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Review

Risk of diabetic ketoacidosis during Ramadan fasting: A critical reappraisal



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ABSTRACT

Objectives: To evaluate the validity of the perceived increased risk and the actual occurrence of DKA observed during fasting in Ramadan.

Methods: This is a non-systematic narrative review of the literature on the occurrence of DKA during Ramadan. Online databases (PubMed, Google Scholar, Cochrane Database, Medline OVID and CINAHL EBSCO) were searched. Three research questions are addressed 1. What is the basis of the expert opinion on the risk for DKA? 2. What is the likelihood that DKA is precipitated by Ramadan fast? and 3. What is the frequency of observed DKA during Ramadan?

Results: The expert opinion suggesting a risk of DKA during Ramadan fasting was proposed with no evidence in the early writing on Ramadan fasting and has been reiterated and propagated since then. However, from first principles, DKA is not readily precipitated by the usual stress-free metabolic environment induced by Ramadan fasting with the exception of cases involved in the usual risk factors for metabolic decompensation. Furthermore, recent studies could not document any increase in observed DKA during Ramadan fasting in retrospective, prospective and database studies.

Conclusions: The current state of knowledge and evidence suggests the risk of DKA is not increased during Ramadan fasting.

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1. Introduction

Daytime fasting during Ramadan is observed by Muslims worldwide. Fasting lasts for 14–20 h during the day for 29–30 days [1,2]. However, people suffering from illness, travellers, those who may experience undue hardship from fasting, and those who have any considerable health risk from fasting are exempt [1,2]. People with chronic illnesses such as diabetes mellitus (DM) may be so passionate about fasting that they may find it unacceptable to make use of these exemptions [3–5].

Physicians are frequently asked by their patients about their ability to fast and the possible impact of fasting on their glycaemic control (see Table 1). Common understanding and harmony have recently been reached between the medical profession and religious scholars and organizations [2]. These have resulted in a widely-based consensus on the stratification of health risks from fasting to 3 or 4 risk categories mostly derived from general medical knowledge, some observations, and common sense [3–7].

Diabetic ketoacidosis (DKA) has been repeatedly listed among the acute metabolic risks from fasting in the early writings about the subject [8–10] and has ever since been reiterated in more recent articles [3–7]. Furthermore, having had an episode of DKA shortly before Ramadan is deemed to be a valid reason for not fasting in a given year as it may reflect generally poor control of diabetes [3–10]. There is, however, no solid evidence on the actual frequency of DKA during the fasting month. Therefore, we wished to explore the risk of DKA during Ramadan fasting using three separate approaches, Firstly, by revisiting the potential pathophysiological basis of DKA in relationship to fasting during Ramadan; secondly, by evaluating the widely accepted anecdotal professional doctrine on DKA risk, and thirdly by examining the observed actual rates of DKA during fasting.

2. Material and methods

2.1. Objectives

We aimed to explore the consistency and discrepancy between the perceived risk of DKA during Ramadan fasting

expressed by experts and the observed occurrence of DKA in observational studies

2.2. Design

This is a non-systematic narrative review of the literature on the risk of DKA during Ramadan. Three research questions were addressed. First, what is the expert opinion on the increased risk for DKA during Ramadan that has been proposed and reiterated over the last quarter of a century? Second, what is the potential of precipitation of DKA by the impact on the metabolic environment brought together by the dietary changes and medical management of diabetes during Ramadan? Third, what is the actual frequency of DKA episodes observed during Ramadan fasting from retrospective, prospective and database analyses?

2.3. Data synthesis

Online databases, (PubMed, Google Scholar, Cochrane Database, Medline OVID and CINAHL EBSCO) were searched for “DKA” and “Ramadan fasting” in various combinations. The resulting records were evaluated for relevance and the relevant publications were retrieved and reviewed. Recent Ramadan management guidelines, expert opinion, and reported research articles were reviewed. An initial descriptive report was drafted by one author and further developed by the rest of the authors via several rounds of multilateral telephone and electronic communications. All authors approved the final version. We have quested to ascertain and establish the best evidence for the arguments we pursue to the best of our knowledge. No human or animal experiments performed by the authors were included in this report. No ethical approval was required.

3. Results

3.1. What is the professionals' perception of DKA risk during Ramadan?

The listing of DKA among the acute complications of Ramadan fasting as described above seems merely a precautionary

Table 1 – Commonly suggested acute metabolic derangements and complications attributed to the impact of Ramadan fasting in people with diabetes.

Complications	Groups and circumstances putting patients at most risk
Severe hyperglycemia	Mostly attributed to an overzealous reduction of medications particularly insulin (intending to reducing the risk of daytime hypoglycemia) in patients who are either poorly or suboptimally controlled. It may also occur due to overindulgence (compensatory overeating) at the end of the fast
Diabetic ketoacidosis (DKA)	Potentially the extreme of state of the above associated with the classic precipitants (acute illness) or in association with Sodium Glucose Transporter-2 (SGLT-2) inhibitors
Hyperosmolar hyperglycaemic states (HHS)	Similar to the above but in the patient groups at risk of hyperosmolar hyperglycaemic states (elderly, impaired renal function)
Dehydration	Due to reduced intake of fluids during the fasting period, particularly in hot weather. Increased risk in patients on diuretics and possibly on SGLT-2 inhibitors
Thrombosis	Secondary to dehydration
Hypoglycaemia	Insulin or insulin- secretagogue treated patients
Risk of work and motor vehicle accidents	Secondary to hypoglycemia
Refs. [3–10]	

strategy on the basis of “safety first” [3–10]. It is reasonable to assume that a history of DKA within three months before Ramadan may reflect poor and unstable glycaemic control. Hence, these patients are counted at “high risk” group on the proposed risk stratification scales and are advised not to fast to avoid recurrence during Ramadan [3,4,7]. The risk of severe hyperglycaemia and DKA has long been thought to be greater during Ramadan [3–10]. This was proposed in the early writings [8–10] and reiterated ever since. Table 2 summarizes expert opinion on the risk of DKA during Ramadan fasting is reviewed [3–18]. These are discussed below.

Bessemans and Paquot [11] claimed that fasting exposes the person with diabetes to major acute complications, including DKA and severe hypoglycemia and they supported the benefit of individualized care before Ramadan, including a risk assessment, a specific education integrating, in particular, the adaptation of the pharmacological treatment in order to limit the occurrence of these acute complications. Ra et al. [12] suggested that fasting during Ramadan may cause wide fluctuations in blood glucose levels and increase the risk of acute metabolic complications including hypoglycaemia, hyperglycaemia, DKA, dehydration, and thrombosis. They also concluded that proper patient education, risk stratification, and modification of anti-diabetic medications could reduce the risk of complications. Fariduddin et al. [13] also concurred that fasting is associated with some risks like hypoglycaemia, DKA, HHS, and dehydration. They also suggested that all of these risks can be significantly reduced by pre-Ramadan counselling. Zantar et al. [14] suggested that persons with diabetes when they fast are at risk of complications including severe hypoglycaemia, hyperglycaemia, ketoacidosis, dehydration, and thrombosis. On the other hand, Alabood et al. [15] focused their review on 16 selected papers. On this basis, they concluded that the incidence of major complications was negligible. Specifically, minor hypoglycaemic events were reported in some studies but did not adversely affect fasting. They added, that postprandial hyperglycaemia was a major concern in other studies; the

incidence of severe hyperglycaemia and DKA were, however trivial. Hassan et al. [16] developed a three-step PRE-approach model based on Presentation, Risk stratification, Education in people with diabetes who fast during Ramadan. For the establishment of this model, they identified 40 published studies, and concluded that lack of education, poor healthcare, and no structured guidance caused adverse health consequences patients with diabetes who fast and are at risk of severe hypoglycemia, hyperglycemia, dehydration, thrombosis, strokes and retinal artery occlusion. In the context of diabetes mellitus and Ramadan in elderly patients, Azzoug et al. [17] listed all the traditional complications including hypoglycemia, hyperglycemia and metabolic decompensation including hyperosmolar coma, DKA, dehydration, and thrombosis. On the contrary, Ahmad et al. [18] proposed that DKA may not be increased during Ramadan fasting, yet, they provided a small list of scenarios when the risk of DKA may be increased.

Therefore, there is a large body of unfounded literature suggesting an increased risk of DKA during Ramadan. This was proposed in the early writings on the subject [8–10] and was reiterated ever since without due scrutiny. Perhaps, this was suggested initially from first principles as discussed above.

3.2. Is the metabolic environment of Ramadan fasting sufficiently stressful to cause DKA?

DKA is a common, serious, and preventable complication of diabetes, with mortality varying between 3% and 10% depending on the quality of diabetes care and patients own individual circumstances [19,20]. It may be the first presentation of type 1 diabetes, although may also occur in type 2 diabetes. The diagnosis may not always be obvious and should be considered in any person with diabetes who is unwell. Diagnosis is based on the three classical biochemical criteria reflected in the name (hyperglycaemia, acidosis, ketosis). Hyperglycaemia, however, may not always be present

Table 2 – Perceived risk of diabetic ketoacidosis during Ramadan in statements, guidelines, and expert opinions that listed severe hyperglycemia and diabetic ketoacidosis as increased in general or in a specific context. Articles are listed in chronological order.

Ref	First author (year)	Document type	Authors' perception
8	R Sulimani (1988)	Perspective	Enumerated all concerns and risk including DKA in the context of diabetes mellitus
9	SA Beshyah (1989)	Review	Enumerated risk including DKA in general from on theoretical basis and proposed possible mechanisms. Not much evidence was provided
10	IH Sherif (1989)	Book chapter	Described risks including DKA in general from on theoretical basis and proposed possible mechanisms
11	S. Bessemans (2017)	Narrative review	“fasting exposes the diabetic subject to major acute complications, including diabetic ketoacidosis and severe hypoglycaemia”
12	RA V (2017)	Narrative review	“increasing the risk of acute metabolic complications including hypoglycemia, hyperglycemia, diabetic ketoacidosis, dehydration, and thrombosis”
13	M. Fariduddin (2011)	Narrative review	“Fasting also associated with some risks like-hypoglycemia, DKA, HHS, and dehydration”. All of these risks can be significantly reduced by pre-Ramadan counselling”
14	A Zantar (2012)	Literature review	“The problem is when they fast, diabetics are at risk from complications such as severe hypoglycemia, hyperglycemia, ketoacidosis, dehydration and thrombosis”
15	MH Alabbod (2017)	Narrative review	“The incidence of severe hyperglycaemia and diabetic ketoacidosis were trivial”
16	A. Hassan (2014)	Literature review	Developed a 3 step PRE-approach model based on Presentation, Risk stratification, Education in people with diabetes who fast during Ramadan. Conclusion: lack of educations puts patients at increased risk of DKA
17	S Azzoug (2015)	Narrative review	Enumerated all concerns and risk including DKA in the context of Diabetes mellitus and Ramadan in the elderly patient
18	J Ahmad (2012)	Expert statement	“Fasting during Ramadan for patients with diabetes carries a risk of an assortment of complications. Authors reviewed the management of the diabetic emergencies including hypoglycemia during Ramadan”

As much as possible, opinions are presented verbatim. Opinions reiterated by authors are presented individually as a measure of the dominant opinion. Original data are not included here.

(so-called “euglycaemic ketoacidosis”) and low blood ketone levels (<3 mmol/L) do not always exclude DKA [19,20].

DKA occurs when insulin deficiency and counter-regulatory hormone excess coexist [19], of which glucagon is the most important, but also includes cortisol, growth hormone, and epinephrine. This imbalance leads to increased glucose production via gluconeogenesis and glycogenolysis, whilst glucose utilization in peripheral tissues is impaired. This hormonal environment also favours the liberation of fatty acids that are subsequently oxidized to form ketones, (predominantly β -hydroxybutyrate and acetoacetate), which leads to the high anion gap metabolic acidosis that is characteristic of DKA. As glucose and ketones accumulate in the bloodstream, the reabsorptive threshold of the renal tubule is surpassed, resulting in glycosuria and ketonuria, respectively. The ensuing osmotic diuresis results in the loss of sodium, potassium, and water in the urine (Fig. 1). There are many precipitating causes of metabolic decompensation leading to DKA. Non-adherence with an insulin regimen frequently causes DKA, but other triggers must be sought. Infections, particularly urinary tract infections (UTIs), pneumonia, myocardial ischemia, stroke, pancreatitis, drugs (for example glucocorticoids and Sodium-glucose co-transporter 2 (SGLT2)

inhibitors), pregnancy and alcohol consumption may precipitate DKA [21].

Can fasting during Ramadan cause DKA? Ketosis induced by starvation (so-called “starvation ketosis”) is well recognised and has been reported as a cause of severe ketoacidosis in people with and without diabetes. This can occur in the context of pregnancy, anorexia nervosa, sepsis or ketogenic diets [22–24]. Importantly, however, short duration of fasting (for example pre-operatively) does not appear to induce significant amounts of ketosis [25]. Strictly, Ramadan fasting is not true fasting in the physiological sense of starvation. It constitutes cycles of fasting and feeding of varying durations repeated every 24 h for a month. The “starvation” effects of daytime fasting are not sustained for long enough to lead to significant ketosis, and are nullified by the night time feeding (perhaps, more correctly described as overfeeding or gorging). Thus, there is no cumulative effect from the fasting by the end of the fast at sunset.

Two potential causes for hyperglycaemia and DKA have been proposed [3–10]. Firstly, it may be caused by an overzealous dose reduction or omission of insulin and other anti-diabetic medications made by patient to avoid hypoglycaemia. Secondly, the compensatory over eating with no or

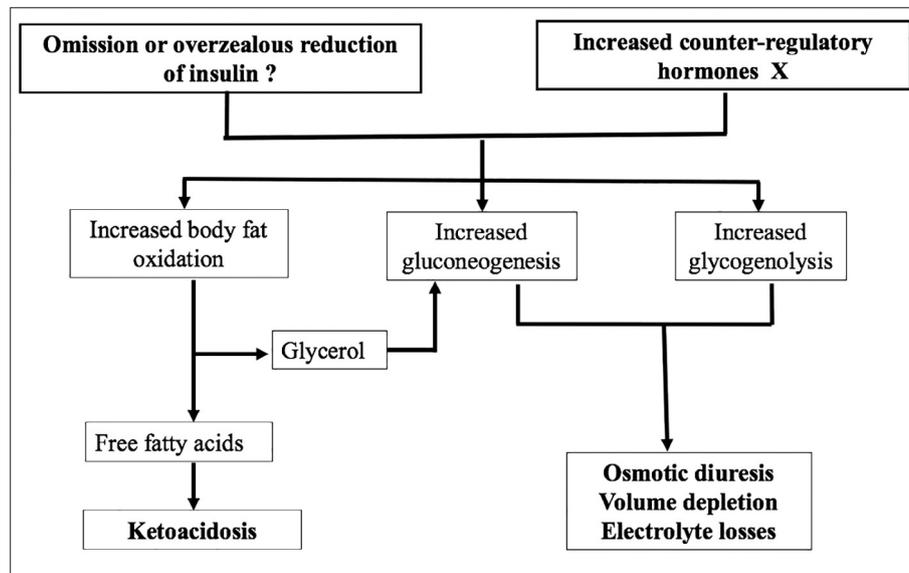


Fig. 1 – The established pathogenesis of DKA. The Ramadan metabolic environment lacks the major drivers for the DKA cascade namely the increased counter-regulatory hormones unless other major stressors are present, making the DKA in Ramadan not different from DKA outside Ramadan.

insufficient adjustment in insulin or anti-diabetic medications may cause marked postprandial hyperglycaemia. However, other than in a patient with T1DM, patients with poor glycaemic control before Ramadan or those who take excessive amounts of carbohydrate-rich foods and drinks, these metabolic circumstances are unlikely to be sufficient to precipitate DKA unless accompanied by precipitating factors such as infection [19]. Consequently, these circumstances lack the counter-regulatory hormones essential for precipitation of DKA and thus Ramadan fasting per se is not a plausible cause for DKA.

3.3. What is the actual frequency of DKA episodes observed during Ramadan fasting?

There are limited actuarial data on the incidence of DKA during Ramadan. Perhaps the largest study hitherto is the EPI-DIAR study that included 1070 T1DM and 11,173 patients with T2DM [26]. During Ramadan, 42.8% of patients with T1DM and 78.7% with T2DM observed the fast. Rates of severe hyperglycaemic episodes with or without ketoacidosis per month were significantly different in Ramadan and the preceding year only for patients with T2DM. However, it is noteworthy that the investigators have counted hyperglycaemia with or without DKA as one group.

Table 3 provides a summary of the studies which aimed specifically to ascertain the incidence of hyperglycaemia and DKA during Ramadan as the primary objective or included reports on DKA in Ramadan fasting [27–35]. The reports of Kadiki et al. [27,28] and Abusrewil et al. [30] showed DKA rates in their adult and adolescent patients respectively, similar to that observed in non-Ramadan months in their institutions and a further study demonstrated that the incidence of DKA during Ramadan was significantly less than during other lunar months [27,28,30]. A large study from Tunisia described 383 cases of DKA. A quarter of these were

delayed presentations of newly diagnosed diabetes. An association with Ramadan fasting and DKA in T1DM patients was indicated but was not fully elaborated [29]. A cross sectional survey of patients returning to clinic after Ramadan in Abu Dhabi revealed no excess DKA reported [6]. A study of the incidence of DKA during Ramadan fasting was also reported by Elmehdawi et al. [31]. The authors retrospectively reviewed all the charts of patients admitted with DKA to all Benghazi hospitals during Ramadan of 2007–2008. Only 15 episodes occurred during Ramadan compared to a mean of 19.45 episodes/month during the other lunar months of the same year ($p < 0.001$). The commonest precipitating factor for DKA during Ramadan was infection followed by missing insulin doses. More recently, using a similar approach, the “DKA Ramadan International” prospectively compared the incidences of DKA admissions during Ramadan to those in the month before (Shaaban) and the month after (Shawal) as well as the average six months’ admissions pre-Ramadan [33]. One hundred and seventy patients were admitted during the study duration, 56 during Ramadan and 63 in Shawal. All those admitted during Ramadan had T1DM. No structured education on diabetes management in Ramadan was received by 29.8% of those admitted during Ramadan. Non-compliance to medications was the commonest cause for admission during the whole study period. Thus higher rates of DKA occurred during Ramadan when compared to preceding lunar month. However, the rates of DKA admission in the following lunar month were even higher than the average monthly DKA admissions. The authors found no clear explanation for their observation. Beano et al. [34] reported a prospective, observational, open-label study of 301 T2DM patients who wished to fast followed during Ramadan and the preceding month. The incidence of DKA was monitored. They classified patients into four groups according to medication type and medications were adjusted according to predetermined proportions from the pre-Ramadan doses. No cases of DKA were reported. Most

Table 3 – Descriptive summary of the studies which ascertained the frequency DKA during Ramadan as a primary outcome variable or secondary observation in a Ramadan context.

Ref	The first author (year)	Study type	Sample size	Source	Study results
27	Kadiki O (1984)	Observational	207 patients (177 T1DM)	Benghazi, Libya	7 cases (3.4%) developed DKA during Ramadan
28	Kadiki O (1989)	Interventional	88 insulin-treated DM patients	Benghazi, Libya	2 cases (2.3%) developed DKA (similar to non-fasting rates)
29	Amimi S. (1995)	Observational retrospective	383 DKA cases	Sousse, Tunisia	A quarter of these were delayed presentations of newly diagnosed diabetes. An association with Ramadan fasting and DKA in T1DM patients was suggested
30	Abusreiwil S (2003)	Observational	106 patients;T1DM	Tripoli, Libya	1.8% of diabetic children and adolescents developed DKA during Ramadan (similar to non-Ramadan months)
6	Beshyah SA (2009)	Observational retrospective	313 patients	Abu Dhabi, UAE	Hyperglycemia reported in 33 patients; 3 admissions but no DKA
31	El-Mehdawi R (2009)	Observational retrospective	15 DKA Cases	Benghazi, Libya	The incidence of DKA during Ramadan was significantly less than during other lunar months
32	Al-Alwan I (2010)	Retrospective observational	20 patients (12 fasting)	Riyadh, KSA	No cases of DKA patients with T1DM aged 8–14 years who fasted Ramadan
33	Abdelgadir E. (2016)	Observational prospective	170 DKA cases	MENA Region	Ramadan DKA admissions >the preceding lunar month but DKA admission in the following lunar month was >average monthly
34	Beano AM (2017)	A prospective, observational, open-label study	301 T2DM patients	Amman, Jordan	No cases of DKA were reported
35	Beshyah AS (2019)	Retrospective chart & database review	432 DKA's in 283 patients	SKMC, Abu Dhabi, UAE	DKA during Ramadan was not different from the average monthly in the same calendar year

recently, the risk of DKA during Ramadan was studied by comparing the relationship of admissions to a single tertiary hospital during Ramadan and outside Ramadan over ten years [35]. There were 432 episodes of DKA involving 283 patients. Of these, 370 episodes (85.6%) involved 231 patients (81.6%) with T1DM. The number of admission episodes was not different during Ramadan from the average calendar month [3.6 ± 2.6 (Range 0–15) episodes/month versus 3.3 ± 2.1 (Range 1–7) episodes/month respectively, $P = 0.77$] [35]

The risks of fasting for patients with T1DM may be viewed differently. Al-Alwan et al. found no cases of DKA patients with T1DM aged 8–14 years who fasted during Ramadan [32]. Also, Alamoudi et al. [36] compared glucose profiles during Ramadan in patients with T1DM who use continuous subcutaneous insulin infusion (CSII) compared with those who use multiple daily injections (MDI) insulin regimen. 61 patients on CSII and 95 on MDI were recruited. No DKA was reported in either group. Al-Agha et al. [37] assessed the benefit of using the flash glucose monitoring system (FGMS) in children and adolescents with T1DM during Ramadan fasting in a prospective study of 51 participants. None of the participants developed DKA. Also, Zabeen et al. [38] monitored 33 adolescents with T1DM over Ramadan in India, and no cases of DKA were noted in their cohort.

The effects of active glucose monitoring, alteration of drug dosage and timing, dietary counselling and patient education on the occurrence of acute diabetic complications in fasting individuals with diabetes during Ramadan were investigated [39]. A total of 3946 readings were obtained in 110 subjects. With active glucose monitoring, alteration of drug dosage and timing, dietary counselling and patient education, the majority of the patients did not have any serious acute complications specifically, none of the patients developed DKA. The highest frequencies of hypo- and hyperglycemic episodes were observed pre-dawn. Another report from the same group observed the outcome of the implementation of Ramadan-specific diabetes management recommendations in fasting individuals with diabetes [40]. Out of 388 patients with either type of diabetes, none developed DKA during Ramadan.

Isolated case reports of DKA during the Ramadan fast do not reflect a wider phenomenon and has to be taken on their own merits [41,42]. For instance, the DKA reported by Levy [41] occurred in a 15-year-old boy with T1DM occurred due to omitting pre-lunch insulin combined with dehydration and overeating during the permitted sunset-to-sunrise meals reflecting the poor pre-Ramadan assessment and education [41]. Similarly, euglycemic DKA in a newly diagnosed person with T1DM during Ramadan fasting described by Baş et al. [42] may be easily predicted in long-lasting starvation in a newly diagnosed 14-year-old male patient. All current guidelines advise against fasting for newly diagnosed T1DM and unstable T2DM. Therefore, this should not be a major problem in clinical practice.

Addressing the risk of SGLT2 inhibitors-associated euglycemic DKA is noteworthy since fasting may entail dehydration and reduction of insulin doses by patients wishing to avoid hypoglycemia. Hence, Adnan [43] suggested to categorize these SGLT2 inhibitors of agents differently from other

agents such as metformin, and incretin-based therapy studied vastly during Ramadan. However, several reports investigated this issue using different study designs with no real concern. Wan Seman et al. [44] assessed the safety of dapagliflozin compared with sulphonylurea during the fasting month of Ramadan. In this 12-week, randomised, open-label, two-arm parallel group study in 110 patients with T2DM who were receiving sulphonylurea and metformin; no DKA incidents were reported. Also, Shao et al. [45] investigated the effect of continuing SGLT2 inhibitor use during Ramadan on ketonemia in 68 Muslim patients with T2DM in a single-centre prospective observational controlled cohort study. They found that continued use of SGLT2 inhibitors during Ramadan did not increase ketonemia. The CRATOS study [46] evaluated the tolerability of canagliflozin ($n = 162$) compared with sulphonylureas ($n = 159$) added to metformin \pm dipeptidyl peptidase-4 inhibitor among patients with T2DM who fasted during Ramadan in a non-randomised, parallel-cohort, prospective, comparative, observational study. Fewer patients experienced symptomatic hypoglycaemia with canagliflozin than sulphonylurea and more patients on canagliflozin experienced volume depletion events compared with a sulphonylurea. However, no patients experienced any serious adverse events in either group. Furthermore, Bashier et al. [47] assessed 417 patients on SGLT2 inhibitors during Ramadan. No admissions due to DKA were reported.

Therefore, the data available from most of the published studies reviewed above suggest no increase in the incidence of DKA during Ramadan. Indeed, some studies suggest a reduction in the incidence of DKA. On the other hand, the use of SGLT2 inhibitors in phase 3 clinical trials in T1DM was associated with an observed increase in DKA in patients receiving an SGLT2 inhibitors [48].

4. Conclusions

In conclusion, we have demonstrated that the generally held perception propagated in the literature on the increase in the risk of DKA appears to be based on limited data and may be unfounded. The theoretical risk is not supported by the established pathophysiological mechanisms of DKA. While DKA may occur during Ramadan fasting, it is likely to be precipitated by factors unrelated to fasting. The documented actual rates of DKA admissions observed during Ramadan in the studies where such rates were captured, does not lend support to the notion of an increased risk. We, therefore, propose to de-emphasise the risk of DKA in people with diabetes during Ramadan fasting and put more focus on other concerns. This should create a much more balanced approach to Muslim people with diabetes wishing to observe the fast.

5. Authors' contribution

SAB proposed the review theme and drafted the manuscript. TAC, NG and AAL critically revised the manuscript for intellectual content, provided more ideas and references. All authors approved the final version of the manuscript.

6. Compliance with ethical principles

Not applicable.

7. Availability of data and materials

Not applicable.

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Conflicts of interest

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.diabres.2019.02.027>.

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