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Original Article

A systematic review on efficacy and safety of the current hypoglycemic agents in patients with diabetes during Ramadan fasting

Fauzia Rashid, Elamin Abdelgadir*

Endocrine Department, Dubai Hospital, P.O.Box: 7272, Dubai, United Arab Emirates

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ABSTRACT

The fasting in the holy month of Ramadan is passionately practised among the Muslims population around the world. Patients with diabetes are generally considered to have various risks with fasting. The recent pharmacologic and technical advances in the management of diabetes may have enabled these patients to practice safe fasting. The purpose of this review is to scientific evidence on the safety and efficacy of the current hypoglycemic agents during Ramadan.

Methods: An extensive Electronic search via PubMed and Google scholar was accomplished through using different search terms. The eligible studies were limited to only published Randomised controlled trial (RCT) and prospective observational studies from 2007 to 2018 on patients with all types of diabetes on any pharmacological management, who intended to fast in Ramadan.

Results and Conclusions: The current era witnessed a gradual shift in the management of these patients with diabetes who elected to fast in Ramadan, despite the variable health-related risks with fasting. Results from available RCTs and observational studies in patients with type 2 diabetes showed lower risk of hypoglycemia, similar or better efficacy for glycemic and weight control with SGLT2 inhibitors, incretin mimetics and the newer insulin analogues compared to Sulfonylurea. Gliclazide is a relatively safer option among all sulfonylurea. Patients requiring insulin did better with insulin analogues, especially the newer premixed formulation at the time of breaking fast compared to the former insulin formulation. Current commonly used newer hypoglycemic agents are generally safe during Ramadan, however, their safety in the higher risk diabetes patients is highly needed.

1. Introduction

There is an increase in the prevalence of diabetes all over the world more so in the last few decades [1]. As per 2015 indices, approximately 415 million of the global population are having diabetes which may rise to 642 million in 2040. Muslim constitute almost a third of entire world's population with around 1.6 billion as of 2010 estimates [2].

The distribution of prevalence in diabetes is not uniform in all the regions of the world, where North America and Europe may have less prevalence compare to Middle East, North Africa and other South Asian countries where the Muslims are in predominance. Even as per some studies, those regions where diabetes is predicted to be less, it is more prevalent among ethnic minorities from south Asian Muslim countries such as Pakistan and Bangladesh[3,4]. Diabetes and its complications are also more endemic in the under-developed and developing countries; the areas where the Muslims are the majority, therefore, fasting Ramadan will be an essential consideration in the management of diabetes during fasting Ramadan.

1.1. Fasting in Ramadan

Ramadan is the 9th lunar month in the Islamic calendar and fasting in this holy month is one of the five pillars of Islam and considered as a religious obligation for the Muslims, all over the world. Fasting means they refrain from eating, and drinking from dawn (suhoor) to dusk (futoor). Ramadan is a lunar month; it may consist of 29–30 days. The duration of fast varies between 10 and

* Corresponding author.
E-mail addresses: alaminibrahim@hotmail.com, eelaminabdelgader@dha.gov.ae (E. Abdelgadir).

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List of abbreviation

DM	Diabetes Mellitus
T1DM	Type 1 Diabetes
T2DM	Type 2 Diabetes
HbA1c	Glycated haemoglobin
EPIDIAR	Epidemiology of Diabetes and Ramadan
BG	blood glucose
SMBG	Self- Monitoring of Blood Glucose
HE	Hypoglycemic Events
CSII	Continuous Subcutaneous Insulin Infusion
ADA	American Diabetic Association
IDF	International Diabetes Federation
DaR	Diabetes and Ramadan international Alliance
BL	Base Line
FPG	Fasting Plasma Glucose
RCT	Randomised controlled trial
SU	SulphonylUrea
GLP-1 RA	glucagon-like peptide-1 receptor agonist
SGLT 2 I	Sodium Glucose Co-Transport Inhibitor
DPP4I	Dipeptidyl Transferase 4 Inhibitors
n	number of patients included in the study
NR	Not Reported
UAE	United Arab Emirates
UK	United Kingdom
IS	Insulin Secretagogues
UTI	Urine Tract Infection
eGFR	Estimated Glomerular Filtration Rate
CKD	Chronic Kidney Disease
HSS	Hyperosmolar Hyperglycemia

20 h per geographical location of the region and season. Due to religious obligation and numerous spiritual benefits Fasting in Ramadan is practised with a deep passion among Muslims all over the world. Although people with certain health conditions are religiously exempted, such as pregnancy, lactation, or any chronic or acute illness where prolonged fasting may predispose them to untoward health-related risk. Diabetes is a metabolic disease with risk of hypoglycemia and hyperglycemia and thus, considered as a high-risk condition for Ramadan fasting. However, in clinical practice, most of these patients still prefer to fast. Their risk further augments with the fact that Ramadan is celebrated as a festive month and breaking fast at dusk time (Iftar) is accompanied by sweetened drinks and high-calorie food. That also contributes to severe hyperglycemia and unstable glucose profile.

All of these practical challenges became first time evident in the landmark study of Epidemiology of Diabetes and Ramadan (EPIDIAR) conducted across 13 countries and data was collected from 12,243 Muslim patients with diabetes in 2001. This study showed that 43% of type 1 DM and 79% of T2DM patients fast in Ramadan. Out of them only 68% with type 1 and 62% of type 2 DM received Ramadan-focused education for diabetes management. Self-monitoring of blood glucose (SMBG) which is an essential prerequisite for safe Ramadan fasting is also only done by 67% of type 1 and 37% of patients with type2 diabetes. This study also reported the fact that large proportion of patients did not change their oral hypoglycemic agents and insulin dose during fasting and 9% of type 1 DM and 2% of type 2 patients with diabetes hospitalised with at least one episode of severe hypoglycemia during Ramadan. Severe hyperglycemia with or without Diabetic ketoacidosis is also remarkable, and 13% of type 1 and 4% of type 2 DM required hospitalisation [5].

A question-based survey about fasting Ramadan was done in Pakistan in 2004 showed a significant prevalence of hypoglycemia (21.7%) and hyperglycemia (19.8%) in 327 patients with diabetes who fast in Ramadan. 4.0% of subjects had major hypoglycemic while 8% had major hyperglycemic episodes [6].

EPIDIAR was the first study to raise awareness about Ramadan fasting related issues in diabetes. That subsequently gave rise to different management strategies including Ramadan related education, change of medication with meals and recommendations for this area in diabetes. [7],

1.2. Physiology of fasting in Ramadan

In the holy month of Ramadan, the duration of fasting is more than 12 h per day in most of the regions in the world. Muslims usually take two large meals at the beginning of their fast before Dawn called as 'Suhoor' and break their fast at sunset called as 'Futoor'. Between these two meals, they abstain themselves from eating or drinking anything. In normal physiological conditions insulin level rises in the body after feeding, to help the restoration of liver glycogen stores, inhibits glycogenolysis and gluconeogenesis. The first few hours of fasting, stores of hepatic glycogen serves to supply adequate glucose for necessary function. After a few hours of fasting insulin level decrease in the body and the level of glucagon increases followed by a rise in catecholamines and growth hormones level to help in glycogenolysis to keep blood glucose level from falling. Once the glycogen stores are depleted, levels of fatty acids released from lipid cells are elevated, and these fatty acids participate in the process of gluconeogenesis. Which is the alternative body fuel reserves in many cells. The remaining glucose is preserved for brain and erythrocytes metabolism. The fine regulation of these hormones in normal healthy individuals keep normal glucose level in blood and maintain its supply to essential organs like the brain even in extended hours of fasting [8].

However, due to a fundamental defect in insulin and glucagon secretion or resistance to their action in patients with diabetes, prolonged fasting may lead to some serious consequences. In diabetic patients, during fasting glycogenolysis accelerates due to insulin absence or resistance, and gluconeogenesis and ketogenesis are enhanced as well. The depletion of stored Glycogen at around Iftar time promotes ketogenesis [8]. Moreover, in the fasting state, impaired glucagon response to hypoglycemia precipitates risk of severe hypoglycemia in them. These risks further complicated if there is coexistent autonomic neuropathy with impaired catecholamines and glucagon release [9]. This risk may increase further by the effect of antidiabetic agents like sulfonylurea, and insulin that may result in more potent and unpredictable hypoglycemia [10], especially if not modified in Ramadan, as evident in many previous studies [5].

The complexity of Ramadan Fasting in patients with diabetes is also related with the festivity of this holy month as breaking fast is usually accompanied by intake of highly sweetened drinks and food rich in refined carbohydrate that may cause severe hyperglycemia and its associated risks [11].

1.3. Risks of Ramadan fasting in diabetes

The risks associated with fasting Ramadan include hypoglycemia, hyperglycemia, acute metabolic complication like diabetic ketoacidosis and hyperosmolar hyperglycemia, dehydration and hypotension, and thrombosis. Risk stratification was done to avoid

above complications for different types of diabetes in the latest guidelines for the management of diabetes in Ramadan (2017) in collaboration with the International Diabetes Federation (IDF). This risk categorisation is extremely important to give patients appropriate standardised advice for or against fasting as being a religious obligation it carries an enormous responsibility for health care provider [12].

From Recommendations for Management of Diabetes During Ramadan Update 2017 Diabetes Research and Clinical Practice.

2. Rational of this review

The physician used to give patients strict advice against fasting and usually did not consider them for a pre- Ramadan assessment for targeted education about dose modification of their antidiabetic agents and frequent SMBG in Ramadan. The CREED study, an observational, retrospective and multi-country study conducted in 2010 for Ramadan Fasting with the objective to assess the risk of adverse events after using the ADA recommendations [13]. This study unfolds the fact that patients who are considered at high and very high risk, still practised fasting against medical advice and with 8.8% of patients had one episode of hypoglycemia compared to 5.4% before Ramadan. This percentage differs from EPIDIAR study which showed 6-fold higher risk of hypoglycemia in fasting individuals. The EPIDIAR study showed the incidence of severe hyperglycemia was increased to five folds in type 2 diabetes that requires hospitalisation and three folds in type 1 diabetes with or without ketoacidosis [5]. This risk reduction was also recorded in a few other recent studies. All of them showed less hypoglycemia reflecting the effect of Ramadan-focused education and modern medications as a cause for a lesser risk of hypoglycemia in improving the outcome in these patients compared to before [14–16].

There are many studies on the subjects with type 1 diabetes, but with the use of close glucose monitoring and insulin adjustment, this subgroup also showed safer fasting without a higher risk of ketoacidosis and severe hyperglycemia or hypoglycemia [17]. This observation despite the significant difference between the design of these studies and EPIDIAR study highlighted the fact that closed alliance of patient with their health care provider improves the outcome. This observation also emphasizes the fact that there should be a better understanding of current practice and adherence with it, at the global level, so there is no variation in the management of diabetes.

Since the development of last updated recommendations, many Randomised Controlled Trials (RCT), prospective and retrospective studies have been done with different antihyperglycemic agents for their safety and efficacy in the diabetic patient for Ramadan fasting. Ramadan-focused diabetic education was proved to be a valuable tool in this change of practice. Current era witnessed an improvement in Ramadan fasting even in higher risk groups, due to numerous new antidiabetic agents, and the presence of better facilities for monitoring and education of these patients during Ramadan fasting. All these factors led to a better understanding and the revision of recommendations for Ramadan fasting (DaR Alliance, 2016) [18].

This focused systematic review aimed to evaluate all these studies done in Ramadan Fasting in patients with diabetes during the last decade to conclude the efficacy and safety of various antihyperglycemic agents. To observe the incidence of hypoglycemia during Ramadan fasting, the changes in HBA1c, and with measurement of secondary outcomes such as weight change, the risk of dehydration, deterioration of renal function, and hospitalisation during Ramadan fasting, if available.

3. Methods and data selection

A thorough electronic search was done on PubMed and Google Scholar between the years 2007–2018. All possible resources were used to retrieve the whole article. Different search terms were used in combination like Ramadan and Diabetes, fasting Ramadan in diabetes, the safety of fasting in Ramadan, fasting in Ramadan with sulfonylurea, fasting in Ramadan with DPP4 inhibitors, fasting in Ramadan and insulin, Ramadan education and fasting in Ramadan, fasting in Ramadan with GLP 1 agonist, and finally individual drug names in Ramadan. Related references cited in each study also manually looked through.

3.1. Studies selection

Two authors have looked into the data pool and included the eligible studies for outcome measurement were only randomised and nonrandomized controlled trials, prospective observational studies including cohort, case-control and cross-sectional studies from 2007 till 2018. All retrospective studies, and expert opinion, systemic review and meta-analysis were excluded. A detailed review of all studies done. Those involving all patients with type 1, type 2 diabetes and diabetes with pregnancy, intended to fast in Ramadan and on insulin and non-insulin antidiabetic agents including metformin, meglitinides, sulfonylureas, thiazolidinedione, GLP-1 receptor analogues (glucagon-like peptide), alpha-glucosidase inhibitors, DPP-4 inhibitors (dipeptidyl peptidase-4) and SGLT2 inhibitors (sodium glucose co-transport 2) were included.

The studies with continuous subcutaneous insulin infusion(CSII) included the high-risk population like Type 1 diabetes. All Maximum efforts were made to collect frequency of symptomatic or documented hypoglycemia during Ramadan fasting as primary endpoint where available as it was not consistent throughout the studies. Pre and post-Ramadan glycemic changes, weight change and lipid profile also recorded if documented in the review. Hypoglycemia is defined as subjective symptoms of patients or documented blood glucose less than 70 mg/dl. Severe hypoglycemia is defined as the episode of hypoglycemia requiring third-party assistance.

4. Literature systematic review

The Epidemiology of Diabetes and Ramadan (EPIDIAR) study is indeed a pivotal study in the field of diabetes management in the month of Ramadan [5]. In this review, we will be using its results to compare the attitude and behaviour of health care physicians and patients with diabetes for fasting Ramadan and, the prevalence of complications associated with the fasting. As after publication of this study the need for Ramadan related education in patients with diabetes was highlighted, and consequently series of recommendations and guidelines for Ramadan fasting emerged to help the Muslim community globally.

4.1. Studies on the impact of Ramadan focused education on fasting outcomes

The Ramadan Education and Awareness in Diabetes (READ) is a prospective Study from Pakistan was done with the aim to see the impact of education on acute diabetic complications [19]. The study involves two sessions of education for alteration in drug doses and administration timings and diet counselling. Patients were instructed to monitor their blood glucose in fasting state. The result showed out of 3946 readings, 82 were in the hypoglycemic range.22 episodes were only symptomatic and happened in seven

patients, while 60 episodes were documented, biochemical low blood glucose that occurred in twenty patients. The frequency of symptomatic hypoglycemia got better with from first week onward. No DKA or hyperosmolar hyperglycemic state (HSS) was reported among study subjects.

A multicenter prospective study in 2014 done in Pakistan with the aim to observe the outcome of Ramadan fasting in those patients with diabetes who received the Ramadan-focused education [20]. A total of 682 patients received pre -Ramadan recruitment interview and teaching and guided about dose alteration, blood glucose checks on any symptom of hypoglycemia and hyperglycemia and attend the second session after Ramadan for their readings and 388 completed the second interview after Ramadan. Symptomatic hypoglycemia was observed in 23.7% of all diabetic patients. All type 1 diabetes and 71.43% of type 2 patients with diabetes checked their blood glucose on their hypoglycemic symptoms, and 33.3% of type 1 and 48% of type 2 diabetic broke their fast on symptoms. There were overall 16.3% hyperglycemic symptoms reported and none of type 1, while 18.87% of type 2 patients discontinued their fast on hyperglycemia. No hospitalisation with any Diabetes related complication was recorded.

Later, one recent multinational survey was done by the same author for characteristics of diabetic Ramadan education where a larger cohort of patients from different countries participated in it. It was observed out of 6610 participants, 3142 (47.5%) received Ramadan-focused education, and severe hypoglycemia was recorded in 29 (1.0%), severe hyperglycemia was reported by 44(1.7%) patients. Patients who received education before Ramadan followed better Ramadan related recommendation during Ramadan compared to those who did not get an education [21].

Another multinational study by McEwen at al. (2015) done on 774 patients with type 2 diabetes. Patients were recruited from the clinics in Egypt, Iran, Jordan and Saudi Arabia who fasted for $\geq$ two days during Ramadan 2014 [16]. This study is unique as it compared the effect of individualised Ramadan selected diabetic education versus usual care. The results showed that the group of patients received individualised care reported more symptoms of hypoglycemia (77% vs 67%, $p = 0.0031$), equal proportion reported mild and severe hyperglycemia, but severe hypoglycemia along with hospitalisation was more frequent in patients with usual care (23% vs 34%, $p = 0.0017$). Another important observation was an improvement in HBA1c ($0.7 \pm 1.1\%$ versus $0.1 \pm 1.3\%$, $p < 0.0001$) and weight (2.9 ± 6.4 kg versus of 0.5 ± 4.6 kg $p < 0.0001$) in patients receiving individualised Ramadan education versus usual care. ([16]. A recent single-centre study from Saudi Arabia compared the effectiveness of Ramadan-focused individual education versus usual diabetes care based on ADA (2010) recommendations [22]. Results showed a more significant reduction in the post-Ramadan HbA1c levels and hypoglycemia score in intervention compared with control groups (-13.0% vs. -4.5%, $P = 0.004$ for HbA1c levels and -61.7% vs -33.8%, $P < 0.001$ for hypoglycemia score) but no difference in weight. The importance of targeted education regarding Ramadan, about dose adjustment in fasting hours and behavioural modification, proved to ameliorate the risk of fasting even in countries with Muslims minority. This risk reduction is evident in a study of Thai Muslims with less incidence of hypoglycemic symptoms and results in safe fasting [23]. With growing awareness among physicians and patients, Ramadan-related Diabetic education proves even less frequent hypoglycemia in Ramadan compared to before Ramadan even in patients with insulin injections as shown in a latest prospective study showed the beneficial effect of patients empowerment by providing DSME in Ramadan [24]. This effect has been observed retrospectively in Ramadan Education and Awareness in Diabetes(READ) for Muslims with type 2 diabetes [25].

4.2. Pharmacologic management of diabetes during Ramadan fasting in the current era

The last decade witnessed a revolution in antidiabetic medications and patients have multiple antidiabetic agents available now for the management of their hyperglycemia. Compared to conventional hypoglycemic agents with a higher risk of hypoglycemia these newer drugs have a lesser risk and some potential added cardiovascular benefits [26].

Previous ADA guideline proposed the alteration in dose and timings of insulin and sulfonylurea (SU) due to an inherently high risk of hypoglycemia with them and classified patients to be moderate to high risk of fasting. However, recent guidelines released in 2016 by IDF in collaboration with Diabetes and Ramadan (DaR) International Alliance proposed three risk categories and considered patients on 2nd generation SU, SGLT2 inhibitors, incretin-based therapy, metformin, Acarbose and basal insulin as low risk for fasting (DaR Alliance, 2016).

This change in risk stratification peruse of antidiabetic agents is a significant advance in patients with diabetes to fulfil their desire for fasting without undue fear of hypoglycemia.

We will review the currently available evidence in the following section for the use of the oral and injectable anti-diabetic therapies during Ramadan in patients with Type 2 diabetes. I will also look for studies about Ramadan fasting on a high risk of fasting, for example, people with type 1 diabetes, pregnancy, chronic kidney disease and hemodialysis.

4.2.1. Ramadan Fasting in patients with T2DM using insulin

Insulin use in patients with diabetes was considered as high risk for fasting even in patients with type 2 diabetes. This belief was due to the results of EPIDIAR study that showed severe hypoglycemia was significantly higher in insulin-treated patients during Ramadan (0.14 episodes in Ramadan versus 0.03 episode/month outside Ramadan (p 0.0174) [5]. Earlier only a few studies with crossover design were done in very low-risk patients using insulin and comparison was done with soluble insulin to insulin analogues with the aim to compare glycemic control and adverse events between the two. These studies proved a better safety profile and control of postprandial glucose excursion with the use of the insulin analogues [27,28]. These studies helped to realise health care personals that necessary adjustment in insulin doses during fasting have less adverse effects as was believed in past. This fact encouraged many researchers to do observational studies in patients on different insulin regimens in combination with various other antidiabetic agents to access the safety of fasting with insulin. A study done in Turkey by Cesur et al. (2007) observed three groups of patients who were either on glimepiride, Repaglinide or Glargine. They recorded the outcomes in the cohort patients who observed Ramadan fasting, versus those who did not fast. Authors concluded that there is no significant difference in the rate of hypoglycemia, the level of HBA1c and lipids among these three therapies and between the two groups except the degree of plasma blood glucose was higher post-Ramadan in the non-fasting group [29].

Bakiner et al. (2009) did a prospective observational study between two groups of patients who are fasting versus non-fasting and both receiving insulin glargine with Repaglinide and concluded that there is no significant difference in hypoglycemia and glycemic control was noted between them [30]. Contrary to the above findings Salti et al. (2009), showed a higher incidence of hypoglycemia during Ramadan. In their relative larger, multicentre prospective study safety of fasting, Ramadan was recorded in patients receiving glimepiride in combination with glargine. The study showed the total number of hypoglycemia increased to 346

episodes from 156 to 153 before Ramadan and after Ramadan respectively. However, only 85 patients out of 359(24.3%) experienced hypoglycemia during Ramadan, of these 45% had hypoglycemic events before Ramadan [31].

Due to the paucity of studies with the use of premixed insulin during Ramadan, Hue and colleagues (2010) did an observational study in patients on Mixtard 30. They wanted to assess the effect of premixed insulin analogue, i.e. Humalog Mix 50 that has a high proportion of rapid-acting insulin compared to Mixtard 30, at sunset as a larger meal at that time is associated with greater glucose excursion. They took 52 patients, divided into two groups of 26 patients each, group 1 on Mixtard 30 at before sunrise and Humalog Mix 50 at sunset, while group 2 on Mixtard 30 twice a day. They aimed to monitor the efficacy of insulin at postprandial glucose control without increasing the risk of hypoglycemia in both groups. Results showed the reduction of HBA1c of 0.48%($p = 0.0001$) before and after Ramadan in group 1 and 0.04 ($p = 0.81$) decrease in a mean number of hypoglycemic events compared with before Ramadan. While the group 2 experienced, an increased in mean HBA1c of 0.28%(p 0.007) and hypoglycemic events by 0.15($p = 0.43$) [32].

Due to lack of standard protocol for optimal insulin type and dose investigators did few studies to find the best regimen for patients on insulin and one study done in Indonesia to address this issue discovered that the use of premixed apart in Ramadan lead to the reduction in hypoglycemia, and weight compared to before Ramadan [33].

The only recent RCT available in this regard is by Shehada and colleagues(2015). They described that dose reduction by 40% in Levemir administered at Suhur and premixed insulin at night with active dose titration as per 4 points SMBG, is not inferior and related with significant less hypoglycemia than standard care (4.8% versus 21.4% $p < 0.001$).While exploring this new regimen, they also discovered that frequency of breaking fast is less in patients on the intervention group ($n = 124$) than controlled group($n = 114$) 7.2% versus 21.4% respectively [34].

Recently with the launch of insulin Degludec, a study done by Kalra and colleagues on a very small number of patients in India. They performed this study in a real-world setting, where six patients were either switched from their premixed insulin to insulin Degludec and insulin Degludec and Aspart (IDegAsp) or changed the time of administration of IDegAsp at the onset of the Ramadan. This group was unable to complete more than 15 days of fasting in Ramadan in previous Ramadan due to hypoglycemia on premixed insulin or SU based regimen. All of these subjects received their Ramadan education and have close surveillance throughout the Ramadan and dose were titrated to keep blood glucose on target. Results at the end of the study showed none of the patient's had severe hypoglycemia, there were three episodes of confirmed hypoglycemia during the non-fasting period, and three patients reported 11 episodes of subjective hypoglycemia but not requiring checking of blood glucose or breaking their fast. Individuals on IDegAsp experienced total 1.6 kg of total weight gain and all patients experienced fulfilling fasting experience [35] (see Table 1).

The value of Ramadan related education and empowerment is very well studied in the most recent study from Egypt showed fulfilling and safe fasting in patients on even MDI therapy after receiving diabetic self-management education session(DSME) before Ramadan [24]. Among 16 participants on MDI and received this program, showed that mean hypoglycemia events got better during Ramadan compared to before (1.4 ± 0.5 versus 3 ± 1.04 respectively. Six subjects experienced hypoglycemic events without any comparable difference in HBA1c and fructosamine with patients without hypoglycemia (Table 2).

Another study from Jordan assessed 301 T2DM patients, looking basically into the incidences of Diabetic ketoacidosis (DKA), the hyperosmolar non-ketotic state and the hypoglycemia during Ramadan, compared within the preceding month. Patients were segregated according to their pre-Ramadan medication profile into four groups, group A (metformin, sulfonylurea [glimepiride] and insulin); group B (metformin and sulfonylurea [glimepiride]); group C (metformin and insulin); and group D (insulin alone). Doses of the pre-Ramadan medications were adjusted into 75% for sulfonylureas, 75% for glargine, 75% for premixed insulin 70/30 in two doses, and 75% for regular insulin. Metformin was adjusted to a twice-daily regimen. The hypoglycemia rate was lower in all groups during Ramadan compared to Pre-Ramadan period. Interestingly, this was associated with a little increment of HbA1c in the non-insulin groups (A and B), while it got better in the insulin groups (C and D). No cases of DKA or NKHS were reported during the study period in any of the treatment groups [36].

More recently, a study Patients who were on basal, pre- or self-mixed insulin ± oral antidiabetic drugs for ≥90 days were randomised (1:1) to IDegAsp twice daily (BID) or BIAsp 30 BID. The insulin doses were reduced by thirty to fifty per cent for the pre-dawn meal (Suhur) on the first day of Ramadan and readjusted to the pre-Ramadan levels at the end of Ramadan. Despite the reduction in the insulin doses, the glycemic control was maintained until after Ramadan. Both hypoglycemia and the nocturnal was significantly lower in the IDegAsp arm compared within the BIAsp 30 arm. There were five serious adverse events in the IDegAsp arm and three in the BIAsp 30 arm. One death was reported during the study, but the cause of death was undetermined and could not have been related to the treatment [37].

4.2.2. Ramadan Fasting in patients with type 2 diabetes using secretagogues {Sulfonylurea (SU) and Repaglinide}

Secretagogues are the agents that work by glucose independent releases of insulin from the pancreas. This class was traditionally used after metformin before the discovery of newer antidiabetic agent. So plenty of studies were done before to observed their effect during fasting in Ramadan using Sulfonylurea and Repaglinide either alone or in comparison with each other [38–40]. Prior studies yield that first-generation SU, e.g. Glibenclamide was associated with a high incidence of hypoglycemia despite a reduction in dose during Ramadan fasting due to its longer duration of action and high affinity for its binding receptors [41].

Due to the results of these earlier studies, many researchers than observed the comparative safety among old and second-generation SU or SU with insulin.

Cesur et al. (2007), in a small group of patients from Turkey, checked the relative safety and efficacy of Repaglinide, glimepiride and insulin given separately. They concluded that there is no significant difference in either group regarding the risk of hypoglycemia or glycemic change [42]. A later study by Salti et al. (2009) further observed that insulin could be combined with glimepiride if the insulin dose is titrated and SU is taken at the time of breaking fast [31].

A similar study from Turkey in 2009, assessed two groups; low-risk patients with type 2 diabetes who insisted on fasting, and a control group of similar patients who were not observing fast. Both groups were on insulin Glargine and Repaglinide and did not differ in gender, systolic and diastolic blood pressure, fasting blood glucose (FBS), Postprandial plasma blood glucose(PBG) and fructosamine level. Fasting group was older of age. Results showed that fasting and non -fasting groups had no minor or significant hypoglycemia event and a difference in glycemic control [30]. To find the optimal timings for sulfonylurea administration, Zargar et al. (2010) performed a study on 145 males with type 2 diabetes, well controlled on Gliclazide MR monotherapy. All the patients safely

Table 1
Categories of risk in patients with type 1 or type 2 diabetes who fast during Ramadan.

Very high risk (MUST NOT fast)
One or more of the following: • Severe hypoglycaemia within the 3 months prior to Ramadan • Unexplained DKA within the 3 months prior to Ramadan • Hyperosmolar hyperglycaemic coma within the 3 months prior to • Ramadan • History of recurrent hypoglycaemia • History of hypoglycaemia unawareness • Poorly controlled T1DM • Acute illness • Pregnancy in pre-existing diabetes or GDM treated with insulin or SUs • Chronic dialysis or CKD stage 4 & 5 • Advanced macrovascular complications • Old age with ill health
High risk (Should NOT fast)
• One or more of the following: • T2DM with sustained poor glycaemic control • Well-controlled T1DM • Well-controlled T2DM on MDI or mixed insulin • Pregnant T2DM or GDM controlled by diet only or metformin • CKD stage 3 • Stable macrovascular complications • Patients with comorbid conditions that present additional risk factors • People with diabetes performing intense physical labour • Treatment with drugs that may affect cognitive function
Moderate risk (Decision to use a license not to fast based on the discretion of medical opinion and ability of the individual to tolerate fast)
Well-controlled T2DM treated with one or more of the following: • Lifestyle therapy • Metformin • Acarbose • Thiazolidinediones • Second-generation SUs • Incretin-based therapy (DPP-4 inhibitors or GLP-1 RAs) • SGLT2 inhibitors • Basal insulin

switch their pre-Ramadan morning time dose of Gliclazide MR, and during Ramadan started taking it at night with-out excessive hypoglycemia and better lipid profile at the end of the study [43].

An observational non-randomised study comparing the difference between different SU was conducted in 5 countries in 2011 [44]. The study aimed to compare the hypoglycemia in subjects taking Glibenclamide, glimepiride and Gliclazide. The study showed that out of 1378 patients 271 had one or more symptomatic hypoglycemia events during Ramadan. The highest rate of severe hypoglycemia (6.7%) was noticed in Glibenclamide users. The overall frequency of hypoglycemia was variable among different SU, with hypoglycemia indices of 25.6%, 16.8% and 14.0% in individuals treated with Glibenclamide, glimepiride and Gliclazide respectively (Table 3).

With the advent of newer antidiabetic agents in the last decade, many recent studies were performed to compare the relative safety of SU with the more modern antidiabetic agents, e.g. DPP4 inhibitors, GLP 1 agonist and SGLT 2 inhibitors. The detailed description is covered in the following subsections (Tables 4–6).

4.2.3. Ramadan fasting and DPP4 inhibitors

DPP4 inhibitors are oral ADA that works through the glucose-dependent release of insulin and thus considered to carry a low risk of hypoglycemia even in fasting state [45]. Since the last IDF guideline about Ramadan and diabetes [12], the patients on DPP4 therapy were considered as a low risk of fasting without a need for dose titration and many trials were conducted for the safety of this class of antihyperglycemic agents with or without SU during Ramadan fasting.

Al-Safiri et al. (2011) conducted a prospective randomised trial in six countries and 43 clinical sites. They aimed to monitor the incidence of hypoglycemia during Ramadan with the use of Sitagliptin Versus different sulfonylurea, e.g., Glibenclamide, glimepiride and Gliclazide in patients with type 2 diabetes. The patients were randomised into two groups. Total 1066 patients were randomised, but 1021 finally completed the study.507 were from Sitagliptin and 514 from SU group. Results showed that none of the two groups had an incidence of severe hypoglycemia requiring medical assistance. Patients in the Sitagliptin group had a lower incidence of hypoglycemia (8.5%) compared to the SU group (17.9%). Besides 22 patients in Sitagliptin and 52 patients in the SU group experienced hypoglycemia at least three times during Ramadan.

Further analysis showed that patients who recorded one or more symptomatic hypoglycemia were relatively lower in the Sitagliptin group (6.7%) compared to SU (13.2%). Out of Sulfonylurea treated, 19.7% of patients were on Glibenclamide followed by glimepiride (12.4%) and then Gliclazide(6.6%). Authors also concluded that the incidence of hypoglycemia with Gliclazide was equal to Sitagliptin [46].

Aravind et al. (2012) conducted another multi-country, randomised controlled trial with Sitagliptin and SU including glimepiride, Glibenclamide and Gliclazide. Their trial also yielded the same result as Al Safri et al. (2011) that Sitagliptin has a lower incidence of hypoglycemia (3.8%) compared to all SU (7.3%). Further sub-analysis among all SU, showed that out of all SU users, Gliclazide has the minimum (1.8%), versus glimepiride(5.2%) and again Glibenclamide carried the highest risk (9.1%) of hypoglycemia in fasting [47].

Table 2
Summary of Studies Evaluating use of Insulin in T2DM − ½

Author	Drug	Type of Study	Hypoglycemia	Glycemic Changes
Cesur et al., 2007	Repaglinide, Glimepiride Glargine, three groups Control: non- fasting	Observational multicenter, Turkey no. fasting = 49 no. non- fasting = 16	HE: Fasting:12.2% Nonfasting:12.5% Between drug groups = Glimepiride:14.25 Repaglinide:11.1% Glargine:10% No difference among drug group	No difference in HBA1c & Fructosamine among three drugs high fructosamine in both control and fasting group.
Salti et al., 2009	Glargine combined with, glimepiride	observational, multicounty, n = 359	HE = Before Ramadan:156 During: 346 After: 153	Improved during titration phase than static
Bakiner et al., 2009	Glargine combined with repaglinide	observational Turkey no. fasting = 7 Control = 7	HE: No minor or major event recorded	No difference in both groups
Hue et al. 2010	Group1: mixtard 30 suhoor & Humalog mix 50 at iftar Group2: Mixtard 30 BD	Observational UK No = 52	HE = Group1: 0.04% Group2: +0.15%	Change in HBA1c Group1: 0.48% Group2: +0.28%
Soewondo et al., 2009	Premixed insulin analogues Aspart	Observational, Indonesia No = 152	HE No change from BL to end o f the study	Improved

Summary of Studies Evaluating use of Insulin in T2DM − 2/2

Author	Drug	Type of Study	Hypoglycemia	Glycemic Changes
Shahada et al., 2015	Intervention group: Insulin detemir at suhoor and premixed insulin Aspart70 at dinner Control: standard care	Open-label RCT Israel No = 238 Intervention: 124 Control:114	HE (<70 mg/dl) Intervention:4.8% Control: 24% P < 0.001	HBA1C: Intervention: −0.26% Control: 0.29% Fructosamine: Intervention: −168 Control: −195
Kalra et al., 2016	Patients switched from premixed and NPH to IDegAsp or IDeg	Observational, India, single centre No = 6	No severe hypoglycemia Three patients with 11 episodes of s ymptomatic HE	NR
Eid et al., 2017	Patients on MDI received DSME	Observational, Egypt, Single centre No = 16	HE Pre-Ramadan:3 ± 1.04% Ramadan:1.4 ± 0.5%	No change in HBA1c, Fructosamine 10% reduced after Ramadan
Beano AM et al., 2017	Four groups according to their medication regimen: group A (metformin, sulfonylurea [glimepiride] and insulin); group B (metformin and sulfonylurea [glimepiride]); group C (metformin and insulin); and group D (insulin alone)	prospective, observational, open-label study. Jordan, No. = 301	Hypoglycemia occurred only in group C (Insulin + Metformin) during Ramadan.	No cases of DKA or NKHS were reported.
Hassanein et al., 2018	Patients who were on basal, pre- or self-mixed insulin ± oral antidiabetic drugs for ≥90 days were Randomised (1:1) to IDegAsp twice daily (BID) or BIAsp 3 0 BID. insulin doses were reduced by 30–50% for the pre-dawn meal (Suhur) on the first day of Ramadan, and readjusted to the pre-Ramadan levels at the end of Ramadan	multinational, randomised, treat-to-target trial. Algeria, India, Lebanon, Malaysia and South Africa No. = 263	Both hypoglycemia and the nocturnal was significantly lower in the IDegAsp arm compared within the BIAsp 30 arm	The hba1c reduction was −0.2% in IDegAsp and −0.2% in BIAsp group. Similarly, no change in the Fructosamine.

BG, blood glucose; HE: Hypoglycemic Events, BL, baseline; SU, sulphonylurea, IDegAsp, insulin degludec and aspart, MDI multi-dose insulin, BP blood pressure HbA1c, glycated hemoglobin, RCT:Randomised Controlled Trial, n, number of patients included in the study; NR, not reported; DSME, Diabetes Self- Management Education; UAE, United Arab Emirates; UK, United Kingdom.

Table 3
Summary of studies about secretagogues in T2DM during Ramadan.

Author	Drug	Type of Study	Hypoglycemia	Glycemic Changes	Other Observations
Cesur et al., 2007	Repaglinide, Glimepiride Glargine, three groups	Observational Single centre, Turkey No: fasting = 49 Control, non-fasting = 16	No difference among drug group	No difference in HBA1c AND Fructosamine among three drugs, high fructosamine in both control and fasting group.	No change in lipid profile
Salti et al., 2009	Glargine combined with, glimepiride	Observational, multicounty, n = 412	HE: Increased during Ramadan 346 Events	Improved during titration phase than static	Hypoglycemia more common in patient with low BMI and waist circumference
Bakiner et al., 2009	Glargine combined with repaglinide	Observational, turkey no. fasting = 7 Control = 7	No minor or major event recorded	No difference in both groups	No change in weight or BP
Zargar et al., 2010	Extended-release Gliclazide Switched from evening to morning during Ramadan	Observational Multi-country Pakistan, India Bangladesh N = 145 all males	HE before, during and after Ramadan: 5->3->3 p 0.16	Change in FPG (mmol/L) before, during and after Ramadan: 6.6 ± 0.7-> 6.3 ± 0.9->6.6± ->1.0 Change in FPG before and after Ramadan: 7.6%->6.8%	Improved lipid profile. Mildly increased weight
Aravind et al., 2011	Glibenclamide, gliclazide, & glimepiride	Observation, multi-country n = 1378	High incidence of hypoglycemia during fasting rate of hypo varies 25.6%, 16.8% and 14.0% among glibenclamide, glimepiride and gliclazide respectively.	NR	Higher incidence of hypoglycemia in Israel followed (40%) followed by those from Malaysia (24%), the UAE (18%), India (13%), and Saudi Arabia (10%).

BG, blood glucose; HE: Hypoglycemic Events, BL, baseline; SU, FPG, Fasting Plasma Glucose, sulphonylurea, HbA1c, glycated haemoglobin; n, number of patients included in the study; NR, not reported;; UAE, United Arab Emirates;
UK, United Kingdom, RCT, Randomised controlled trial.

Table 4
Summary of Studies evaluating the use of DPP4 Inhibitors in T2DM in Ramadan Fasting 1/3.

Author	Drug	Type of Study	Hypoglycemia	Glycemic Changes	Other Observations
Al Safiri et al., 2011	Sitagliptin compared with SU e.g. Glibenclamide, glimepiride, gliclazide	RCT multicenter, multi-country n = 1021 SITAGLIPTIN = 507 SU = 514	The hypoglycemia incidence was 6.7% with sitagliptin and 13.2% with sulphonylurea P < 0.001	NR	Symptomatic hypoglycemia glibenclamide had the highest incidence (9.1%) followed by glimepiride (5.2%)and then gliclazide (1.8%)
Aravind et al. 2012	Sitagliptin compared with SU e.g. Glibenclamide, glimepiride, gliclazide	RCT, in 2 centres n = 848 SITAGLIPTIN = 421 SU = 427	Symptomatic hypoglycemia sitagliptin (3.8%) compared to sulfonylurea (7.3).	NR	Symptomatic hypoglycemia was recorded more in SU (13.2%) than sitagliptin (6.6%), and out of all SU, glibenclamide had highest incidence(19.7%) followed by glimepiride (12.4%)and then gliclazide (6.6%)
Hassanein et al., 2014	Vildagliptin with or without metformin compared with gliclazide	double-blind RCT No = 557 Vildagliptin gliclazide	Hypoglycemia (<3.9 mmol/L) = vildagliptin 3.0% Gliclazide7.0% P = 0.039	HBA1C = 0.05% ± 0.04% with vildagliptin and −0.03% ± 0.04% with gliclazide ($P = 0.165$).	the mean decrease in weight was −1.1 ± 0.2 kg ($P = 0.98$) in both groups.
Hassanein et al., 2011	Vildagliptin with or with-out metformin compared with gliclazide	Prospective cohort observation, n = 59 Vildagliptin = 23 Gliclazide = 36	With vildagliptin, there were no HEs or severe HEs, compared with 34 HEs (15 patients, 41.7%) and one severe HE with SU	Vildagliptin lowered mean HbA1c from 7.6% (SD 0.9%) at baseline to 7.2% (SD 0.7%) SU had no effect (7.2% [SD 0.6%] vs 7.3% [SD 0.7%]; mean between-group difference −0.5% [95% CI -0.9%, −0.1%], p = 0.0262).	No change in body weight in both groups. Missed doses were more frequent in the gliclazide group.

Summary of Studies evaluating the use of DPP4 Inhibitors in T2DM in Ramadan Fasting 2/3

Author	Drug	Type of Study	Hypoglycemia	Glycemic Changes	Other Observations
Al-Arouj, M 2013	Vildagliptin with or without metformin compared with SU, e.g. Glibenclamide, glimepiride, gliclazide	Prospective cohort observation Multi-country Asia and middle east n = 1315 Vildagliptin = 684 Gliclazide = 631	Hypoglycemia with vildagliptin: 5.4% SU: 19.8%	Mean HBA1c difference from baseline (p < 0.001) Vildagliptin: 0.24% SU: +0.02%	Mean difference in weight from baseline (p < 0.001) Vildagliptin: 0.76 kg SU: −0.13 kg
Devendra et al., 2009	Vildagliptin with or with-out metformin compared with gliclazide	Prospective cohort UK. Single centre observation n = 52 vildagliptin (n = 26) Gliclazide (n = 26)	Hypoglycemic events(HE) (BG < 3.5 mmol/L) Vildagliptin:7.7% Gliclazide: 61.5%	Similar HBA1c change in both groups	Mean increased in weight from baseline (p < 0.001) Vildagliptin: + 0.34 kg SU: +0.8 kg
Halimi et al., 2013 VERDI STUDY	Vildagliptin with or without metformin compared with Insulin secretagogues: IS (SU & Repaglinide)	Prospective, non-interventional study France, multi-centre N = 198 vildagliptin:120 IS: 78	Subjective hypoglycemia = Vildagliptin:34% of IS: 37% Confirmed HE = Vildagliptin: 23.5% IS:30.8% Severe episodes = vildagliptin: 1.7% IS:3.9% severe episodes and/or unscheduled medical visits due to hypoglycemia = vildagliptin:2.6% IS:10.4% (P = 0.029).	Similar in both groups	Stable in both groups adherence to drug i.e.≥5 missed-dose = vildagliptin:8.5% IS:15.4%

Summary of Studies evaluating the use of DPP4 Inhibitors in T2DM in Ramadan Fasting 3/3

Author	Drugs	Type of Study	Hypoglycemia	Glycemic Changes	Other Observations

(*continued on next page*)

Table 4 (*continued*)

Summary of Studies evaluating the use of DPP4 inhibitors in T2DM in Ramadan Fasting 3/3					
Author	Drugs	Type of Study	Hypoglycemia	Glycemic Changes	Other Observations
Malha et al., 2014	Control: SU (glimepiride/gliclazide) Intervention: Vildagliptin with or without metformin	interventional, open-label RCT Lebanon N0 = 69	HE: Vildagliptin:19 SU:26	change in HBA1c: Vildagliptin: −0.83% SU:0.96%	BMI Change from baseline = Vildagliptin: −0.7kg/m2 SU: + 0.9kg/m2 No of patients Broke their fast: SU:8 Vildagliptin:0
Shete et al., 2013	Vildagliptin with or without metformin compared with SU (Glibenclamide, gliclazide, glimepiride)	India, multi-centre, Prospective, non-interventional study No = 97 Vildagliptin:55; SU:42	HE: Vildagliptin:0 SU:4.8%	change in HBA1c: Vildagliptin: −0.43% SU: + 0.01%	Mean increased in weight from baseline ($p < 0.001$) Vildagliptin: −1.2 kg SU: −0.03 k8

BG, blood glucose; HE: Hypoglycemic Events, BL, baseline; IS, Insulin Secretagogues SU, sulphonylurea, DPP4I, Dipeptidyl transferase inhibitors HbA1c, glycated hemoglobin; n, number of patients included in study; NR, not reported:; UAE, United Arab Emirates;
UK, United Kingdom, RCT Randomised controlled trial.

Another DPP4 inhibitor, Vildagliptin is the most widely studied drug among the newer class of antidiabetic agents. Many small and large observational and RCT are available with this drug in comparison with SU. Earlier small observational studies showed reassuring result during Ramadan fasting prompted the investigators to conduct the larger scale studies and even RCT in this drug.

Davendra et al. (2009) carried observational study in the UK in 52 patients noticed significant less hypoglycemic events, similar HBA1c and less weight gain in patients on Vildagliptin compared to those on Gliclazide [48].

In 2011, one small observational study by Hassanein et al. (VECTOR) done in patients on Vildagliptin (n = 23) with or without metformin. The incidence of hypoglycemia, change in weight and glycemic control were compared with the group of patients on Gliclazide (n = 36), and results showed overall a safer profile for Ramadan fasting in patients on Vildagliptin compared to Gliclazide [49].

In the STEADFAST study (2014), a multiregional, double-blinded RCT involving 557 patients with type 2 diabetes and mean baseline HBA1c 6.9%. Patients were randomised to receive either Gliclazide with metformin or Vildagliptin with metformin and were offered Ramadan focus education via many visits in office and phone visit before and during Ramadan. This study concluded that the incidence of confirmed hypoglycemia (blood glucose < 3.9mmmol) was 3.0% with Vildagliptin and 7.0% with Gliclazide and any hypoglycemia was 6.0%and 8.0% respectively. There was an insignificant change in weight and HBA1c in both groups before and after Ramadan (table). This study showed comparable safety in both groups due to a relatively lower incidence of hypoglycemia with Gliclazide compared to previous findings in other observational studies, and it was attributed to frequent contact with patient and physician, the effect of Ramadan-focused diabetic education and baseline controlled glycemic state [50].

VIRTUE (VildagliptIn expeRience compared wiTh sulphonylUreas observed during Ramadan), is a large prospective, observational study that reported Vildagliptin is associated with less incidence of study on 1315 patients from middle east and Asia also showed reassuring data like previous studies with DPP4 inhibitors [51]. Results showed less incidence of hypoglycemia (5.4% vs 19.8%) in patients treated with vildagliptin with or without metformin (n = 684) compared to SU (n = 631) respectively. This large cohort also showed a significant change in weight and HBA1c in patients treated with Vildagliptin compared to SU group (Table 4).

Later further observational studies from different countries as Lebanon [52](2014), India [53], and France [54] also reaffirmed the above findings. They also documented the Safety of Vildagliptin in Ramadan fasting regarding the lesser incidence of hypoglycemia. It may also carry the additional benefits of better glycemic and weight control than Sulfonylurea (Table 4).

4.2.4. Ramadan fasting and GLP-1 RA

This class mimics the function of endogenous incretins hormones and reduce blood glucose by glucose-dependent insulin release. It also decreases glucagon secretion, enhances glucose uptake and storage in muscles, reduces glucose production by the liver. Moreover, it delays gastric emptying and stimulating satiety centre by its central effect [55]. GLP -1 receptor agonists are considered as low risk for hypoglycemia as monotherapy but in combination with secretagogues or, insulin may have the potential for hypoglycemia [56]. This class include many approved agents, e.g. The Exenatide, Liraglutide, Albiglutide, Dulaglutide and Lixisenatide.

Out of all other GLP1 agonists, only Exenatide and Liraglutide have few RCT and observational studies available on their use during fasting in Ramadan (Table 5).

Table 5
Summary of Studies evaluating the use of GLP1 Agonists in T2DM in Ramadan Fasting.

Author	Drug	Type of Study	Hypoglycemia	Glycemic Changes	Other observations
Bravis et al. 2010	Exenatide with or without Metformin compared with SU (gliclazide)	Observational UK n = 43	HE Exenatide:0.08% Gliclazide: +53%	Not Recorded	Change in weight Exenatide: +0.12 kg (0.55) Gliclazide: + 0.68 kg (p0.01)
Azar et al., 2015	Exenatide with or without Metformin c ompared with SU	Open-label, RCT Multi-countries: Algeria, India, Israel, Lebanon, Malaysia, South Africa, UAE n = 343 Liraglutide = 171 SU = 172	Symptomatic HE from BL till end of Ramadan: Liraglutide = 2.0% SU = 11.0%(p = 0.0009)	% of patients achieving HBA1c< 7% till end of Ramadan Liraglutide: 53.9% SU: 23.5% FPG: Liraglutide: −0.18 mmol/L SU: +0.17 mmol/L	Reduction in Body weight during Ramadan: Liraglutide > SU (p = 0.0091) Reduction in Body weight: from BL to end of Ramadan: Liraglutide > SU (p < 0.0001)
Brady et al., 2014	Liraglutide with or without metformin Compared with SU (gliclazide, glipizide or glibenclamide)	Open label RCT UK, n = 99 liraglutide = 47 SU = 52	Self-reported HE (<3.9 mmol/L) Liraglutide = 25% SU = 46.2% (p < 0.0001) No severe episodes	Change in HbA1c: from BL to 3rd week in Ramadan: Liraglutide −0.54% SU -0.27% (p = 0.03) Change in HbA1c from BL to 12-week post Ramadan: Liraglutide: −0.32% SU: + 0.02% (p = 0.05)	Change in Body weight: 3 weeks post-Ramadan: Liraglutide: 2.23 kg SU: −0.42 kg (p = 0.02) 12 weeks post-Ramadan: Liraglutide: −2.57 kg SU: +0.25 kg (p = 0.002)
Khalifa et al., 2015	Liraglutide with or without Insulin &SU No control arms	Observational n = 111	HE 18 Patients (16.2%)	Change in HbA1c from BL to end of Ramadan: 8.0% vs 7.4% (p = 0.000)	NR
Hassanein et al., 2018	Lixisenatide, randomised 1:1 to receive Lixisenatide + basal insulin Vs SU + basal insulin.	RCT, Total no = 14 Lixisenatide = 92 SU = 92	≥One documented symptomatic hypoglycemia event in the Lixisenatide group 3.3% (3/91) vs 8.9% (8/90) of people in the SU group. Only one severe hypoglycemia in the SU group.	Change in HbA1c from BL to end of Ramadan in the Lixisenatide group −0.43% Vs −0.49 in the SU group	Treatment-emergent adverse events (TEAEs) for Lixisenatide vs SU, respectively, were 17.4% vs 16.3% during Ramadan. However, it was significantly higher before Ramadan in the Lixisenatide group.

BG, blood glucose; HE: Hypoglycemic Events, BL, baseline; SU, sulphonylurea, GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT 2 I, HbA1c, glycated hemoglobin; n, number of patients included in study; NR, not reported; UAE, United Arab Emirates;
UK, United Kingdom, RCT, Randomised controlled trial.

Table 6
Studies in Ramadan Fasting and SGLT2 inhibitors.

Author	Drug	Type of Study	Hypoglycemia	Glycemic Changes	Other Observations
Wan Juani et al., 2016	1:1 arms Dapagliflozin with SU Both arms with metformin	Malaysia, open-label RCT, No = 110	Symptomatic HE from BL to end: Dapagliflozin:24% > 3.4% SU: no change, p = 0.004 Documented HE Dapagliflozin:7.3% SU: 27.1% p = 0.007	HBA1c Change from BL: Dapagliflozin: 0.05% SU: 0.32%	Adverse effects dapagliflozin versus SU Postural hypotension: 13.8% Vs 5.8% UTI: 10.3% Vs 3.8% Other effects only in Dapagliflozin Polyuria &polydipsia:3.55 Dry & itchy skin: 1.7%
Mohamed Hassanein et al., 2017	1:1 arms Canagliflozin with SU Both arms with metformin ± DPP IV inhibitors	The Middle East, non-randomised, parallel-cohort, prospective, comparative, observational study	Documented HE: Canagliflozin:3.7% SU: 13.2% p = 0.009	HBA1c Change from BL: Canagliflozin: 0.04% SU: 0.2%	Adverse effects Canagliflozin versus SU: Postural hypotension: 13.8% Vs 5.8% Hypoglycemia: 2.5 Vs 10.7%UTI: 0.6% Vs 0% Other effects only in Canagliflozin Volume depletion[a]:9.3% Vs 3.8%
Shao et al., 2018		Singapore,	One hypoglycemic event during Ramadan fasting increased in the non-SGLT2i group (12.1 −20.7%, P = 0.289), but decreased in the SGLT2i group (22.9−15.4%, P = 0.687).	NA	No difference in eGFR, serum ketones between the groups

BG, blood glucose; HE: Hypoglycemic Events, BL, baseline; SU, sulphonylurea, SGLT 2 I, Sodium-Glucose Co-Transport Inhibitor, HbA1c, glycated haemoglobin; n, number of patients included in the study; UTI, Urine tract infection, RCT: Randomised Controlled trial, UAE: United Arab Emirates.

[a] Includes dehydration, postural dizziness, and hypovolemia.

Brady et al. (2014) conducted an RCT in the UK from two sites in 99 patients. They were randomised to receive Liraglutide n = 47) with metformin versus SU (n = 52, Gliclazide, Glimepiride, one patient on Glibenclamide) as mono or dual therapy. Their HBA1c, weight, lipids, blood pressure and incidence of hypoglycemia were recorded two weeks before, the 3rd week during and 12 weeks after Ramadan. Results showed that there is no severe hypoglycemia in both groups. The self -reported episodes of hypoglycemia (<3.9 mmol/L) was significantly lower in the Liraglutide group (25.0% of patients), compared to the SU group (46.2%of patients). Median 3 events per patient in the SU group while two events were reported in the Liraglutide group. The incidence rate ratio 0.29, 95% CI 0.19, 0.41, p < 0.0001.more patients in SU Similarly at 12 weeks patients on Liraglutide showed better HBA1c (−0.32% versus +0.02%) reduction in weight(−2.57 Vs + 0.25 kg), Diastolic BP than patients on SU [57].

Another recent, larger multinational open-label RCT (LIRA −RAMADAN) was done to assess the effect of Liraglutide in Ramadan compared to SU involving 343 subjects with T2DM who intend to fast. These 343 patients were on SU (Gliclazide, glipizide or glyburide/Glibenclamide) before trial and 171 patients were randomised to receive Liraglutide and 172 were continued on SU. The 33-week trial consisted of 2 weeks of screening and then dose titration over the next 3–4 weeks for Liraglutide patients, then 6–19 weeks of treatment maintenance. The treatment period during and after Ramadan was four weeks [58].

These patients received 1.8 mg of Liraglutide and maximally tolerated dose of SU. The primary outcome was to measure the serum fructosamine level, and secondary endpoints were the incidence of hypoglycemia, and achieving HBA1c <7%, change in weight, systolic and diastolic BP in both groups. Safety parameters were to monitor the frequency of hypoglycemia and treatment-related adverse effects. Severe hypoglycemia defined as the need for third-party assistance or BG < 3.1 mmol/L and Hypoglycemia was defined as blood glucose less than 3.9 mmol/L. Results showed none of the patients in either group experienced severe hypoglycemic episodes during Ramadan. Liraglutide group had no major hypoglycemic events, and they achieve target HBA1c of <7.0% (53.9%) compared with SU (23.5%) P < 0.001. However symptomatic hypoglycemic episodes were present in 3 patients on Liraglutide (2.0%), while 18 patients on SU (11.0%). Further stratification among SU showed that patients on glimepiride/Gliclazide/glipizide (n = 14/143, 9.5%) had a lower incidence of hypoglycemia than those on Glibenclamide/glyburide (n = 4/27, 14.8%), however patients on Liraglutide were more likely to have gastrointestinal side effects (10.5%) versus SU (3.7%). During Ramadan subjects on Liraglutide had a reduction in FPG (−0.18 mmol/l) relative to SU (+0.17 mmol/L). Additionally, they experienced statistically significant weight loss during Ramadan [ETD: −0.54 kg (95% CI: −0.94; −0.14); p = 0.0091].

An observational study done on 111 subjects, receiving Liraglutide 1.8 mg with other OAD drugs including SU and insulin but without a control arm in UAE. Patients were recruited before Ramadan and advised to attend Ramadan focus education and advised to keep a record of their hypoglycemia symptoms. Patients were followed during Ramadan via phone contact for their hypoglycemic symptoms. Results showed none of the patients developed severe hypoglycemia requiring emergency room visit or third party assistance.16.2% experienced hypoglycemia [59].

A recent study by Hassanein et al. evaluated the safety of Lixisenatide versus SU on a background of basal insulins. A total of 184 T2DM patients were randomised into 1:1 manner. The Primary endpoint was the percentage of people with ≥one documented symptomatic hypoglycemia event (plasma glucose ≤70 mg/dL) during the Ramadan fast, while the secondary endpoints, BI dose, and safety. Lixi group had significantly lower incidences of hypoglycemia during Ramadan 3.3% (3/91) vs 8.9% (8/90) in the SU group. Weight reduction was more in the Lixisenatide group [60].

4.2.5. Ramadan fasting and sodium glucose co-transporter 2 (SGLT2) inhibitors

Sodium-Glucose co-transporter 2 (SGLT2) inhibitors are the most recent oral ADA approved for treating diabetes. This class works on proximal convoluted tubules of kidneys and inhibits through selective inhibition of sodium glucose co-transporter to inhibits reabsorption of glucose and results in its excretion in urine [61].

This action causes a net loss of calories and also promotes weight loss. The glucose-lowering action of this class is insulin independent and thus carry less risk of causing hypoglycemia unless combined with insulin and other secretagogues [62]. The novel mechanism of action results in mild diuresis and is a concern for volume depletion especially in hot climates and during fasting for long hours. However, recent studies showed that this is risk comparable to other antidiabetic agents in such countries with hot climates [63].

Due to the potential concerns of dehydration and volume depletion exaggerating by SGLT 2 inhibitors during Ramadan fasting some investigators conducted a multi-country survey to know the physician's belief about the prescription of this class in fasting Ramadan. Most of the doctors from the Middle East and North Africa felt safe for prescribing this drug [64].

Till the time of writing this review only three published studies is available in the literature (Table 6).the first published study was an open-label randomised trial done in 119 patients [65]. Half of the patients were randomised to receive 10 mg of Dapagliflozin, and a half on SU. The primary endpoint was the incidence of any symptomatic hypoglycemia without documentation and documented hypoglycemia <3.9 mmol/L with or without hypoglycemia. Secondary outcomes were to observe any adverse events and glycemic changes during and after Ramadan in both treatment and control arms. Results showed that patient on Dapagliflozin showed the incidence of subjective symptomatic hypoglycemia at $^{\text{the fourth}}$ week of Ramadan markedly reduced compared to baseline (3.4% versus 24.1%, p 0.004). While in SU arm there is no difference. The risk of documented hypoglycemia was also significantly less in Dapagliflozin group compared to SU (7.3% versus 27.2% p 0.007). No major hypoglycemic events were recorded in either arm. Secondary endpoints showed the non-significant difference in HA1c in treatment arm 0.05%) and Control arm (0.32%) compared to baseline. Regarding adverse events only Dapagliflozin group showed higher risk of urinary tract infection and postural hypotension compared to patients in SU (13.8 vs 5.8%; p = 0.210) 10.3 vs 3.8%; p = 0.277) respectively. Following adverse events were only present in Dapagliflozin arm. Polydipsia (3.5%), polyuria (3.5%), dry and itchy skin (1.7%), and lethargy (1.7%).

Another study evaluated the safety of Ramadan fasting using Canagliflozin. The study was a non-randomised, parallel-cohort, prospective, comparative, observational study which enrolled patients who were taking canagliflozin (n = 162) or any sulphonylurea (n = 159) added to metformin ± dipeptidyl peptidase-4 inhibitor [66]. Comparing the two agents, Canagliflozin was associated with better glycemic outcome, with a higher hypoglycemia rate (adjusted odds ratio: 0.273 [95% CI: 0.104, 0.719]). Nine per cent of Canagliflozin arm reported one volume depletion event compared with 3.8% of patients treated with a sulphonylurea [66]. Another study from Singapore evaluated the effect of using SGLT2i during Ramadan and the impact on the kidney function and the ketone levels [67]. This study was a single-centre prospective observational controlled cohort study; the SGLT2i group was on

stable doses of the drugs for at least three months. The total number of patients was 68, all with eGFR >45 5 ml/min/1.73 m^2. Both groups group had a similar change in weight (LS mean change of −1.8 versus −1.1 kg, p = 0.205), eGFR (LS mean change of −6.0 versus −4.2 ml/min/1.73 m^2, p = 0.399, sitting systolic, sitting diastolic BP and plasma β-hydroxybutyrate level. The proportion of patients experiencing at least one hypoglycemic event during Ramadan fasting increased in the control group (12.1–20.7%, P = 0.289), but decreased in the study group (22.9–15.4%, P = 0.687) [67].

4.2.6. Ramadan Fasting with thiazolidinedione and acarbose

No prospective observational studies or RCT is available in Acarbose, but as with metformin due to very low risk of hypoglycemia, no dose adjustment has been suggested during fasting. For pioglitazone, only one double-blind RCT done in India. It showed significant improvement in fructosamine and less hypoglycemic events compared to placebo [68]. This particular study is outside the review timeline. However, since it was the only study in the TZD group, we just highlighted the conclusion.

5. Discussion

This review summarises the absolute importance of Ramadan-focused diabetes education. The Structured diabetes education includes the provision of knowledge about possible risks of fasting and helps them make an informed decision about their behaviour and empower them to efficiently self -manage their fast if they select for fasting. Self -management of diabetes in Ramadan means the ability to alter the dose and timings of their hypoglycemic agents, frequent self-monitoring of blood glucose as per their type of diabetes and medicines and control of diet and fluid intake with enough knowledge to break the fast when necessary [12].

The main prerequisite to spread awareness among all the health care provider, i.e. physician and diabetic nurse educator at all levels of care about this need. The recent studies showed the growing trend of pre -Ramadan assessment for patients with diabetes who intend to fast, and better outcome among those fasting patients who received and followed the advice during Ramadan [21].

Though many of these studies showed improved endpoints for the frequency of hypoglycemia, hyperglycemia and hospitalisations compared to EPIDIAR but still not all the physicians are aware of the current Ramadan and diabetes guidelines, and there is a wide gap between the knowledge and practice in this regard. Another missing part of these intervention studies is the information from economically deprived and rural parts globally as most of these studies were done in a sophisticated setup where patients were interviewed and given the best available advice [25].but whether the same situation exists around the world in all economic strata needs further exploration.

Ramadan specific intervention is more crucial compared to usual diabetes care as it involves religious sentiments and has humanitarian aspects. For most of the Muslims, this time of the year is to practice their faith, and they might not be able to relate the professional advice with their sentiments and could find it inapplicable to follow their HCP suggestion. It is vital to understand and deal with respect the religious sentiments when delivering this information to patients [69]. There is a strong need to deliver the need for pre- Ramadan assessment and specific education to their patients equally at the level of community health care [70].

It is emphasised by some researchers to incorporate the pharmacist as an also in intervening allied health care provider for Ramadan related education as they have equal or more chances for interaction with the patients and can give opportunistic advice for dose titration and safer fasting [71]. It is recommended by authors that to fill all the gaps in the delivery of the knowledge; it is crucial to upskill the community pharmacist, if possible also to involve religious leaders like Imam within the community so their participation would help to improve the barrier among patients and HCP.

There is considerable heterogeneity among the studies, for their design, baseline inclusion criteria, description of results and reporting of hypoglycemic events as some counted on self -reported events, some of the documented hypoglycemic events, the glycemic change was also variably recorded.

Though the best regimen for Ramadan fasting is still to be decided in patients with T2DM on insulin, as seen in studies that use of insulin analogues carry better risk reduction than human insulin. Basal ultra-Lente insulin-like glargine and Degludec due to their flat action are better than SU. It can be concluded from 4 prospective observational studies and RCT from different parts of the world that insulin therapy during Ramadan fasting is safer with insulin analogues compared to human insulin. Premixed insulin at the time of breaking fast gives better glycemic control as a higher proportion of rapid-acting insulin regulates the glucose excursion accompanied by high intake of carbohydrate at that point. All the patients need active dose titration and pre-Ramadan counselling to avoid hypoglycemia [72].

Most of these recent studies found the use of short-acting secretagogues like Repaglinide and Gliclazide safer than longer acting and potent SU, e.g. Glibenclamide and glimepiride [30,47].

Since the FDA approval of Sitagliptin as a first DPP4 Inhibitors in 2006 followed by many other DPP4 Inhibitors, and then GLP 1 agonist, management of diabetes is revolutionised as these agents are not only efficacious but also carry a small risk of hypoglycemia relative to conventional hypoglycemia agents available before [73].Their use is now 2nd line after diet and metformin as per all the current guidelines for diabetes management. Earlier all the studies done for Ramadan fasting were on human insulin and SU with or without metformin and as expected due to an inherent risk of hypoglycemia with these agents. Patients on these medicines are considered as high risk for fasting Ramadan, and this label was also potentially stressful for the patients and their family. Most of the Muslims are passionate to fulfil this religious obligation. Due to the regular use of these rather expensive agents, since 2009 many observational studies in Ramadan, were conducted. All of these studies were in comparison with sulfonylurea (SU). Due to encouraging data for their safety, first large RCT in DPP4 inhibitors was carried out by al. Safiri et al. on the use of Sitagliptin with the sulfonylurea, Followed by Aravind et al. where the results showed significantly less risk of hypoglycemia compared to SU. This observation is further replicated in many subsequent RCT. GLP 1 agonist is also another valuable addition in diabetes management algorithm. This class is not as widely studied in Ramadan fasting as DPP4 inhibitors, but still few RCTs [57,74], and observational studies [59] are available on Exenatide and Liraglutide. These agents were compared with SU, showed significantly less hypoglycemia, better glycemic efficacy and the additional advantage of weight loss. A recent meta-analysis for the effective and safe use of all newer antidiabetic medication in Ramadan fasting. After a careful literature review, the authors recognised these newer agents to be low risk for Ramadan fasting and require no change in dose with fasting as needed for SU and insulin [75].

Till date, only three published studies are available in SGLT 2 inhibitors and Ramadan [62–65]. Generally, the studies did not show any alarming sign of fasting while using the SGLT2i. In fact, the basic comparisons including the HbA1c, BP and weight were in favour of SGLT2 arms. Postural hypotension, dry skin and UTI were, as expected, higher in SGLT2i groups. At the same time no signs of higher risk of ketonemia, deterioration of renal parameters in those patients on SGLT2i during Ramadan [65–67]. Safety of SGLT2i is

reasonably studied, however further investigations on their use in higher risk groups are highly needed.

There is no recent study done in TZD and Acarbose, except one study for pioglitazone in 2006, that showed less hypoglycemia and better fructosamine levels. Generally, the use of these agents was considered as low risk for fasting from the beginning.

6. Conclusions

Data from the recent years proved that with proper pre-Ramadan assessment for risk categorisation, education for dietary and therapeutic modifications, self -monitoring for blood glucose and timely intervention during fast to avoid precipitation of severe hypoglycemia, and hyperglycemia, revolutionised the concept of fasting in the patients with diabetes.

Collectively over the last decade, the studies in newer antidiabetic agents included SGLT2 inhibitors, DPP4 inhibitors, GLP1 agonist, and insulin analogues has demonstrated fewer hypoglycemic episodes, and better efficacy with added potential advantage of weight loss, relative to sulfonylurea and human insulin used earlier.

The advice for fast should be individualised and consider the comorbid condition, type of medications, availability of household and medical assistance. The implication of available management guidelines in routine care of fasting patients with diabetes resulted in improved outcome compared to what was observed in EPIDIAR due to awareness among physicians and patients about fasting Ramadan fasting.

Since most of the current hypoglycemic agents are generally considered safe and effective during Ramadan fasting in lower risk diabetes patients. A step forward to assess their safety in higher risk groups are highly needed.

Conflicts of interest

Dr. Fauzia Rashid and Dr. Elamin Abdelgadir have no conflict of interest to disclose at the time of writing this document.

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