

## VIEW POINT

## Use of Sodium-Glucose Co-Transporter 2 Inhibitors during the Fasting of Ramadan: Is There Cause for Concern?

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### Abstract

**Background:** There is some anxiety among physicians about the safety of using sodium-glucose co-transporter 2 (SGLT2) inhibitors in Muslim type 2 diabetes mellitus (T2DM) patients who wish to observe the fast during Ramadan particularly during the summer in hot regions. There is a dearth of research data to help guide physicians and reassure patients.

**Objectives:** To try and extrapolate to the “Ramadan” scenario, we reviewed the pharmacology of SGLT2 inhibitors and those side effects that may be relevant to Ramadan fasting such as osmotic diuresis, dehydration, use in the elderly and concomitant use with diuretics as well as the potential risk of ketoacidosis. We also reviewed the perceptions among physicians along with the currently available expert opinions and recommendations. **Approach:** The following aspects are addressed 1. Characteristics and pharmacology of SGLT2 inhibition 2. Side effects having a potential relevance to Ramadan fasting 3. Studies of patient

outcomes and physician perceptions and 4. Expert opinions and management recommendations.

**Emerging concepts:** 1. SGLT2 inhibitors are a new glucose-lowering therapy for T2DM with documented benefits on blood glucose, hypertension, weight reduction and long term cardiovascular benefit. They have an inherent osmotic diuretic effect and lead to some volume loss and possible dehydration. 2. One study confirmed better glycemic control with less risk of hypoglycemia and no marked volume depletion when compared with sulphonylureas. The experiences with their use in the elderly and in combination with diuretics are reassuring for the safety of their use in Ramadan. 3. SGLT2 inhibitor-related diabetic ketoacidosis has not been reported during Ramadan fasting to date. 4. A survey of physicians’ opinions revealed that the majority felt that SGLT2 inhibitors are generally safe in T2DM patients during Ramadan fasting but should be discontinued in certain high risk patients. Most respondents also indicated that they would advise taking the SGLT2

inhibitors with the sunset meal (*Iftar*) and recommend consuming extra clear fluids in the evening. 5. So far, only a few professional groups with interest in Ramadan fasting updated their guidelines and recommendations on management of diabetes to include the SGLT2 inhibitors. These opinions acknowledged the lack of trial data, recommended caution in high risk groups, advised regular monitoring and emphasized pre-Ramadan patients' education and awareness about possible complications.

**Conclusions:** The current knowledge of SGLT2 inhibitors in clinical practice is reviewed with a focus on their use during Ramadan fasting. There are limited data however, extrapolating from their current use, it is likely that stable patients with no high risk of dehydration and with normal kidney functions may safely continue using the SGLT2 inhibitors therapy. It may be prudent that higher risk patients be observed carefully and any decision concerning SGLT2 inhibitors is taken on individual basis. Planned clinical trials, objective observational studies, clinical audits and patients' reports of their own clinical experience should provide ample opportunity to help answer many of the as yet unanswered questions. Results from studies conducted during the current Ramadan period are eagerly awaited.

#### **Key words:**

SGLT2 inhibitor; Type 2 diabetes mellitus Type 1 diabetes; Canagliflozin, Dapagliflozin; Empagliflozin; Non-glycemic benefit of SGLT2 inhibitors; Blood pressure; Elderly; Dehydration, Diuretics, Volume depletion, Ketoacidosis, Ramadan fasting, Ethnicity.

#### **Introduction**

Ramadan, the ninth month of the Islamic calendar, involves fasting for 29-30 days every year. During the fast, Muslims refrain from eating food, drinking, using medications, and smoking from dawn until after sunset with no restrictions on food or fluid intake overnight. People are exempt from observing the fast if they are sick, or if fasting is likely to adversely affect their health (1). Fasting for patients with diabetes has been recognized to increase the risk of day-time hypoglycemia, postprandial hyperglycemia, and metabolic complications, associated with dehydration. Nonetheless, two large epidemiological studies (2,3) confirmed that a high percentage of people with diabetes still choose to fast during Ramadan despite the advice of their doctor, and the permission received from religious authorities (1).

General recommendations for diabetes management during Ramadan have been published by individuals and interest

groups (4-6). These have been based mostly on extensive clinical experience, expert opinion and or clinical trials involving conventional medications such as insulin, metformin and sulphonylureas and also some of the newer medications such as incretin-based therapy (7-9). On the other hand, there are limited data in the literature to guide the use of the newest classes of oral antidiabetic agents such as Sodium-glucose co-transporter 2 (SGLT2) inhibitors during Ramadan fasting.

SGLT2 inhibitors improve glycemic control by increasing the excretion of glucose by the kidney with additional benefits. Special advantages of this class include glucose lowering at all stages of disease, potential for combination therapy with a wide range of oral glucose-lowering drugs and insulin, weight loss, blood pressure lowering and low risk of hypoglycemia. However, the safety and efficacy of SGLT2 inhibitors have not been established in patients with T1DM and thus they have not been approved for use in these patients (10-12). Concerns regarding the use of SGLT2 inhibitors include an increase in urinary tract and genital infections (due to glycosuria), and the potential for volume depletion, electrolyte imbalance, ketoacidosis and increased bone fracture risk (10-14).

#### **The context**

Since the introduction of the SGLT2 inhibitors in 2014, there has been some anxiety among physicians about safety of SGLT2 inhibitors in Muslim patients who wish to observe the fasting of Ramadan. This is particularly so during the summer months and in hot regions. Ramadan in 2016 started on 6<sup>th</sup> June. Several recent diabetes congresses in our region witnessed heated debates between physicians on the issue. The dearth of original research data so far, makes it difficult to guide physicians and patients objectively. Consequently, to extrapolate to "Diabetes in Ramadan" scenario, we have reviewed here the pharmacology of SGLT2 inhibitors, examined side effects that may be particularly relevant to Ramadan fasting such as osmotic diuresis, dehydration; considered analogous situations such as use of SGLT2 inhibitors in the elderly and their concomitant use with diuretics and the potential risk factors for ketoacidosis. We also reviewed the only available study and re-examined perceptions of physicians and reviewed currently available expert opinions and recommendations. The following aspects are addressed: characteristics and side effects of SGLT2 inhibitors, side effects of potential relevance to Ramadan fasting, relevant studies of patients' outcomes and physicians' perceptions and published expert

opinions and clinical practice recommendations.

## SGLT2 Inhibitors in Clinical Practice

### Pharmacology

SGLT2 inhibition is proposed as a novel approach for the management of type 2 diabetes mellitus (T2DM). Several SGLT2 inhibitors are already available in many countries (dapagliflozin, canagliflozin, empagliflozin and ipragliflozin). The available SGLT2 inhibitors share similar pharmacokinetic characteristics, with a rapid oral absorption, a long elimination half-life allowing once-daily administration, an extensive hepatic metabolism mainly via glucuronidation to inactive metabolites, the absence of clinically relevant drug-drug interactions and a low renal elimination as the parent drug. In T2DM patients with upregulated renal glucose reabsorption, SGLT2 inhibitors improve glycemic control to a clinically meaningful extent. HbA1c reductions by 0.5-1.5% are brought about by SGLT2 inhibitors in a dose-dependent fashion without causing hypoglycemia (11-12). SGLT2 inhibitors exert their glucose lowering action when combined with any other oral antidiabetic drug as well as with insulin (11-12). Predictably, responses to SGLT2 inhibitors decline with increasing severity of renal impairment.

### Efficacy

Numerous placebo-controlled randomized clinical trials have shown the class' efficacy. Significant reductions in HbA1c, resulting in a significant increase in the proportion of patients reaching HbA1c targets, and a significant lowering of fasting plasma glucose were documented with SGLT2 inhibitors as monotherapy or in addition to other

glucose-lowering therapies (including insulin) in patients with T2DM (13-14). SGLT2 inhibitors exerted similar glucose-lowering activity to metformin, sulphonylureas or sitagliptin as shown in head-to-head trial up to 2 years. The durability of the glucose-lowering effect of SGLT2 inhibitors appears to be better; however, this remains to be more extensively investigated. Hypoglycemia was similarly low as that reported with metformin, pioglitazone or sitagliptin and was much lower with SGLT2 inhibitors than with sulphonylureas (13-14). Furthermore, the trial using empagliflozin have shown a cardiovascular benefit with a 38% relative risk reduction in heart failure and 32% relative risk reduction in all-cause mortality despite the short duration of the study (15). Increased renal glucose elimination also assists weight loss and could help to reduce blood pressure. Both effects were very consistent across the trials and they represent some advantages for SGLT2 inhibitors when compared with other oral glucose-lowering agents. These are very relevant in patients with diabetes in whom obesity and hypertension are seen frequently.

### Safety

SGLT2 inhibitors are generally well-tolerated. The most frequently reported adverse events are female genital mycotic infections, while urinary tract infections are less commonly observed and generally benign (13-15). Of note however severe urogenital sepsis has been documented by the FDA in 19 patients (17), which is a very small number related to the documented number of users at the same time period (1.7 million users), however due to the severity of the infections, the FDA has added a specific warning

**Table 1.** Widely recognized risks and concerns of Ramadan fasting in people with diabetes in general and the concerns about use of SGLT2 inhibitors (perhaps more serious in high risk groups).

Risks of Ramadan fasting in diabetes	Concerns about SGLT2 inhibitors in general
Hypoglycemia	Increase in urinary tract infections
Hyperglycemia	Increase in genital infections
<i>Diabetic ketoacidosis</i>	<i>Euglycemic ketoacidosis?</i>
<i>Dehydration (due to abstinence from fluid intake)</i>	<i>Potential for volume depletion (due to osmotic diuresis)</i>
Thrombosis	Electrolyte imbalance
Risk to pregnancy	Bone fracture risk?
concerns and risk in the two scenarios are shown in italics.	

**Table 2.** Practical tips on safe use of SGLT2 inhibitors before, during and after Ramadan fasting.

<b>Before Ramadan:</b> ( <i>assess</i> )	<ul style="list-style-type: none"> <li>• that patients were appropriately selected for SGLT2 inhibitors.</li> <li>• Ascertain no contraindications e.g. worsening renal function, use of diuretics occurred; if in doubt reconsider SGLT2 inhibitors.</li> <li>• Avoid in the elderly, those at risk of dehydration, patients on antihypertensive medications (assess each case individually especially if not on a diuretic).</li> <li>• Advice on management during Ramadan.</li> <li>• Refrain from starting SGLT2 inhibitors immediately before Ramadan (4 weeks?).</li> </ul>
<b>During Ramadan:</b> ( <i>monitor</i> )	<ul style="list-style-type: none"> <li>• Take the medication with the first evening meal (<i>Iftar</i>)</li> <li>• Encourage intake of adequate fluids at night (approximately extra 500 ml; minimal 2 Liters in total).</li> <li>• Avoid excess salt and coffee and tea.</li> <li>• Observe hydrations status (simple: volume and color of urine).</li> <li>• Observe blood pressure if home monitoring is readily available.</li> <li>• Report symptoms to clinic/surgery or diabetes educator.</li> <li>• If in doubt stop medications and have an interim diabetic review (walk-in visit).</li> </ul>
<b>After Ramadan:</b> ( <i>review</i> )	<ul style="list-style-type: none"> <li>• Review patient in clinic or surgery with 4-6 weeks after Ramadan.</li> <li>• Appraise the experiences and outcomes.</li> <li>• Review the risk/benefit ratio of the SGLT2 inhibitors class on individual basis.</li> <li>• Review the need or otherwise for SGLT2 inhibitors use and decide on continuation/resumption or discontinuation.</li> <li>• Consider additional/alternative therapies.</li> </ul>
Modified from Beshyah SA. et al. Br J Diabetes 2016;16:20-24	

(17). Caution is recommended in the elderly population because of a higher risk of renal impairment, orthostatic hypotension and dehydration, despite the fact that absence of hypoglycemia may represent an obvious advantage in this particular subgroup of patients (13-14).

### Side effects of SGLT2 inhibitors of potential relevance to Ramadan fasting:

#### *Volume depletion*

Since SGLT2 inhibitors act by excreting glucose, an extra volume of fluid is lost by osmotic diuresis. For example, there is approximately an extra 375 ml of urine/day excreted on dapagliflozin dose of 10 mg/day. Volume depletion-related adverse effects include reduced blood pressure, dehydration, postural dizziness, orthostatic hypotension, orthostatic intolerance, syncope, and reduced urine output (13-15). Volume depletion-related adverse events occurred in 2.3-3.4% of canagliflozin groups versus 1.5% in the comparator groups in one pooled analysis. Risk factors for these events were more in elderly subjects, those with eGFR <60 ml/min/1.73 m<sup>2</sup>, and when used in combination with loop diuretics.

#### *Osmotic diuresis*

Glycosuria caused by SGLT2 inhibitors leads to osmotic diuresis. Reported adverse effects of osmotic diuresis-related include pollakiuria, nocturia, micturition frequency, and thirst related such as increased thirst, dry mouth, polydipsia, dry throat, or dry tongue (13-15). During Ramadan it would obviously be very wise to avoid inducing or further worsening osmotic diuresis by other mechanisms such as hyperglycemia, excessive intake of sugary drinks and perhaps even excessive use of tea and coffee.

#### *Hypoglycemia*

The risk of hypoglycemia with SGLT2 inhibitors when used as monotherapy or in association with metformin or DPP4 inhibitors is similar to that of placebo. However, when used with insulin and sulphonyureas, SGLT2 inhibitors may predictably potentiate the risk of hypoglycemia produced by the concomitant therapy (15). The low risk of hypoglycemia was indeed viewed as the most attractive attribute of SGLT2 inhibitors as candidate drugs for use during Ramadan fasting as hypoglycemia has been highlighted as the most feared complication of diabetes during Ramadan since treatment of hypoglycemia would naturally nullify the fast.

### ***Diabetic ketoacidosis***

Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) issued warning that treatment with SGLT2 inhibitors may increase the risk of DKA. This was based on 20 cases reported; one-third of these cases was in off-label use in T1DM (18,19). Over 100 cases of DKA in patients treated with SGLT2 inhibitors for T2DM had been reported worldwide. Disproportionately high representation of subjects with T1DM subjects, subjects with beta cell autoimmunity and those using insulin among those developing DKA with the use of SGLT2 inhibitors. In most of these cases, a precipitating event was also recognized. Whether DKA is increased during Ramadan in general remains controversial as most of the studies are small and their results are contradicting to each other. The concern of DKA in Ramadan is relevant to T1DM patients in whom the SGLT2 inhibition therapy is not relevant currently.

### ***Use in the elderly***

Review of the use of canagliflozin in elderly patients with T2DM revealed that elderly patients have less HbA1c reduction (20). The benefit on HbA1C is however significant. Systolic blood pressure and body weight reduction in the elderly were consistent with younger patients. Adverse effects such as increased urinary frequency, genital mycotic infections, and urinary tract infections may discourage its use in the elderly patient. In a postmarketing surveillance in Japan, physicians recorded adverse drug reactions in elderly patients ( $\geq 65$  years old) who were first prescribed with ipragliflozin within 3 months of its launch (21). Ipragliflozin was well tolerated and reduced surrogate endpoints in elderly Japanese patients with T2DM. These two reports suggest that safety in elderly patients is consistent with that of other phase 3 trials in the general population and risks and benefits of treatment with SGLT2 inhibitors should be assessed in geriatric patients on a case-by-case basis. Perhaps these agents are not particularly harmful in the elderly patients observing the fast. Establishing safety of SGLT2 inhibitors during Ramadan fast particularly in the elderly is very relevant as elderly Muslim men and women are usually the most keen individuals on observing the fast, diuretics are more likely to be prescribed and thirst sensation is not particularly strong.

### ***Hypercalcemia and hypernatremia***

A 60-year-old man with uncontrolled T2DM treated with insulin, glimepiride, metformin and canagliflozin was admitted with altered mental status after a syncopal episode

(22). Acute kidney injury, DKA, and parathyroid hormone-independent severe hypercalcemia were evident. DKA resolved with insulin treatment, and saline hydration led to improvement in hypercalcemia and renal function over 48h. However, this was accompanied by a rapid increase in the serum sodium concentration despite changing fluids to 0.45% saline. Urine studies were consistent with osmotic diuresis. The authors' suggested that hypercalcemia was due to dehydration from osmotic diuresis, with reduced calcium excretion and possible increased intestinal calcium absorption. Saline therapy and osmotic diuresis could have led to hypernatremia from electrolyte-free water loss (22). The concern is that a similar situation could possibly occur in a dehydrated patient who observing fast. This calls for careful attention to fluid and electrolyte management in patients who may develop similar situations during Ramadan.

### **Safety of SGLT2 inhibitors in Ramadan: Observations and perceptions**

#### ***Dapagliflozin versus glibenclamide in Ramadan***

The authors assessed the hypoglycemia risk and safety of dapagliflozin was assessed and compared with sulphonylurea during the fasting month of Ramadan in a 12-week, randomized, open-label, two-arm parallel group study (23). 110 patients with T2DM who were receiving sulphonylurea and metformin were randomized either to receive 10 mg of dapagliflozin daily or to continue receiving sulphonylurea. The primary outcome was to compare the effects on the proportions of patients with at least one episode of hypoglycemia during Ramadan, as well as to assess the safety of dapagliflozin when used to treat patients observing Ramadan. A lower proportion of patients had reported or documented hypoglycemia in the dapagliflozin group than in the sulphonylurea group ( $p=0.002$ ). The relative risk of any reported or documented hypoglycemia in the 4th week of Ramadan was significantly lower in the dapagliflozin group ( $p=0.002$ ). No significance differences were observed between the two groups regarding postural hypotension ( $p=0.210$ ) or urinary tract infections ( $p=0.277$ ). Therefore in this first ever study, fewer patients exhibited hypoglycemia in the dapagliflozin group than in the sulphonylurea group.

#### ***Physicians' perception of SGLT2 inhibitors***

In advance of Ramadan of 2015, recognizing the lack of research data, a survey of 197 physicians who routinely manage patients with diabetes during Ramadan on the utility of SGLT2 inhibition during this time (24). The majority



felt that SGLT2 inhibitors were generally appropriate and safe during Ramadan fasting but should be discontinued in selected patients. Most respondents would advise taking an SGLT2 inhibitor with the sunset meal (*Iftar*). Taking extra clear fluids in the evening of Ramadan was recommended by the majority of respondents. The dataset was further expanded to include a total of 231 respondents with some more experience with SGLT2 inhibitors; similar conclusions were reached (unpublished data).

### Guidelines and Recommendations

There are three recently published guidelines that include SGLT2 inhibitors. Their recommendations are presented here:

**International Group for Diabetes and Ramadan Recommendations (2015):** Strangely, this group claims ownership of the previous guidelines known as the ADA guidelines despite major change of the membership and affiliation (25). They also started favorably by stating: “By increasing glycosuria, SGLT-2 inhibitors are associated with significant improvements of fasting hyperglycemia and HbA1c concentration, and with low risk of hypoglycemia in patients with T2DM. They also warned on dehydration and infections “These agents, however, are associated with increased risk of urinary tract and genital infections, and with a mild increase in the risk of volume contraction and dehydration”. They went on to state that “The lower rates of hypoglycemia compared with sulfonylurea and insulin treatment make SGLT-2 inhibitors an attractive drug in patients with diabetes during Ramadan”, but cautiously remarked “the associated volume contraction and risk of dehydration represent a concern during prolonged fasting in warm or hot climates, in particular in elderly patients” They too called for more research work such “Randomized controlled studies are needed to determine the safety and efficacy of SGLT-2 inhibitors during Ramadan, especially after the recent Food and Drug Administration (FDA) warning concerning the possible ketoacidosis.”

**First IDF-DAR Guidance (2016):** Here the authors also started favorably as well; “SGLT2 inhibitors have demonstrated effective improvements in glycemic control and weight loss, and are associated with a low risk of hypoglycemia (25). Because of this, it has been proposed that they provide a safe treatment option for patients with T2DM during Ramadan”. However, they too were cautious in their recommendations: “certain safety concerns have been raised, such as an increase in some infections (urinary

tract infections and genital mycotic infections) and a risk of ketoacidosis. An increased risk of dehydration in vulnerable patients has also been described, which may be a particularly pertinent issue during Ramadan”

**The UK Diabetes in Ramadan Guidelines (2016):** The section started positively stating the “The low risk of hypoglycemia and benefits of weight reduction make this new class of glucose lowering agents a potential candidate for use during Ramadan” (26), they proceed to warn from side effects “caution must be taken because this class results in glycosuria, and hence induce osmotic diuresis. Therefore, there is a risk of dehydration, particularly in warm countries. Since these agents can also lower blood pressure, during fasting, there is a risk of postural hypotension”. They state that at the time of publication that “there is no available clinical evidence for their use and safety during Ramadan”. Consequently they conclude: “Therefore, randomized controlled trials for SGLT2 inhibitors in Ramadan are required”. Adding “Certainly, we would recommend that they are used with caution and patients drink at least 2 litres of water a day to reduce the risk of dehydration. In addition, initiating a patient on an SGLT2 inhibitor just prior to Ramadan should be avoided”. Regarding risk of DKA; the group proposed “in the context of Ramadan fasting, it is not recommended that SGLT2 inhibitors are used in those with type 1 diabetes, indeed it is not currently licensed for use in this population. In the current climate, it may be pertinent to test for ketones in patients with T2DM on SGLT2 inhibitors periodically throughout the fasting period.” Although we feel that the last recommendation may not be readily feasible in some resource-short settings. A more pragmatic advice was also included: “furthermore, we would advise, as per FDA recommendations, that patients pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness”.

### Final Remarks

In this perspective, the current state of knowledge on the use of SGLT2 inhibitors in clinical practice with a focus on their use during Ramadan fasting was elaborated. SGLT2 inhibitors may be potential drugs for management of diabetes during Ramadan on basis of their “no risk of hypoglycemia” which is the most feared complication during fasting. A single study has confirmed this. Although, limited data exist regarding their potential for dehydration and/or hypotensive effects; there is an increasing body of

opinion in favor of their potential use in patients who are not at increased risk though properly conducted studies are still needed.

In conclusion, despite the limited research data, extrapolating for other clinical settings (e.g. elderly patients treated with SGLT2 inhibitors), it may be possible that stable patients without a high risk for dehydration or impaired kidney functions may safely continue to use SGLT inhibitors during Ramadan. However, it is prudent that all higher risk patients be carefully observed and any decisions concerning SGLT2 inhibitors are taken on an individual patient basis. Clinical trials specifically targeted to establish their efficacy and safety during Ramadan fasting are needed. However “real world evidence” can be readily generated by well conducted collaborative observational studies, clinical audits along with capturing patients’ reports of own experiences. Results from this Ramadan studies are eagerly awaited. They should help answer many of the as yet unanswered critical questions. For the time being, following the recommended practical tips for safety before, during and after Ramadan is warranted (Table 2).

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