = 113$), while only 18.7% had a confirmed blood glucose < 70 mg/dL ($n = 78$). Patients on SGLT2i and insulin had higher hypoglycemic episodes than those on SGLT2i plus SU (52 and 26 patients, respectively), p 0.0005. Moreover, patients on multiple daily insulin regimens had higher hypoglycemic episodes than patients on basal insulin alone (36 and 16 patients, respectively), p 0.02. This study reported no significant change in the eGFR, no reported DKA admissions, and no thrombotic events.

Another study from Singapore recruited 68 patients and grouped them into SGLT2i versus SU; all patients had a low to moderate risk of fasting.[13] The unique addition to this study is that Shao et al measured the serum ketones after 8 to 10 hours of fasting after 2 weeks of Ramadan had passed. Serum ketone of > 6 mmol/L is considered significant. During Ramadan, only one patient from the SGLT2i group had serum ketone > 6 mmol/L. However, he was asymptomatic and continued his fasting without clinical

compromise. There was no significant change in the systolic or diastolic blood pressure or the eGFR between the groups. This study reported no DKA admissions; two patients were admitted with nondiabetes illnesses (gouty arthritis and stroke). From a different perspective, a study was conducted using the flash glucose monitoring system in patients at high risk of fasting.[14] The study population was categorized as high risk for fasting as they were having T2DM treated with insulin or were with T2DM and a stable CVD or with chronic kidney disease stage 3. This study tests the concept of optimum care, including flash glucose monitoring, Ramadan-focused patient education, and treatment dose adjustment after fasting. Abdelgadir et al recruited 95 patients treated with insulin. Patients were further divided into the SGT2i group and another group on any hypoglycemic agent other than SGLT2i.[14] The hypoglycemic episodes during Ramadan were numerically less in the SGLT2i group compared to the control group, 3.9 ± 5.1 versus 3.3 ± 3.8, p 0.97. There was no difference in the severity or timing of hypoglycemia between groups. There was no significant change in the serum creatinine ($0.8 + 0.2$–$0.7 + 0.2$, respectively), p 0.85. Similarly, there was no significant change in the eGFR between groups. In this study, no DKA admissions or no thrombotic events were reported. All previously mentioned studies are summarized in ►Table 1. Furthermore, two recent studies from Pakistan have again investigated the efficacy of SGLT 2i in type 2 diabetic patients while fasting during Ramadan.[15,16] Das and colleagues recruited 82 patients, 63% were on empagliflozin and 37% were on dapagliflozin. The study showed a nonsignificant drop in HbA1c from $7.9 \pm$ to $7.7 \pm 1.2\%$ before and after Ramadan, with no significant increase in hypoglycemia (7.3%) and dehydration (4.8%). However, there was a significant decrease between the pre-Ramadan eGFR and post-Ramadan eGFR with a p-value of < 0.001. The study did not report any hospitalization due to hypoglycemia, DKA, dehydration, or thromboembolism.[15] In another multicentric observational study, Ahmed et al studied the efficacy and safety of empagliflozin against DPPv4 in 132 patients during fasting during Ramadan. The study reported a nonsignificant decline in HbA1c in the SGLT2i group compared to the control group before and after Ramadan, with a p-value of 0.038 versus 0.019, respectively. There was no difference in hypoglycemic episodes in both groups, at 15.9%, p 1.0. Additionally, no statistically significant difference was seen in the rate of dehydration in the DPPv4 group and the SGLT2i group.[16] Interestingly, in this study, the SGLT2i group did not have any incidences of urinary tract infections compared to the DPP IV group (6.8%), $p = 0.07$.

A real-world open-label two-arm-parallel study by Pathan et al[17] evaluated 493 patients who were divided into the SGLT2i group (empagliflozin arm) and non-SGLT2i group (other oral hypoglycemics). The study revealed a statistically significant decrease in HbA1c in the SGLT2i group, a decrease of 0.49 compared to 0.1 only in the control group, p-value < 0.001. There was no significant increase in hypoglycemic episodes and dehydration in either group, with values of 0.26

and 0.55, respectively. In this study, no significant event of DKA, severe dehydration, severe hypoglycemia, and thromboembolism happened, which would warrant hospitalization. Three more studies have assessed the safety of empagliflozin during fasting with more or less similar results to the preceding data.[18–20]

A recent study from Pakistan by Yousuf and Ahmedani showed a significant HbA1c, body mass index, and eGFR reduction after Ramadan in people on empagliflozin + metformin compared to SU + metformin.[21] Interestingly, people on empagliflozin without metformin did not drop their eGFR after fasting Ramada; the authors theoretically attributed that to the gastrointestinal jeopardy of metformin use, which might have added to the hypovolemia and reduction of the eGFR.[21] Once again, hypovolemia was more evident in the empagliflozin group.

Some gaps in knowledge identified from this study include (1) the need for more research on the safety of SGLT2i in older people with diabetes during Ramadan and (2) the lack of long-term follow-up of the decline in eGFR and the time to revert it to the pre-Ramadan baseline.

Conclusion

The available evidence shows that SGLT2i in people with diabetes during Ramadan fasting seem safe and well tolerated. Hypovolemia and a drop in eGFR were reported in a few studies, with no reported clinical significance. Given the remarkable indispensable cardiorenal protective privileges of the SGLT2is and the Ramadan safety evidence so far, authors suggest that SGLT2i should be initiated at any time when indicated, including peri-Ramadan and even within Ramadan following an optimum education.

Authors' Contributions
All named authors contributed to the study's conception and conduct and to the manuscript's drafting and finalization. They have all reviewed and approved its final version.

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Conflict of Interest
None declared.

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