

Sodium–glucose cotransporter-2 inhibitors (SGLT2) during Ramadan fasting: A narrative review of metabolic, cardiovascular and renal benefits and clinical safety

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Abstract

Background: Sodium–glucose cotransporter-2 inhibitors (SGLT2) are increasingly prescribed for type 2 diabetes mellitus (T2DM) due to their glucose-lowering effects and demonstrated cardiovascular, heart failure, and renal benefits. The insulin-independent mechanism of SGLT2 inhibitors, along with their low intrinsic risk of hypoglycaemia, makes them particularly suitable for use during Ramadan fasting. Nevertheless, the risks of osmotic diuresis, volume depletion, and the potential for euglycemic diabetic ketoacidosis (euDKA) present specific challenges during extended periods of fasting without fluid intake.

Objective: To critically evaluate the efficacy and safety of SGLT2 inhibitors in adults with T2DM fasting during Ramadan, with particular emphasis on hypoglycaemia, dehydration, renal function, and ketosis.

Methods: A narrative review and critical appraisal were conducted of Ramadan-specific randomized, prospective, and real-world studies evaluating dapagliflozin, canagliflozin, and empagliflozin, with consideration given to study design, patient selection, clinical outcomes, and methodological limitations.

Results: Current evidence supports the continuation of established SGLT2 inhibitor therapy in appropriately selected patients. In a randomized trial involving 110 participants, hypoglycemia occurred in 6.9% of those receiving dapagliflozin compared with 28.8% of those receiving sulfonylurea (RR 0.24; 95% CI 0.09–0.68; P=0.002). The CRATOS study also demonstrated a lower incidence of symptomatic hypoglycaemia with canagliflozin compared to sulfonylurea (adjusted OR 0.273), although there was an increased risk of volume-depletion events (adjusted OR 3.5). Prospective studies of empagliflozin generally showed stable renal function and no significant increase in confirmed hypoglycaemia or ketonemia. However, most studies were observational, included relatively low-risk populations, and lacked sufficient power to detect rare events such as euglycemic diabetic ketoacidosis (euDKA).

Conclusion: SGLT2 inhibitors represent a reasonable treatment option during Ramadan for clinically stable and appropriately selected adults with type 2 diabetes mellitus (T2DM), primarily due to their low intrinsic risk of hypoglycaemia. However, current evidence regarding the safety of these agents in relation to dehydration and euglycemic diabetic ketoacidosis (euDKA) is less robust. Comprehensive pre-Ramadan risk assessment, sufficient hydration during non-fasting hours, medication review, glucose monitoring, ketone awareness, and adherence to sick-day management protocols remain essential. Further large-scale randomized studies involving high-risk populations are necessary.

Keywords: Ramadan fasting; SGLT2 inhibitors; type 2 diabetes; hypoglycaemia; dehydration; euglycemic diabetic ketoacidosis..

Introduction

Fasting during Ramadan is an important event for patients with diabetes. With fasting, people do not eat or drink anything from dawn till sunset. This can be difficult, especially during hot summer months or if patients with diabetes live in a place where the days are super long [1]. To make things more manageable, people break their fast with a meal called Iftar at sunset, and they eat another meal called Suhoor before dawn to give them energy for the day ahead [1]. It's a challenging time, but with the right plan, people with diabetes can still observe Ramadan safely [1]. Ramadan is different from other types of fasting because people cannot drink fluids during fasting hours [2]. It also often involves changes in diet, sleep schedule, and physical activity [2]. Even medication schedule might need to be adjusted [2]. This is not like regular fasting, where you might just skip meals. During Ramadan, you must be careful about everything, including when you drink water [3]. These changes can expose people with diabetes to several potential complications, particularly hypoglycaemia, hyperglycaemia, dehydration, acute kidney injury and, in susceptible individuals, diabetic ketoacidosis [3]. When it comes to managing diabetes during Ramadan, the properties of Sodium Glu-

cose Cotransporter 2 inhibitors (SGLT2is) are important to consider [4]. These medications have some great benefits, they don't often cause low blood sugar, and they can help protect heart and kidneys [4]. However, they can also cause release of more glucose in urine and increase urine production, which can be a problem with fasting [4]. So, there is a bit of a trade-off between the good things these drugs can do and the potential risks that come with fasting. The American Diabetes Association (ADA) has new guidelines for people with diabetes who fast for religious reasons [5]. The American Diabetes association looked at studies of people who took this medicine during Ramadan, a time when Muslims fast from dawn to sunset and they found that the medicine did not affect kidney function, or cause dehydration or ketosis, which are serious side effects [4,5]. So, the ADA recommends that people who take this medicine can keep taking it, without changing the dose after counselling their health care providers.

Mechanism of SGLT2 Inhibition (Figure 1)

SGLT2 is located predominantly in the proximal renal tubule and normally reabsorbs most filtered glucose [6]. SGLT2 inhibitors reduce re-

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nal glucose reabsorption, producing urinary glucose excretion which will lower plasma glucose [6].

This mechanism is largely independent of insulin secretion (6). Several consequences are clinically relevant during Ramadan: Glycosuria leads to reduced glucose with low intrinsic hypoglycaemia risk but simultaneously increase osmotic diuresis and urinary fluid loss which

lead to potential volume depletion and under conditions of substantial insulin deficiency glucagon will be increased which leads to lipolysis and ketogenesis which increase the potential of euDKA [6]. So, the same reasons that make SGLT2 inhibitors a good choice for people fasting during Ramadan also mean that doctors need to be careful about which patients they prescribe them to.

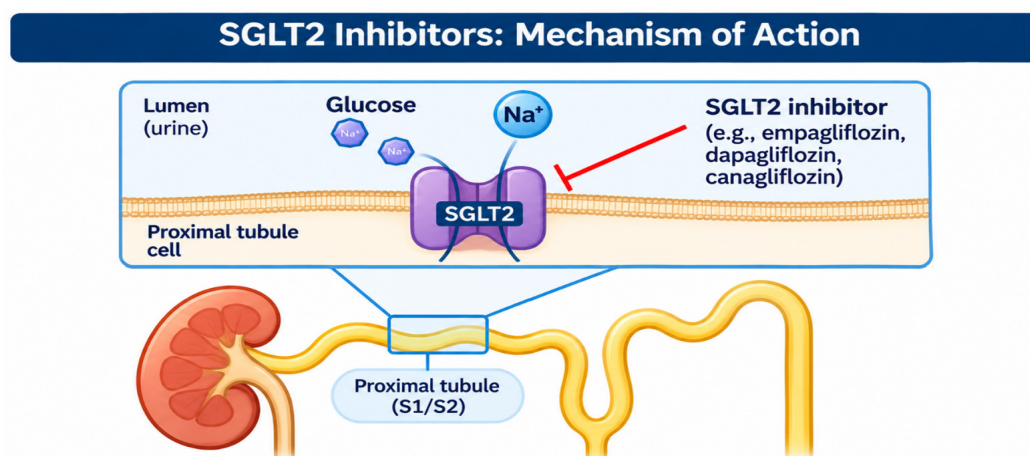


Figure 1: Mechanism of SGLT2 Inhibition.

Why SGLT2 Inhibitors Are Attractive During Ramadan?

Low risk of hypoglycaemia:

One of the major advantages of SGLT2 inhibitors is that glucose lowering is not dependent upon stimulating insulin secretion [6]. So, when used by itself or with other medicines like metformin or DPP-4 inhibitors, the risk of hypoglycaemia is small. This in contrasts with sulfonylureas which induce insulin secretion despite fasting, this will lead to increase the risk of hypoglycaemia.

The American Diabetes Association (ADA) consequently recommends prioritizing treatments with a low hypoglycaemia risk for people undertaking prolonged religious fasting [5]. Because SGLT2 inhibitors have a low risk of causing hypoglycaemia on their own, it does not mean that people taking them are completely safe from it. What is important is the other medications they are taking along with it. For example, if someone is taking an SGLT2 inhibitor with insulin or other drugs that boost insulin production, their risk of hypoglycaemia can increase significantly.

Evidence from Ramadan Studies

Although evidence is considerably smaller than the major cardiovascular and renal SGLT2 inhibitor trial literature, several Ramadan-specific studies provide clinically useful information (Table 1).

A recent study by Bashier et al. [7] included 417 patients found that about 9.3% of them experienced dehydration symptoms. People who were taking insulin at the same time were more likely to have hypoglycaemia, and those on intensive insulin treatment were at higher risk than those on basal insulin [7]. Luckily, the study showed that kidney function did not get significantly worse during Ramadan, there were no significant changes creatinine levels by the end of the study [7]. Another study in Bangladesh [8] looked at how well two different treatments worked for people with diabetes during Ramadan, it included 274 on empagliflozin along with metformin, with or without DPP-4 inhibitor. The competitor group included 219 people took metformin, with or without the DPP-4 inhibitor [8]. The study checked how well the treatments-controlled blood glucose levels, weight, and blood pressure, and if they caused any problems like hypoglycaemia

or dehydration. This study [8] helps us understand how empagliflozin works in real-life situations, especially during Ramadan. The researchers found that the empagliflozin group demonstrated significantly greater improvements in glycaemic control and body weight. Additionally, blood pressure improved, with investigators reporting an approximately 10/3 mmHg greater reduction compared to the non-empagliflozin group [8]. Interestingly, there was no statistically significant difference in hypoglycaemia or volume depletion between groups [8]. No serious adverse events or hospital admissions related to the reported mild events occurred during the study. However, these findings do not confirm the absence of risk [8].

Samkari et al. [12] studied a group of 1,104 patients and chose 220 to be part of their study, with 89 of them taking empagliflozin. They found that the patients taking empagliflozin had fewer symptoms of hypoglycaemia, but the actual cases of hypoglycaemia were about the same. Patients on empagliflozin did not have worse problems with dehydration or kidney function. Another study from Malaysia [9], researchers investigated how empagliflozin affects people during Ramadan. Researchers were focusing on dehydration, ketonemia, and hypoglycaemia. They found that taking empagliflozin during this time doesn't increase the risk of dehydration, ketosis, or hypoglycaemia [9]. This is important to know, especially for people who fast during Ramadan.

These studies are helpful, but we should not read too much into them. Most of them are based on observations rather than large scale experiments, and the people in the studies are quite different from one another. They are also using different treatments at the same time, which can affect the results. And because serious events like DKA are rare, small studies can't always say for sure if there's a higher risk or not.

Clinical Trials and Ramadan-Specific Evidence for SGLT2 Inhibitors

There is not much research on how SGLT2 inhibitors work during Ramadan, especially compared to what we know about their effects on heart and kidney health. However, some studies have looked at how well dapagliflozin, canagliflozin, and empagliflozin work during this time. These studies show that people taking these medicines do not

have a high risk of getting hypoglycaemia, or low blood sugar, which is a big plus compared to other diabetes treatments like sulfonylureas. But we do need to be careful about volume depletion, which is when the body loses too much fluid, this is an important thing to watch out for when taking these medicines.

Dapagliflozin versus Sulfonylurea: Randomized Ramadan Trial [10]. One of the most informative studies, it was a 12-week randomized, open-label, parallel-group trial comparing dapagliflozin with sulfonylurea treatment in 110 adults with type 2 diabetes who intended to fast during Ramadan. Some people taking metformin and a sulfonylurea were chosen to either switch to dapagliflozin or keep taking the sulfonylurea. There were 58 people who started taking dapagliflozin, and 52 people who kept taking the sulfonylurea. The main result we were looking for was how many people had at least one episode of hypoglycaemia, either reported by them or found in their medical records (Table 1).

So, when people switched from one medication to dapagliflozin, they had about 76% fewer cases of hypoglycaemia. This is an important finding, because hypoglycaemia can be a real problem for some people. This study is important because people with diabetes often worry about their blood glucose levels dropping too low when they fast for a long time. The results make sense to the dapagliflozin works by helping the body get rid of extra glucose through urine, rather than by telling the body to make more insulin. This study had some limitations. For one, it was small and didn't blind the participants to what treatment they were getting. That means people might have been more likely to notice and report symptoms of hypoglycaemia just because they knew what group they were in. Also, the main goal of the study was to see how safe it is to manage diabetes during Ramadan in the short term, not to look at rare but serious problems like diabetic ketoacidosis. This study gives some of the best proof that SGLT2 inhibitors can be a good choice instead of sulfonylureas, especially when trying to reduce low blood glucose during fasting. It is a randomized comparison, which makes the results more reliable. Basically, it shows that SGLT2 inhibitors can help with this specific problem, making them a viable alternative.

Table 1: Comparison of clinical outcomes.

Outcome	Dapagliflozin + metformin (n=58)	Sulfonylurea + metformin (n=52)	P value
Hypoglycaemia	6.9% (4/58)	28.8% (15/52)	0.002
Postural hypotension	13.8%	3.8%	0.210

Table 2: Effect of dapagliflozin on hypoglycaemia.

Measure	Result	Interpretation
Relative risk (RR)	0.24	76% relative risk reduction
95% confidence interval	0.09–0.68	Statistically significant
Absolute risk reduction	21.9	Approximately 22 fewer patients per 100 experienced hypoglycaemia
Number needed to treat (NNT)	5	One fewer patient with hypoglycaemia per five treated during the study period
P value	0.002	Significant difference

Canagliflozin in Ramadan Tolerance Observational Study (CRATOS) [11].

The Canagliflozin in Ramadan Tolerance Observational Study (CRATOS) was a prospective, comparative, non-randomized study conducted across several Middle Eastern centres (Tables 3&4). A total of 162 participants received canagliflozin and 159 received a sulfonylurea. The two treatments were given along with metformin, and in some cases, a DPP-4 inhibitor was also used. The primary outcome was hypoglycaemia during Ramadan. After adjustment using propensity scores, symptomatic hypoglycaemia was significantly less common with canagliflozin than with sulfonylurea: Adjusted OR 0.273 (95% CI 0.104–0.719). When glucose levels were checked, only 2 out of 6 times when patients took canagliflozin had hypoglycaemia, which is below 3.9 mmol/L. On the other hand, 27 out of 37 times when patients took sulfonylurea had confirmed hypoglycaemia. This is a big difference between the two groups ($P < 0.001$). It seems that canagliflozin had fewer cases of hypoglycaemia compared to sulfonylurea. However, an important safety signal emerged. Volume-depletion events occurred more frequently with canagliflozin: Adjusted OR 3.5 (95% CI 1.3–9.2). This finding illustrates the central therapeutic trade-off associated with SGLT2 inhibition during Ramadan: Lower hypoglycaemia risk ↔ potentially greater volume depletion.

The study shows that canagliflozin can be a good alternative to sulfonylureas, but it is crucial to teach patients about staying hydrated and to carefully choose patients who might be at risk of low blood pressure or dehydration. Patients need to be aware of the risks and take steps to stay safe while taking this medication. One big problem with CRATOS is that it was based on observations, not random trial. This means that even though the researchers tried to account for differences between groups, there is still a chance that some other factors could be influencing the results.

Table 3: Comparison of clinical outcomes during Ramadan.

Outcome	Canagliflozin (n=162)	Sulfonylurea (n=159)	Statistical findings
Symptomatic hypoglycaemia	3.7% (6)	13.2% (21)	Adjusted OR 0.273 (95% CI 0.104–0.719); p=0.009
Total hypoglycaemic episodes	6	45	Fewer with canagliflozin
Glucose-confirmed episodes (glucose <3.9 mmol/L)	2/6 measured episodes	27/37 measured episodes	Descriptive comparison
Severe hypoglycaemia	0	0	None reported
Volume depletion	16.1% (26)	5.0% (8)	Adjusted OR 3.5 (95% CI 1.3–9.2); p=0.011

Table 4: Metabolic and renal outcomes.

Outcome	Canagliflozin: mean change	Sulfonylurea: mean change
HbA1c	–0.4	–0.2
Body weight	–2.4 kg	–0.5 kg
Systolic BP	–1.5 mmHg	+1.2 mmHg
Diastolic BP	–2.9 mmHg	+0.5 mmHg
eGFR	–1.2 mL/min/1.73 m ²	+3.1 mL/min/1.73 m ²

Empagliflozin Prospective Saudi Cohort study [12].

This is a prospective cohort study from Saudi Arabia screened 1,104 adults with T2DM, of whom 220 were ultimately included. Eighty-nine received empagliflozin in addition to other oral glucose-lowering therapies. Propensity-score matching was used to improve comparability between treatment groups (Tables 5&6). Empagliflozin was associated with significantly fewer symptoms suggestive of hypoglycaemia: RR 0.48 (95% CI 0.26–0.89; P=0.02). However, objectively confirmed hypoglycaemia was not significantly different: RR 1.09 (95% CI 0.37–3.22; P=0.89). This difference matters for patient care. It means that empagliflozin might cut down on noticeable hypoglycaemic episodes, but the study did not show a clear reduction in hypoglycaemic episodes that were confirmed with blood tests. No significant issues with kidney function or dehydration were found. The study therefore provides reassuring evidence regarding empagliflozin but cannot establish causality as confidently as a randomized controlled trial.

Table 5: Comparison of clinical outcomes during Ramadan.

	Empagliflozin (n=77)	Control (n=77)	RR (95% CI)	P value
Symptomatic hypoglycaemia	15.6% (12)	32.5% (25)	0.48 (0.26–0.89)	0.02
Confirmed hypoglycaemia	4/8 (50%)	6/15 (40%)		0.89
Symptomatic hyperglycaemia	31% (24)	40% (31)	0.75 (0.50–1.16)	0.20
Confirmed hyperglycaemia	10/12 (83%)	11/17 (65%)	1.36 (0.79–2.32)	0.26
Volume-depletion symptoms	19% (15)	29% (22)	0.67 (0.38–1.19)	0.18
Severe dehydration symptoms	10.6% (8/75)	8% (6/75)	1.15 (0.41–3.19)	0.79
Confirmed hypotension	0%	1.2% (1)	Not calculated	
Hospital admission	1% (1)	0%	Not calculated	

Table 6: Renal function and glycaemic parameters after Ramadan.

Parameter	Empagliflozin	Control	P value
Serum creatinine, median (μmol/L)	77.0	72.35	0.78
eGFR, median (mL/min/1.73 m ²)	101.0	95.0	0.85
fasting blood glucose, median (mg/dL)	136.8	122.4	0.17

Malaysian Empagliflozin Study [9].

Another important prospective cohort study specifically examined concerns particularly relevant to SGLT2 inhibitors: volume status, ketonemia and hypoglycaemia (Tables 7&8). The study was conducted in Malaysia involved 98 people who had type 2 diabetes. Some of these people had already been taking empagliflozin for at least three months. The other people in the study were not taking SGLT2 inhibitor, at the time.

The results showed no significant Ramadan-associated differences were observed in:

- Body weight
- Blood pressure
- Serum urea
- Creatinine
- eGFR
- Haemoglobin

Importantly, blood ketone concentrations were: Empagliflozin: 0.17 ± 0.247 mmol/L versus Control: 0.13 ± 0.082 mmol/L with P=0.304. Hypoglycaemia indices were also similar: 19.1% versus 16.0%; P=0.684. This research is important because recently some health care providers worry that a condition called euglycemic diabetic ketoacidosis (euDKA), might happen when people with diabetes use SGLT2 inhibitors while fasting during Ramadan, so they often stop the medicine during this time. It is good to know that there is not a big rise in ketonemia. This study had some limitations. The study was only looked at 98 people, which is a small group. Since euDKA is rare, we can't say

for sure that there is no risk of DKA just from this study. What we can say is that empagliflozin did not seem to raise ketone levels in these particular people but that does not mean it is impossible for SGLT2-related DKA to happen when someone is fasting.

Table 7: Comparison of clinical and laboratory outcomes.

Outcome	Empagliflozin group	Control group (no SGLT2 inhibitor)	P value
Hypoglycaemia indices	19.1%	16.0%	0.684
Blood ketones (mmol/L), mean $\pm$ SD	0.17 $\pm$ 0.247	0.13 $\pm$ 0.082	0.304
Systolic blood pressure	No significant change	No significant change	Not specified
Diastolic blood pressure	No significant change	No significant change	Not specified
Body weight	No significant within-group change reported in abstract	No significant within-group change reported in abstract	Not specified
Serum urea	No significant change	No significant change	Not specified
Serum creatinine	No significant change	No significant change	Not specified
eGFR	No significant within-group change reported in abstract	No significant within-group change reported in abstract	Not specified
Haemoglobin	No significant change	No significant change	Not specified

Table 8: Summary of principal findings.

Parameter	Main finding	Clinical interpretation
Hypoglycaemia	19.1% vs 16.0%; p=0.684	No statistically significant difference
Ketonemia	0.17 vs 0.13 mmol/L; p=0.304	No statistically significant increase in blood ketones

Bangladesh Empagliflozin Real-World Study [13].

This is A large multicentre prospective observational study from Bangladesh evaluated 493 adults with T2DM. Participants received: Empagliflozin + metformin $\pm$ DPP-4 inhibitor (n=274) compared with: Metformin $\pm$ DPP-4 inhibitor (n=219). During follow-up, HbA1c reduction was greater with empagliflozin: -0.49% versus -0.12%; P<0.001. Weight reduction was also greater: -1.4 kg versus -0.09 kg; P<0.001. Importantly, hypoglycaemia remained uncommon: 0.7% versus 0.4%; P=0.267. Volume-depletion events were: 2.6% versus 1.8%; P=0.55. The two groups didn't show any major differences, and the side effects that did happen were minor and didn't need a hospital visit. These findings support the feasibility of continuing established empagliflozin therapy during Ramadan in appropriately selected individuals. This study had a big advantage with its large sample size and the fact that it was carried out in many different centers, which makes the results more applicable to a wider range of people. But, since the patients were not randomly chosen for each treatment group, it is possible that differences between the patients and the researchers' decisions played a role in the outcomes.

Table 9: Comparison of efficacy outcomes.

Outcome	Empagliflozin (n=274)	Control (n=219)	P value
HbA1c reduction	-0.49	-0.10	<0.001
HbA1c before $\rightarrow$ after	8.40% $\rightarrow$ 7.91%	8.10% $\rightarrow$ 8.00%	<0.001
Body weight reduction	-1.40 kg	-0.09 kg	<0.001
BMI reduction	-0.5 kg/m ²	-0.2 kg/m ²	0.197
Systolic BP reduction	-10.1 mmHg	-2.8 mmHg	<0.001
Diastolic BP reduction	-2.8 mmHg	-0.2 mmHg	<0.001
HbA1c <7% before Ramadan	10.58%	25.33%	
HbA1c <7% after Ramadan	25.91%	27.39%	

Table 10: Comparison of safety outcomes.

Safety outcome	Empagliflozin (n=274)	Control (n=219)	P value
Confirmed hypoglycaemia	2 (0.7%)	1 (0.4%)	0.267
Symptomatic volume depletion	7 (2.6%)	4 (1.8%)	0.551

Empagliflozin Comparative Study [14].

Another Ramadan study involving 116 participants compared regimens including empagliflozin with other glucose-lowering therapies. Symptomatic hypoglycaemia was more frequent among patients receiving sulfonylureas, whereas patients taking empagliflozin experienced more genitourinary infections and volume-depletion events. Reported rates with empagliflozin included: Genitourinary infection: 6.9% Volume depletion: 5.17%. Empagliflozin was also associated with reductions in BMI and HbA1c after Ramadan. The results (Table 11) show that the side effects of medications during Ramadan are different for various types of medicines. Sulfonylurea has greater concern about hypoglycaemia whereas SGLT2 inhibitor has greater concern about glycosuria, genitourinary infection and volume depletion.

Table 11: Comparison of efficacy and safety outcomes.

Outcome	Empagliflozin (n=58)	Sulfonylurea (n=58)	Statistical findings
Symptomatic hypoglycaemia	1 (1.7%)	5 (8.6%)	Fewer events with empagliflozin
HbA1c change	-0.50 $\pm$ 0.84	-0.26 $\pm$ 1.40	Within-group p $\leq$ 0.0001 for empagliflozin; p=0.166 for sulfonylurea
BMI	Significant reduction	Not specified	Significant improvement reported with empagliflozin
eGFR change	-4.83 $\pm$ 16.62 mL/min/1.73 m ²	-5.97 $\pm$ 24.74 mL/min/1.73 m ²	Within-group p $\leq$ 0.031 for empagliflozin; p=0.07 for sulfonylurea
Genitourinary infection	4 (6.9%)	Exact rate not available	More frequent with empagliflozin, as described in the abstract

SGLT2 Inhibitors in Insulin-Treated High-Risk Patients [15].

The evidence becomes particularly important in patients receiving insulin because their hypoglycaemia risk is substantially greater than in patients taking metformin and an SGLT2 inhibitor alone. Abdelgadir et al. (15) conducted a prospective interventional study of 95 high-risk, insulin-treated patients with type 2 diabetes who fasted during Ramadan; 49 participants received SGLT2 inhibitors. Flash glucose monitoring showed that estimated HbA1c improved from $7.3 \pm 1.5\%$ to $6.8 \pm 1.1\%$ in the SGLT2 inhibitor group, compared with $8.0 \pm 1.6\%$ to $7.7 \pm 1.5\%$ in the non-user group. Hypoglycaemic episodes occurred mainly between 12:00 and 18:00 during fasting. Serum creatinine levels remained stable in both groups, and fasting was rarely interrupted. Although these findings are promising, the small sample size and nonrandomized design limit the ability to draw causal inferences and reduce generalisability.

The study used a special tool to track their glucose levels, which gave instant readings. Researchers looked closely at hypoglycaemia, blood sugar control, and kidney function (Table 12). They did this because combining fasting, insulin, and a certain type of medication could possibly increase the risks of low blood sugar, dehydration, and kidney damage. This is something they wanted to check on, given the potential effects of mixing these things together. This group of people needs special attention. We cannot assume that the safety seen in patients taking metformin along with an SGLT2 inhibitor will be the same for those on intense insulin treatment. The safety results from one group cannot be directly applied to the other. In real-life medical settings, getting the right insulin dose and keeping a close eye on glucose levels are way more crucial for keeping patients safe between meals than just tweaking the dose of a specific kind of medication, known as an SGLT2 inhibitor.

Table 12: Comparison of clinical outcomes.

Outcome	SGLT2i + insulin (n=49)	Insulin without SGLT2i (n=46)	Main finding
Sensor-estimated HbA1c before Ramadan	$7.3 \pm 1.5\%$	$8.0 \pm 1.6\%$	Lower baseline estimate in SGLT2i group
Sensor-estimated HbA1c during Ramadan	$6.8 \pm 1.1\%$	$7.7 \pm 1.5\%$	Improvement in both groups
Change in sensor-estimated HbA1c%	-0.5	-0.3	Numerically greater improvement with SGLT2i
Hypoglycaemia timing during Ramadan	Predominantly 12:00–18:00	Predominantly 12:00–18:00	Late-afternoon hypoglycaemia was important
Hypoglycaemia before Ramadan	Events occurred during 00:00–06:00 and 12:00–18:00	Events occurred during these periods	Different temporal distribution
Serum creatinine	No significant change	No significant change	No detectable short-term deterioration
Fasting interruption	Minimal	Minimal	Most participants were able to continue fasting
Severe adverse events	Numerical comparative rates not available in the abstract	Numerical comparative rates not available	Cannot quantify between-group risk
Systolic blood pressure	Exact change not available in the abstract	Exact change not available	No reliable comparative estimate
Body weight	Exact change not available in the abstract	Exact change not available	No reliable comparative estimate

Summary of Key Ramadan SGLT2 Studies

Overall Interpretation of the Trials The available Ramadan evidence demonstrates a remarkably consistent pattern. Hypoglycaemia SGLT2 inhibitors generally produce less hypoglycaemia than sulfonylureas, with the strongest evidence (10) coming from the randomized dapagliflozin study: 6.9% vs 28.8%. A study called CRATOS had a similar result with canagliflozin, but it was done in a different way, using observations rather than a controlled experiment. Dehydration and volume depletion The evidence is more nuanced. Many studies on empagliflozin didn't show a big enough difference to matter when it comes to dehydration. CRATOS trial [11] found that canagliflozin had a higher risk of people losing too much fluid. Consequently, absence of a large dehydration signal across the literature should not be interpreted as absence of physiological risk. Renal function Research on Ramadan's impact on kidney function is consistent - it seems that creatinine and eGFR levels stay relatively stable in people who are carefully chosen for these studies. But there can be some temporary dips in kidney function, especially in people who are more likely to get dehydrated. Ketosis and euDKA. A study in Malaysia [9] looked at how a medication called empagliflozin affects the body. It found

that this medicine didn't cause a big rise in blood ketone levels. The studies on Ramadan and euDKA have a major flaw they're not large enough to catch rare problems. This is a big gap in what we know. **Critical Appraisal of the Ramadan Evidence** The most important weakness of the literature is the scarcity of large randomized controlled trials. The dapagliflozin study provides randomized evidence but included only 110 participants. CRATOS [11] included more than 300 participants but was non-randomized. The larger Bangladesh study [13] included nearly 500 participants but was observational.

Studies bias and limitations:

Selection bias: Clinicians are more likely to permit relatively healthy, stable individuals to fast.

Healthy-faster bias: Patients with severe CKD, recurrent hypoglycaemia, unstable cardiovascular disease or previous DKA may be advised not to fast and therefore become underrepresented in Ramadan studies.

Treatment-selection bias: Physicians may preferentially prescribe SGLT2 inhibitors to patients considered able to tolerate them.

Outcome ascertainment bias: several studies rely partly on self-reported hypoglycaemia or dehydration.

Limited statistical power: studies involving hundreds rather than tens of thousands of participants cannot adequately evaluate rare outcomes such as euDKA. Second, limited randomization: The dapagliflozin study remains an important exception; most evidence is observational.

Geographical heterogeneity: Ramadan fasting duration, environmental temperature, dietary patterns and overnight hydration differ substantially between countries. The evidence therefore supports the statement that: Established SGLT2 inhibitor therapy appears reasonably safe during Ramadan in appropriately selected, clinically stable people with T2DM, with a lower intrinsic hypoglycaemia risk than sulfonylureas. This doesn't mean that SGLT2 inhibitors are safe for all people with diabetes who want to fast.

Conclusion from the Clinical Trials

When we look at all the studies on Ramadan and diabetes treatment, the results are promising but not conclusive. For example, two medicines, dapagliflozin and canagliflozin, have been shown to cause fewer episodes of low blood sugar compared to sulfonylureas. Meanwhile, studies on empagliflozin have found that it helps keep kidney function stable, prevent hypoglycaemia, and does not seem to increase the risk of ketonemia. One of the biggest safety concerns is when the body dehydration, especially in patients who are more prone to this issue. However, it is also important to note that a rare but serious condition called euDKA can not be completely ruled out based on the current trials, mainly because they did not involve enough people to accurately assess the risk of such a rare event. When it comes to patients who are already taking SGLT2 inhibitors, the evidence suggests that it's better to keep taking them rather than stopping them before Ramadan. But this is only for patients who have been carefully selected. Before Ramadan starts, these patients should have a check-up, drink enough water at night, monitor their glucose levels, be aware of ketones, and get clear instructions on what to do if they get sick or break their fast.

Dehydration and Volume Depletion

One of the main worries about using SGLT2 inhibitors during Ramadan is how they might affect the body. SGLT2 inhibitors cause glycosuria which leads to osmotic diuresis induces natriuresis with a consequence of reduction in circulating volume. During ordinary circumstances, patients compensate by drinking fluids. During Ramadan: osmotic diuresis plus inability to drink during daylight hours plus heat with or without physical activity could theoretically increase dehydration. So, it looks like there has been some concern about how SGLT2 inhibitors might affect people who are fasting during Ramadan.

But, when we look at the actual evidence from clinical studies, it is not as bad as we might think. In fact, a review by the ADA in 2026 found that these studies did not show a big increase in dehydration [16]. That is good news for people who are taking these medications and want to fast during Ramadan. Risk is unlikely to be uniform; however, caution is appropriate in patients with:

- Advanced age or frailty
- Women in postmenopausal
- Renal impairment
- Low baseline blood pressure
- Previous orthostatic hypotension
- Concurrent loop or other potent diuretics
- Gastrointestinal fluid loss
- Prolonged outdoor exposure
- Strenuous daytime exercise

Long fasting duration

The IDF-DAR practical guidance [17] similarly highlights caution among older individuals, those with renal impairment and patients receiving loop diuretics.

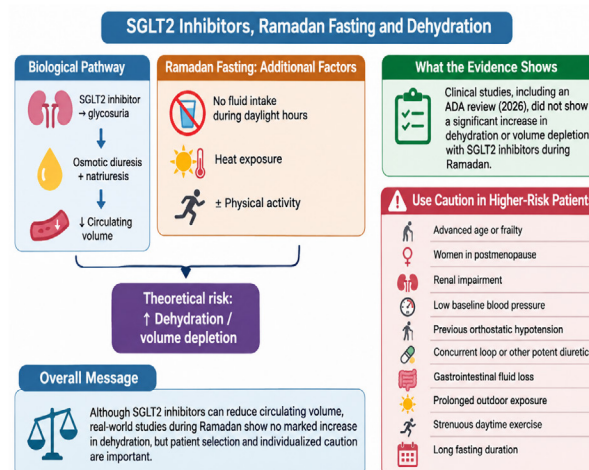


Figure 2: SGLT2is, Ramadan fasting and dehydration.

Euglycemic Diabetic Ketoacidosis (euDKA)

It is a serious side effect of SGLT2 inhibitors that health care providers should know about, especially when patients are fasting.

Traditional DKA involves hyperglycaemia, metabolic acidosis and ketonemia. With SGLT2 inhibitors, substantial glycosuria can prevent marked hyperglycaemia. Consequently, with SGLT2 inhibitor, insulin deficiency plus fasting/stress may produce ketogenesis, metabolic acidosis and normal/modestly elevated glucose. This can delay recognition (Figure 3).

Potential precipitating factors during Ramadan include prolonged fasting, dehydration, acute illness, vomiting, substantial carbohydrate restriction, ketogenic diets and excessive insulin dose reduction.

The important clinical message is that normal or moderately elevated glucose does not exclude DKA in a patient taking an SGLT2 inhibitor. If patient feeling sick with symptoms like nausea, vomiting, or severe abdominal pain, patient should stop fasting right away. Other signs like feeling extremely tired, tachypnoea, or just feeling unwell can also be a problem. When you see these symptoms, it's a good idea to get checked out quickly, which might include measuring ketones if needed.

Traditional DKA vs Euglycaemic DKA (euDKA)		
Feature	Traditional DKA	euDKA (with SGLT2 inhibitors)
Blood glucose	> 250 mg/dL (> 13.9 mmol/L)	< 250 mg/dL (< 13.9 mmol/L)
Ketones	Elevated	Elevated
pH (acidosis)	< 7.30	< 7.30
HCO ₃ ⁻ Bicarbonate (HCO ₃ ⁻)	< 18 mmol/L	< 18 mmol/L
Common triggers	Insulin deficiency, illness, missed insulin	SGLT2 inhibitors, fasting, acute illness, dehydration

Key difference: Both have ketonaemia and metabolic acidosis, but blood glucose is high in traditional DKA and normal or mildly elevated in euDKA.

Figure 3: Traditional DKA vs euDKA.

Renal Function During Ramadan

SGLT2 inhibitors have established long-term kidney-protective effects outside Ramadan. However, fasting introduces the possibility of acute reductions in circulating volume. Ramadan studies have some good news. A study of 417 patients found that fasting during Ramadan did not affect kidney function, as measured by creatinine levels [7]. Another study that looked at empagliflozin found that kidney function, including eGFR, was similar in people who took the medication and those who did not [9]. These findings suggest that patients who are stable and have been properly chosen can keep taking their medication during Ramadan, rather than stopping it just because the holiday is happening. It is important to tell the difference between stable chronic kidney disease (CKD) and acute volume depletion. If a patient is doing well on a certain medicine for CKD, they should not just stop taking it during Ramadan. But if they start vomiting, having diarrhoea, getting a fever, or their blood pressure drops, and they cannot stay hydrated overnight, that is when they need to take special care of themselves on sick days.

Cardiovascular and Renal Protection

The role of SGLT2 inhibitors has evolved far beyond glucose lowering. These treatments are now a crucial part of caring for patients with type 2 diabetes and heart or kidney problems [18-20]. They are also used for heart failure and kidney disease, even in people who don't have diabetes, depending on the specific treatment and what it's being used for [18-20]. It's not necessary to stop taking SGLT2 inhibitors for a whole month just because a patient is fasting. Instead, the question should be: Can the person keep taking their heart and kidney medicine while they're fasting? Yes, many stable patients can do well, if they get the right education and are closely watched. When it comes to Ramadan, studies mainly look at how safe it is fasting for short periods and how it affects metabolism. But these studies do not necessarily show that fasting during Ramadan protects against heart or kidney problems. Any benefits in these areas are usually based on larger, long-term studies of SGLT2 outcomes that were done outside of Ramadan.

When Should SGLT2 Inhibitors Be Started?

Initiating an SGLT2 inhibitor immediately before Ramadan is generally undesirable. The new rules from ADA 2026 say that when people fast, they do not need to change their usual dose of medicine. But they do warn against starting SGLT2 inhibitor, right before fasting starts [16]. This is because it can cause bad side effects like bad thirst [16]. When people plan to fast, especially during Ramadan, it is a good idea for them to start SGLT2 inhibitor for at least a month beforehand [20]. This allows health care providers to see how their body reacts to the medicine and if they have any bad reactions before they start fasting for a long time [20].

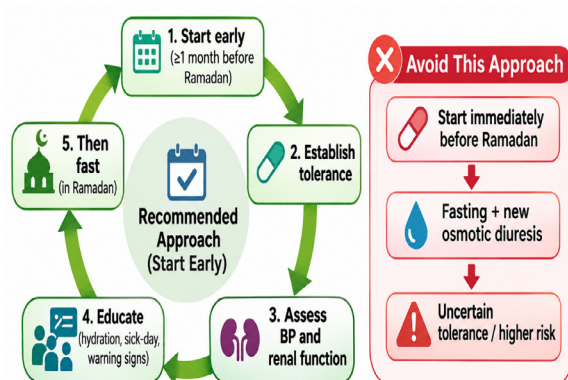


Figure 4: When to start SGLT2is.

Timing and Dose During Ramadan

Routine SGLT2 inhibitor dose reduction is generally unnecessary. The ADA 2026 recommendations [16] indicate: Once-daily SGLT2 inhibitor to be taken with the main meal with, no routine reduction in total daily dose. In practical Ramadan care, administration around Iftar is often convenient because the patient can subsequently consume fluids throughout the non-fasting period. It is crucial to tailor treatment to each person's overall plan, for example:

Metformin + SGLT2 inhibitor usually represents a relatively low-hypoglycaemia-risk combination.

By contrast: SGLT2 inhibitor + sulfonylurea requires consideration of the sulfonylurea dose.

And: SGLT2 inhibitor + insulin requires individualized insulin adjustment and more intensive glucose monitoring. The insulin component not usually the SGLT2 inhibitor itself is frequently the major determinant of fasting hypoglycaemia.

Hydration Strategy

Hydration counselling is fundamental. Patients should consume adequate fluids between Iftar and Suhoor, distributed across the evening rather than consumed as a single large volume [21]. The American Diabetes Association [16] stresses that people with diabetes should get personalized advice on what to drink and eat, and make sure to drink enough fluids every day, even when they are fasting for religious reasons. Patients should also avoid excessive consumption of sugar sweetened beverages at Iftar, because they can produce rapid postprandial hyperglycaemia.

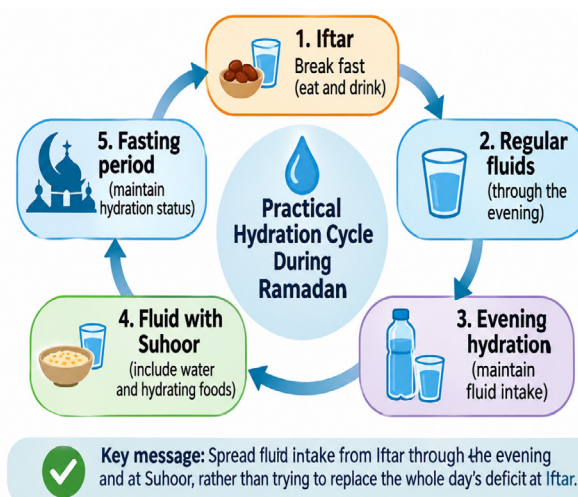


Figure 5: Hydration strategy during Ramadan.

Glucose and Ketone Monitoring

Blood glucose monitoring does not physiologically invalidate fasting, and patients should be encouraged to monitor appropriately.

Monitoring is particularly important:

- Early during Ramadan
- Late afternoon when glucose may be lowest
- Whenever symptoms occur
- After medication changes
- In insulin-treated patients
- Following unusual physical activity

CGM can be particularly useful because Ramadan frequently produces a characteristic glucose pattern: falling glucose during daytime fasting → rapid rise following Iftar → variable overnight glucose → another rise around Suhoor.

When people are taking SGLT2 inhibitors, it is crucial to check for ketones, especially if they are not feeling well or have symptoms that could be related to diabetic ketoacidosis (DKA). This is because just

looking at blood glucose levels might not give the full picture and could even be misleading.

When Should the Fast Be Broken?

Patient education must clearly state that continuing a fast despite dangerous metabolic deterioration is medically inappropriate.

The fast should be interrupted when

Significant hypoglycaemia

Severe hyperglycaemia

Dehydration

Acute illness occurs.

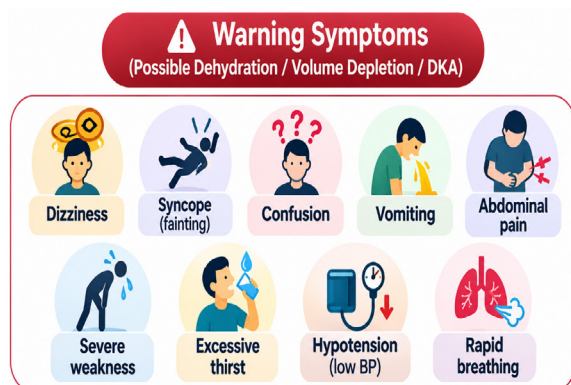


Figure 6: Warning symptoms.

Sick-Day Rules

Sick-day education should form part of every pre-Ramadan consultation (16) (21). An SGLT2 inhibitor should generally be temporarily withheld during circumstances associated with significant dehydration or ketogenesis, such as acute serious illness, persistent vomiting, diarrhoea or inability to maintain fluid intake significant dehydration when undergone major surgery/prolonged fasting suspected keto-acidosis. Just because the patient's glucose level looks okay, it does not mean they can start fasting again right away. Recovery of normal oral intake and hydration should precede reintroduction according to individualized clinical guidance.

Patient Selection

Generally suitable patient is the patient who is stable T2DM + preserved hydration + stable renal function + low hypoglycaemia-risk regimen + previous SGLT2 tolerance may often continue the medication safely. Greater caution is appropriate with: older/frail patient with CKD or impaired renal reserve, low BP/orthostatic symptoms or on loop diuretic treatment or insulin therapy, previous dehydration, very long fasting duration, on hot-climate outdoor work Temporary discontinuation or avoidance of fasting should be considered in situations such as: acute illness vomiting/diarrhoea significant dehydration suspected ketosis/DKA major acute renal deterioration require reassessment rather than routine continuation.

A Practical Ramadan SGLT2 Care Pathway

Diabetes care during Ramadan should be structured following multiple steps (figure 7)

ASSESS: determine Ramadan fasting risk, comorbidities, renal function, blood pressure, medications and previous fasting experience.

OPTIMISE: stabilize the treatment regimen several weeks before Ramadan rather than making major last-minute changes.

EDUCATE: discuss hydration, nutrition, glucose monitoring, DKA symptoms and sick-day rules. **FAST:** continue SGLT2 inhibition in appropriately selected and stable patients.

MONITOR: glucose, symptoms, hydration status and ketones when clinically indicated.

RESPOND: break the fast and temporarily withhold treatment when

significant illness, dehydration or suspected ketosis develops. **REVIEW:** reassess glycaemic control, BP, weight, renal function and treatment after Ramadan.



Figure 7: Diabetes care cycle during Ramadan.

Conclusion

SGLT2 inhibitors have become central to contemporary diabetes, cardiovascular and renal management. Their insulin-independent mechanism and low intrinsic hypoglycaemia risk make them particularly attractive for people with T2DM who wish to fast during Ramadan. Ramadan is a special time for many people, and there has been some research on how it affects people with diabetes who take certain medicines, like empagliflozin. Luckily, the studies so far have been reassuring, they have not found any major problems with kidney function or serious side effects like dehydration or hypoglycaemia in people who are taking these medicines while fasting.

The American Diabetes Association, in their 2026 care standards [16], even says that people do not usually need to reduce their dose of medicine during Ramadan. This is good news for people who want to fast during this important time. When taking SGLT2 inhibitors during Ramadan, there are still some risks to consider. For people who are prone to dehydration, the medication can cause a significant loss of fluids, which can be a problem. There's also a small but serious risk of a condition called euDKA, especially when someone is very ill, not taking enough insulin, eating very little carbohydrate, or getting dehydrated. Some people need to be extra careful, like older adults, those with kidney problems, people taking certain diuretics or insulin, and individuals who fast for a long time or are in hot environments. Optimal management should therefore begin several weeks before Ramadan [21] and combine risk stratification, medication review, hydration and nutritional counselling, glucose monitoring, ketone awareness, sick-day rules and explicit criteria for breaking the fast. Rather than routinely discontinuing SGLT2 inhibitors, individualized management allows many suitable patients to preserve their important metabolic, cardiovascular and renal benefits while using SGLT2is.

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