

Safety of Sodium-Glucose Co-Transporter 2 Inhibitors during Ramadan Fasting: Evidence, Perceptions, and Guidelines

Salem A. Beshyah*

Consultant Physician and Endocrinologist, Center for Diabetes and Endocrinology, Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates

ARTICLE INFO	ABSTRACT
<p><i>Article type:</i> Review article</p> <hr/> <p><i>Article History:</i> Received: 22 June 2016 Accepted: 25 June 2016 Published: 30 June 2016</p> <hr/> <p><i>Keywords:</i> Blood pressure Canagliflozin Dapagliflozin Empagliflozin Fasting Non-glycemic benefit of SGLT2 inhibitors Ramadan SGLT2 inhibitor Type 1 diabetes Type 2 diabetes mellitus</p>	<p>Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new glucose-lowering therapy for type 2 diabetes mellitus (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. There is some concern about the safety of using SGLT2 inhibitors in Muslim T2DM patients during the fast during Ramadan. Currently, there is a dearth of research data to help guide physicians and reassure patients. One study confirmed good glycemic control with less risk of hypoglycemia and no marked volume depletion. Data in the elderly and in combination with diuretics are reassuring of their safe to use in Ramadan in general. SGLT2 inhibitor-related diabetic ketoacidosis has not been reported during Ramadan and is unlikely to be relevant. Survey of physicians 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. Some professional groups with interest in diabetes and Ramadan fasting included SGLT2 inhibitors in their guidelines on management of diabetes during Ramadan. They acknowledged the lack of trial data, recommended caution in high risk groups, advised regular monitoring and emphasized pre-Ramadan patients' education. In conclusion, currently, knowledge, data and experience with SGLT2 inhibitors in Ramadan are limited. Nonetheless, stable patients with normal kidney function and low risk of dehydration may safely use the SGLT2 inhibitors therapy. Higher risk patients should be observed carefully and managed on individual basis.</p>

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Introduction

Fasting during the month of Ramadan is one of the five pillars of Islam. During this month, adult Muslims are obligated to refrain from eating and drinking from dawn to dusk. Although based on Islamic principles patients are exempted from fasting, each year, many Muslim patients express their willingness to observe the fast in Ramadan month to respect the cultural customs. 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. Health-related exceptions from fasting are widely known (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. Despite the harmony between advice provided by physicians and permissions from religious authorities (2), two large epidemiological studies (EPIDIAR and CREED) confirmed that a high percentage of people with diabetes still choose to fast.

General recommendations for diabetes management during Ramadan have been published by individuals and interest groups. These have been based mostly on extensive

* Corresponding author: Salem A. Beshyah, Consultant Physician and Endocrinologist, Center for Diabetes and Endocrinology, Sheikh Khalifa Medical City, PO Box 59472, Abu Dhabi, United Arab Emirates. Email: beshyah@yahoo.com

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clinical experience, expert opinion and or clinical trials involving conventional medications such as insulin, metformin and sulphonylureas and also some of the newer medications (3, 4). On the other hand, there are limited data 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. 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 (5, 6).

Since the introduction of the SGLT2 inhibitors, there has been some concern among physicians about safety of SGLT2 inhibitors in Muslim patients who wish to observe the Ramadan fast. This is particularly so during the summer months and in hot regions. Ramadan in 2016 started on 6th June. The dearth of research data so far, makes it difficult to guide physicians objectively nor reassure patients confidently except by extrapolation from other settings and working on basis of "safety first" and "first do no harm" (2).

Hydration status during Ramadan in health and disease

The fasting of Ramadan entails complete abstinence from oral intake of any food or any fluid. Consequently, a degree of fluid deprivation is inevitable. Obviously, the impact of fluid deprivation and the resulting degree of dehydration would naturally depend on several factors such as duration of fasting, ambient climate, lifestyle and relevant behaviors such as extent of compensatory fluid intake, medications, sun exposure, etc. Shephard has comprehensively reviewed the literature pertaining to the hydration status of individuals

who observe the intermittent fasting required by Ramadan in general and in context of sport activities. Dehydration is evident by well-known by fasting individuals own reporting of symptoms and clinically observed signs. Dehydration has also been confirmed by increased measures of hematocrit, hemoglobin and plasma osmolality in several studies. Both theoretical considerations and empirical data support the view that the restrictions on fluid intake imposed by Ramadan observance have little effect upon sedentary individuals. If the fluid intake is increased during the hours of darkness, such individuals show little if any evidence of either short-term afternoon dehydration or accumulation of a fluid deficit over the course of Ramadan (7). However, concerns about the impact of fluid restriction and dehydration during Ramadan has been expressed in relationship to high risk individuals such as patients with various forms of renal disease, the elderly, those with cardiac disease, those needing loop diuretics and athletes (7-9).

Side-effects of SGLT2 inhibitors relevant to Ramadan

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. Risk factors for these volume depletion-related events were more in elderly subjects, those with eGFR <60 ml/min/1.73 m², and when used in combination with loop diuretics (5, 6). In Ramadan, there are variable fasting durations and patient may well become dehydrated if they do not consume enough fluids at night or work outdoors in hot climates. However, there arguably adequate time to replenish their lost fluids in the night time. 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. During

Ramadan it would obviously be very wise to avoid inducing or further enhancing osmotic diuresis by other mechanisms such as hyperglycemia, excessive intake of sugary drinks and perhaps even excessive use of tea and coffee.

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. 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 as treatment of hypoglycemia would naturally nullify the fast.

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 (10, 11). 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 may not be particularly relevant to T1DM patients in whom the SGLT2 inhibition therapy is not relevant currently.

SGLT2 inhibitors and Ramadan: Some evidence and perceptions

In the only clinical study published so far, the hypoglycemia risk and safety of dapagliflozin were compared with sulphonylurea during the fasting month of Ramadan in a 12-week, randomized, open-label, two-arm parallel group study (12). 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.

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 (13). 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 240 respondents with some more experience with SGLT2 inhibitors; the original conclusions were upheld (unpublished data).

Clinical practice guidelines overview

There are three recently published guidelines that include SGLT2 inhibitors. Their recommendations are presented here (14-16).

The "International Group for Diabetes and Ramadan" recommendations commended the improvements produced by SGLT-2 inhibitors on fasting hyperglycemia and HbA1c concentration, with a low risk of hypoglycemia (14). They warned on the associated increased risk of genital and urinary tract infections and also the mild increase in the risk of volume contraction and dehydration. Whereas the lower rates of hypoglycemia compared with sulphonylurea and insulin treatment make SGLT-2 inhibitors an attractive drug in patients with diabetes during Ramadan, the associated volume contraction and risk of dehydration represent a concern during prolonged

fasting in warm or hot climates, in particular in elderly patients.

The first “International Diabetes Federation-Al Dar Alliance Guideline” were released just before Ramadan of this year (15). They similarly stated that: “SGLT2 inhibitors have demonstrated effective improvements in glycemic control and weight loss, and are associated with a low risk of hypoglycemia. 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”. They added, “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 were published on line early in 2016 (16). These opened by stating that “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”. They too warned that “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”. The group recommended that SGLT2 inhibitors are used with caution and patients are advised to drink at least 2 liters of water a day to reduce the risk of dehydration (16). They pragmatically advised “Initiating a patient on an SGLT2 inhibitor just prior to Ramadan should be avoided”. Regarding risk of DKA; the group proposed that SGLT2 inhibitors are not used in those with type 1 diabetes and pointed out that they are not currently licensed for use in this population. In the current climate, they thought it may be pertinent to test for ketones in patients with T2DM on SGLT2 inhibitors periodically throughout the fasting period. However, some authors felt that this recommendation may not be readily feasible in some resource-short settings (17). A more pragmatic advice was 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”.

Conclusion

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. 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. Table 1 provides some common sense practical tips have been proposed for physicians and patients before, during and after Ramadan is getting an increasing acceptance (13, 17).

The way forward

Clinical trials specifically targeted to establish their efficacy and safety during Ramadan fasting are needed to inform production of good clinical practice guidelines, guide physicians and reassure with greater level of confidence. However, these are usually funded and conducted by pharmaceutical industry. On the other hand, real world evidence particularly from regions with majority Muslim population, can be readily generated by observational studies, clinical audits along with capturing patients’ reports of own experiences and these can be conducted at low cost in resource short settings. Practicing physicians and diabetes educators should not allow miss any opportunity of initiating, joining or supporting such studies within the limits of their resources. Relevant safety outcome measures that may be considered for such studies can include

Table 1. Common sense practical advice on safe use of SGLT2 inhibitors before, during, and after Ramadan fasting

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

Modified from references 13, 17

hydration status (questionnaire-based), impact on polyuria, symptoms of patients own drug treatment satisfaction scores, eGFR before and after Ramadan, frequency of postural hypotension, changes in body weight and changes in body composition with any readily available methods (DXA, bioelectrical impedance analysis) in addition to the usual efficacy measures. Many of these investigations can be conducted within the normal clinical services at no extra cost. Till such data become available, following the practical tips for safety before, during and after Ramadan described above is wisely recommended.

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