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Review Article

Guidelines for managing diabetes in Ramadan

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Abstract

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Introduction

Religious identity can significantly influence the daily practices of individuals, thus impacting on their health. In 2010, a demographic study showed that Muslims constitute 23% of the world's population, some 1.6 billion people; this number is increasing at a rate of ~ 3% each year [1]. The International Diabetes Federation estimates that in 2013 there were 382 million people living with diabetes, a number predicted to rise to 592 million by 2035. If these figures are extrapolated globally there are ~ 90 million Muslims with diabetes. Considering specifically the UK, the current number of patients with diabetes is estimated at just fewer than 3 million [2]. Diabetes affects around 10–15% of the UK Muslim population, with South Asian people having the highest rates of diabetes mellitus [3]. Recent data suggest that there are ~ 2.9 million Muslims living in the UK [4], thus ~ 400 000 British Muslims have diabetes [3].

The holy month of Ramadan forms one of the five pillars of the Muslim faith, with fasting obligatory during this month with some exceptions. The holy *Qur'an* clarifies that people with illness are exempt from fasting [5]. However, most Muslims with diabetes often do not consider themselves unwell and exempted, and are therefore keen to fast. The most extensive study to date investigating the effects of fasting in Muslim patients with diabetes is the Epidemiology of Diabetes and Ramadan (EPIDIAR) study, performed across 13 countries and involving ~ 13 000 patients. The EPIDIAR study reported that 43% of patients with Type 1 diabetes and 79% with Type 2 diabetes fast, irrespective of the advice given to them [6].

Furthermore, ~ 80% of Muslims with diabetes fast for at least 15 days [6]. Extrapolating these figures suggests that ~ 320 000 Muslims with diabetes in the UK and > 50 million Muslims globally with diabetes will fast for at least half of Ramadan [7].

Fasting in Ramadan

Fasting in Ramadan forms one of the five mandatory acts of faith in Islam. The month of Ramadan lasts 29–30 days and Muslims must abstain from eating and drinking during the daylight hours of dawn to sunset. There are no restrictions on intake outside these hours. Those fasting will take two meals per day: Suhoor (preceding dawn) and Iftar (sunset). The Islamic year follows a lunar calendar thus, Ramadan advances forward in the Gregorian calendar by 11 days every year, hence traversing the seasons over time. For non-equatorial countries in the northern hemisphere, such as the UK, the implication of this is that for the next decade, Ramadan will fall in summer. In non-equatorial countries, including the UK, daylight hours vary significantly between summer and winter months; with the length of fasts in summer being 16–20 h, compared with 7–11 h in winter. The EPIDIAR study was conducted during winter months, largely in countries within the northern hemisphere when the duration of fasts was short [6]. There are no available data regarding how many Muslims with diabetes fast in Ramadan during summertime, or the associated physiological consequences when the duration of fasting is much longer.

Two previous reviews and the American Diabetes Association's 2010 recommendations have provided guidance on the management of diabetes in Ramadan [8,9]. However, at the time of publication, there was limited information regarding the use of incretin-based therapies and newer agents, such as the sodium–glucose co-transporter 2 (SGLT-2) inhibitors, during Ramadan. With the emergence of recent randomized controlled trials, STEADFAST [10] and Treat 4 Ramadan [11], together with several observational studies [12,13] and the increasing use of these agents in people with Type 2 diabetes, newer guidance is required. Thus, we have reviewed both current evidence and expert consensus guidelines for the management of diabetes during Ramadan. Here, we present our recommendations for the optimal management of Muslim patients with diabetes who wish to fast during Ramadan.

Risks associated with fasting

In certain circumstances of ill-health, fasting can be detrimental. The *Qur'an* states that in illness, an individual is exempt from fasting. If an individual is advised by a medical professional that fasting would be potentially detrimental, then most Muslims and their religious authorities would agree that the individual should abstain from fasting [14].

The risks of fasting to patients with diabetes are principally hypoglycaemia, hyperglycaemia and dehydration, as well as an increased risk of thrombosis, occurring in association with

dehydration and hyperglycaemia [8]. These risks are greater as the length of fast increases. It is also noteworthy that Ramadan does not entail fasting only, representing instead cycles of daytime fasting and night-time re-feeding. Health concerns therefore stem from both fasting and feeding, which may lead to indulgent eating and feasting.

Hypoglycaemia

It is well recognized that with a decrease in food intake, patients with diabetes are at a higher risk of hypoglycaemic events; particularly, patients on sulfonylureas, other insulin secretagogues or insulin therapy.

Much of our current knowledge surrounding diabetes and Ramadan comes from the EPIDIAR study, which involved 12 243 patients across 13 countries [6]. Salti *et al.* found that the risk of severe hypoglycaemia, defined as hypoglycaemia leading to hospitalization, increased by 4.7-fold in Type 1 diabetes and 7.5-fold in Type 2 diabetes under fasting conditions.

By contrast, smaller studies including patients treated with oral hypoglycaemic medications or insulin have not shown a significant increase in hypoglycaemia [15]. The differences in these results may be largely attributable to differences in the classification and reporting of hypoglycaemic events, the season in which Ramadan fell in these studies and potentially the sample size.

Hyperglycaemia and diabetic ketoacidosis

One would anticipate that by decreasing food intake, individuals would be less likely to have deterioration in glucose control. In fact, the EPIDIAR study showed that during Ramadan, hospitalizations due to severe hyperglycaemia diabetic ketoacidosis increased fivefold in people with Type 2 diabetes (from 1 to 5 events/100 people/month) and in Type 1 diabetes, the incidence of severe hyperglycaemia with or without ketoacidosis increased threefold (from 5 to 17 events/100 people/month) [6]. This increased event rate appeared to be related to excessive reductions in medication doses, and in those who reported increase intake of food and/or sugar. Individuals with Type 1 diabetes were more prone to developing ketoacidosis, particularly if their glycaemic control was suboptimal prior to Ramadan [6]. There are limited data on ketoacidosis and Ramadan in those with Type 2 diabetes, however, a recent study reported no significant increase in the incidence of and mortality due to ketoacidosis for those with Type 2 diabetes fasting during Ramadan [16]. This suggests that

ketoacidosis may not present a risk for this patient population; however, more evidence is required to substantiate this. Interestingly, the authors report that the most common triggers for ketoacidosis during Ramadan was infection followed by mis-dosing [16], supporting the need for up-to-date dosing guidelines.

Dehydration

As expected, long fasts with restrictions on fluid intake will increase the risk of dehydration. This risk is greater in countries and/or seasons where fasts are longer and if hyperglycaemia is present due to osmotic diuresis [8]. Dehydration can present with a number of associated health issues, such as syncope and falls, heat exhaustion and increased blood viscosity leading to thrombosis [8,17].

Thrombosis

Hyperglycaemia and hypovolaemia contribute towards hypercoagulability, increasing the risk of thrombosis and strokes [17]. A number of studies have shown that the incidence of acute cardiac illness during Ramadan fasting was similar to that on non-fasting days [18]. Other retrospective studies suggest that thrombotic events, such as cerebral venous and sinus thrombosis may be more common in fasting diabetic patients, but by and large, the findings are inconsistent and further clarification of whether thrombotic events are truly increased during Ramadan is required [19].

Pre-Ramadan assessment: preparing your patient for Ramadan

Preparation is paramount in achieving optimal management. Therefore, a consultation before Ramadan should be made as early as possible, preferably at least 1–2 months prior to Ramadan. In areas with large Muslim populations, this may not be possible and so the pre-Ramadan assessment should be brought up at the time of the next opportune consultation, as is done routinely with preconception and diabetes [8]. Discussion should be made according to a risk assessment of fasting, see below. Table 1 summarizes recommended topics to cover in the pre-Ramadan assessment. It is imperative that the patient feels supported in their choice to fast and that their choice is respected and managed accordingly. In some centres using structured education, a group consultation can address issues surrounding Ramadan [20].

Risk stratification

Classifying patients into risk groups based on health status assists healthcare professionals, patients and religious authorities to identify individuals who should be exempted from fasting (Table 2); allowing for appropriate advice, education and informed decisions regarding fasting. There will be individuals who fast despite medical advice. As this represents personal choice, it is imperative to support those who choose to fast to ensure they do so safely.

Patient education

The National Institute for Health and Care Excellence (NICE) advocates structured education integral in the management of people with diabetes. Diabetes in Ramadan is a situation in which a structured education programme may be of great benefit [20].

In an observational study ($n = 111$), patients with Type 2 diabetes who had not received structural education and fasted during Ramadan were four times more likely to suffer from hypoglycaemia. Those who received pre-Ramadan education exhibited an ~ 50% reduction in hypoglycaemia, whilst maintaining stable glycaemic control, and lost a small amount of weight compared with weight gain in the control group [21].

A structured education programme entitled ‘A Safer Ramadan’ has been developed to support safer fasting and feasting for those with Type 2 diabetes during Ramadan, and to help patients prepare for Ramadan [22]. It comprises of three individual educational components for the patient, the community and the healthcare professional. The success of this programme, and any others like it, is largely dictated by involvement and engagement with religious leaders and respected elders within the local Muslim communities to spread awareness and support the programme.

Having religious clerics on board is important in spreading awareness and supporting those patients who should be medically exempt from fasting. In the UK, the Muslim Council of Britain is committed to this, organizing a community event educating on diabetes and Ramadan, as well as producing a recent leaflet in collaboration with Diabetes UK [23].

Blood glucose monitoring

Monitoring blood glucose levels during fasting ensures safety and patients should be reassured that this does not break their fast [24]. Patients should be provided with means to test their blood glucose, including those who normally do not test. Patients should check blood glucose levels if concerned about hypoglycaemia or if they feel unwell. Ensuring that patients can respond appropriately to self-monitoring of blood glucose levels is important. Guidance on self-monitoring of blood glucose is shown in Table 3.

Management of treatment regimes

In addition to general advice about diet, exercise and monitoring blood glucose levels, all glucose-lowering medications should be reviewed. Unsurprisingly, some medications are more likely to be associated with hypoglycaemia, which is a significant barrier to treatment adherence [25]. Studies in Ramadan have shown that patients change doses and the timing of medications without seeking medical advice [26]. In doing so, patients believe that they avoid unwanted and unpleasant effects of hypoglycaemia with the ability to continuing fasting.

Considering the potential medical complications and poor treatment adherence associated with fasting, the choices of glucose-lowering medication, dosage and timing are essential issues to address prior to Ramadan. The classes of medications are discussed in more depth below and are summarized in Table 4. It is important to bear in mind that certain classes are less likely to cause hypoglycaemia and require fewer dose adjustments, conversely others are associated with higher risks of hypoglycaemia and therefore will need dose and/or timing adjustments, or even avoidance. Table 5 summarizes the current studies investigating treatment regimes during Ramadan.

Managing patients with Type 1 diabetes

Although the general advice to patients with Type 1 diabetes is that they should not fast, evidence from the EPIDIAR study suggests 43% of patients with Type 1 diabetes do [6]. The safest way for these individuals to fast would be with a basal–bolus regime, preferably with insulin analogues and frequent blood glucose monitoring or an insulin pump.

Glargine was reviewed in a small study ($n = 15$) of relatively well-controlled patients with Type 1 diabetes who fasted for 18 h [27]. Only two episodes of hypoglycaemia and a minimal decline in mean plasma glucose (125 to 93 mg/dl; equivalent 6.9 to 5.2 mmol/l) were reported.

Another small study observed the use of glargine plus insulin lispro or aspart in nine patients with Type 1 diabetes [28]. Seven patients fasted, with five managing to fast for the whole of Ramadan. No patients reported episodes of severe hypoglycaemia or ketoacidosis requiring admission to hospital, and glycaemic control measured by HbA_{1c} remained stable at the end of Ramadan. The insulin requirement in this study group significantly decreased by 28% from baseline, hence reducing the usual insulin dose by 20–30% seems reasonable during the fasting period.

An open-label, comparative, crossover study of 64 patients with Type 1 diabetes found significantly lower postprandial glucose levels after the evening meal (Iftar) and fewer hypoglycaemic events when isophane insulin (Humulin I) was combined with insulin lispro rather than with short-acting human insulin [29].

We recommend that patients with Type 1 diabetes are generally discouraged from fasting owing to the risks of hypoglycaemia, hyperglycaemia and ketoacidosis. Should a patient choose to fast, patient familiarity with carbohydrate counting is of great assistance.

In addition, we suggest that basal long-acting insulin is reduced by 20% and taken with the evening meal (Iftar). We also suggest that patients on a basal–bolus regimen should omit the midday rapid-acting insulin whilst fasting [8]. Patients should be encouraged to test frequently throughout the fasting period.

Insulin pump

Insulin pumps deliver continuous insulin over 24 h with basal infusion rates programmed and individualized according to diet, exercise and lifestyle changes. Patients are able to deliver boluses of insulin at meal times or if hyperglycaemia occurs. This system requires frequent blood glucose monitoring but gives much flexibility to the individual, such that risks of hypoglycaemia from fasting and hyperglycaemia from feasting can be better managed. Ensuring that patients who are already on insulin pumps have full support and education will

give them skills and confidence, and may allow for safer fasting in Ramadan provided they are otherwise metabolically stable, not acutely unwell and do not suffer from any other contraindication to fasting. The limited data on insulin pumps indicate no major problems with hypoglycaemia or hyperglycaemia, showing the feasibility of fasting safely in educated and well-controlled patients with Type 1 diabetes [30]. Insulin pumps, however, are not available to many patients, are costly and may not be recommended as a specific method of managing diabetes during Ramadan, particularly as time and good preparation are required for patients to adjust pump therapy.

Managing patients with Type 2 diabetes

Diet-controlled diabetes

In patients with diabetes controlled with diet and lifestyle alone, the risks of fasting are low. There is a possibility of postprandial hyperglycaemia occurring with indulgent eating. These patients should be reminded to eat sensibly and may benefit from increasing physical activity.

Metformin

Although, to date, there are no studies examining rate of hypoglycaemia during fasting with metformin alone, the hypothetical risk of severe hypoglycaemia is low, because it increases insulin sensitivity rather than insulin secretion. Hence, patients on metformin monotherapy should be able to fast safely. Our recommendation is that the total dose of metformin over 24 h can stay the same. Should patients take a lunchtime dose, this can be taken at Iftar.

Acarbose

Acarbose inhibits the enzyme alpha-glucosidase, needed to digest and absorb glucose from ingested carbohydrates. Although there is no data in Ramadan *per se*, acarbose has a low independent risk of hypoglycaemia [31]. Hence, the dose of acarbose need not change provided it is taken with meals during Ramadan.

Short-acting insulin secretagogues (meglitinides)

Drugs in this class include repaglinide and nateglinide, and are useful due to their rapid and short action on insulin secretion. Because these drugs are insulin secretagogues, they are associated with hypoglycaemia and weight gain. A systemic review in the general population showed no difference in weight gain and the rates of hypoglycaemia when compared with sulfonylurea treatment [32]. Two Ramadan studies showed that when compared with sulfonylureas, repaglinide contributed towards improved glycaemic control with decreased hypoglycaemic events in fasting patients with Type 2 diabetes [33,34]. We suggest that meglitinides be taken with the two meals of Ramadan, but used with caution.

Sulfonylureas

Sulfonylureas act by increasing insulin release from pancreatic β -cells and thereby have an inherent risk of hypoglycaemia.

Sari *et al.* examined the effects of diet, sulfonylurea and repaglinide therapy in Ramadan, reporting only one hypoglycaemic episode in a patient taking glimepiride [34]. Another small study confirmed no significant difference in rates of hypoglycaemia between glimepiride and repaglinide [35].

GLIRA, a large prospective observational study involving 332 patients in six countries, demonstrated that the incidence of hypoglycaemia was 3% in newly diagnosed patients and 3.7% in previously treated patients, which was similar to pre- and post-Ramadan periods. Changing the timing of glimepiride from a morning dose before Ramadan to be taken at Iftar during Ramadan, did not affect the rate of hypoglycaemia or glycaemic control [36].

A more recent study ($n = 235$), identified no difference in glycaemic control between those treated with glibenclamide and those treated with repaglinide, however, the rate of hypoglycaemia was greater with glibenclamide (2.8% vs. 7.9%) [33].

Their widespread use and low cost, means that many patients with Type 2 diabetes will inevitably be taking sulfonylureas. We recommend that sulfonylureas should be used with caution in Ramadan; particularly longer-acting sulfonylureas, such as glibenclamide and

gliclazide MR, because these are more likely to induce hypoglycaemia than shorter-acting sulfonylureas. In the case of once-daily sulfonylureas, patients should switch the timing to take with the evening Iftar. In patients with a history of hypoglycaemia on sulfonylureas, the clinician should consider switching to an alternative class of glucose-lowering therapy with a lower risk of hypoglycaemia, such as dipeptidyl peptidase-4 (DPP-4) inhibitors. In those with an $HbA_{1c} < 58 \text{ mmol/mol}$ ($< 7.5\%$), a significant reduction in the dosing of their sulfonylurea might be advantageous. With shorter-acting sulfonylureas, such as gliclazide, we recommend that the morning dose with Suhoor should be reduced and the larger dose should be taken with Iftar.

Thiazolidinediones

Overall, the use of thiazolidinediones in Ramadan is thought to be safe, because their use itself is not associated with hypoglycaemia, however, they may augment the hypoglycaemia caused by other medications when used in combination, as well as cause unwanted weight gain and increase in appetite [8].

A randomized controlled trial comparing pioglitazone 30 mg with placebo in patients taking other oral hypoglycaemic agents or alone, did not find an increase in hypoglycaemic episodes during Ramadan [37]. The glucose-lowering benefits of thiazolidinediones take some 2–4 weeks to come into effect and hence are not an alternative as an immediate pre-Ramadan switch [8].

DPP-4 inhibitors

DPP-4 inhibitors increase the sensitivity of both pancreatic α - and β -cells to glucose, thus resulting in glucose-dependent secretion of insulin and glucagon. With the preservation of glucagon counter-regulation to hypoglycaemia, DPP-4 inhibitors are not independently associated with an increased risk of hypoglycaemia [38]. Therefore, they may constitute a sensible alternative for sulfonylureas in Ramadan. Among the DPP-4 inhibitors, vildagliptin has been the most studied in Ramadan.

A multi-centre prospective observational cohort study ($n = 59$) (VECTOR), assessed vildagliptin plus metformin or gliclazide plus metformin in fasting British Muslims with

Type 2 diabetes. Patients in the vildagliptin group were reported to have reduced HbA_{1c} levels without hypoglycaemia in contrast to gliclazide group [12]. Adherence to treatment with vildagliptin was better than with gliclazide; mean proportions of doses missed during fasting being 0.2% (vildagliptin) and 7.6% (gliclazide) ($P = 0.0204$). This was most likely due to better tolerability with patients having less fear of hypoglycaemia [39].

A randomized controlled trial comparing another DPP-4 inhibitor, sitagliptin with sulfonylurea treatment also confirmed the lower risk of hypoglycaemia with DPP-4 inhibitors in fasting patients with Type 2 diabetes during Ramadan [40]. In this study, results were attributed to better adherence, less-defensive eating, and/or higher baseline HbA_{1c} in patients in this cohort [61 mmol/mol (7.7%) vs. 55 mmol/mol (7.2%)] than the sulfonylurea group.

In another, larger observational study conducted over 10 countries ($n > 1300$) (VIRTUE), significantly fewer patients had hypoglycaemic events with vildagliptin compared with those taking sulfonylureas [5.4% vs. 19.8%; OR (95% CI) = 0.23 (0.16; 0.34), $P < 0.001$], with improved glycaemic control (HbA_{1c} change -0.24% vs. $+0.02\%$) and weight control (-0.76 kg vs. -0.13 kg) [13].

Consistent with these findings are the results of a recent multi-centre, randomized controlled double-blind study in 16 countries (STEADFAST) [10]. Patients ($n = 557$) with well-controlled Type 2 diabetes, previously treated with metformin and any sulfonylurea, were randomized to receive either vildagliptin or gliclazide, in addition to metformin. Patients in the vildagliptin group reported fewer hypoglycaemic events compared with the gliclazide group (3.0% vs. 7.0%). There was no significant difference in weight loss (-1.1 kg), treatment adherence or glycaemic control (HbA_{1c} $+0.05\%$ vs. -0.03%) between the groups. The number of hypoglycaemic events encountered with gliclazide treatment was lower in this study than shown previously, which may be attributed to the fact that those recruited had good glycaemic control pre-Ramadan in addition to the intensive patient–physician contact received during the trial.

There is large variability in incident hypoglycaemia with sulfonylureas between studies; 41.7% in VECTOR [12], 19.8% in VIRTUE [13] and 8.7% in STEADFAST [10], which may be due to a number of reasons including duration of fasts, pre-Ramadan counselling and education, glycaemic control of patients recruited and cultural practices of patient populations. Furthermore, the recording of hypoglycaemia is often by self-report with different definitions employed and thus is difficult to pool and/or accurately interpret.

Overall, studies with DPP-4 inhibitors in Ramadan demonstrate better tolerability and adherence, less hypoglycaemia, better glycaemic control and potentially less weight gain

compared with sulfonylureas. However, in those patients on dual therapy of DPP-4 inhibitors and sulfonylureas, and with suboptimal control [$\text{HbA}_{1c} < 58 \text{ mmol/mol}$ ($< 7.5\%$)], stopping the sulfonylurea may be challenging for glycaemic control. Therefore, we would recommend altering the medication dose and timings in these patients, as described in the sulfonylurea section above.

SGLT2 inhibitors

SGLT2 inhibitors prevent glucose absorption from the kidney, independent of insulin [41]. The risk of hypoglycaemia is low because plasma glucose levels are decreased without changing insulin secretion or inhibition of counter-regulatory responses [42]. In addition, increased renal glucose elimination may assist with weight loss due to net calorie loss [41]. The low risk of hypoglycaemia and benefits of weight reduction make this new class of glucose-lowering agents a potential candidate for use during Ramadan. However, caution must be taken because this class results in glycosuria, and hence induce osmotic diuresis. Therefore, there is a risk of dehydration, particularly in warm countries. Since these agents can also lower blood pressure, during fasting, there is a risk of postural hypotension [42].

To date, there is no available clinical evidence for their use and safety during Ramadan. Therefore, randomized controlled trials for SGLT2 inhibitors in Ramadan are required. Certainly, we would recommend that they are used with caution and patients drink at least 2 L of water a day to reduce the risk of dehydration. In addition, initiating a patient on an SGLT2 inhibitor just prior to Ramadan should be avoided.

Diabetic ketoacidosis and SGLT2 inhibitors

In May 2015, the U.S. Food and Drug Administration (FDA) announced a warning of an increased risk of diabetic ketoacidosis with atypical mild-to-moderate glucose elevations (euglycaemic diabetic ketoacidosis) associated with the use of all approved SGLT2 inhibitors [43]. Subsequently, the risk of diabetic ketoacidosis with these drugs is currently under investigation. The underlying mechanism for SGLT2 inhibitor-associated diabetic ketoacidosis has not been established.

A recent study investigated all serious adverse events of diabetic ketoacidosis and related events (ketoacidosis, metabolic acidosis and acidosis) in 17 596 patients from randomized studies of canagliflozin [44]. They reported a similar incidence of diabetic ketoacidosis in those receiving canagliflozin compared to observational data from the general population with Type 2 diabetes.

In the context of Ramadan fasting, it is not recommended that SGLT2 inhibitors are used in those with Type 1 diabetes, indeed it is not currently licensed for use in this population.

In the current climate, it may be pertinent to test for ketones in patients with Type 2 diabetes on SGLT2 inhibitors periodically throughout the fasting period. Furthermore, we would advise, as per FDA recommendations, that patients pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness [43].

Glucagon-like peptide 1 receptor agonists

Glucagon-like peptide 1 (GLP-1) receptor agonists mimic the functions of endogenous incretin by stimulating pancreatic insulin release, inhibiting the release of glucagon and slowing gastric emptying. GLP-1 agonists are considered relatively safe during Ramadan, given that they act in a glucose-dependent manner, and thus have a low hypoglycaemic profile. Because these are relatively novel therapies, few studies have reported the use of GLP-1 agonists in Ramadan.

A large randomized control trial conducted in two UK centres ($n = 99$) compared sulfonylureas with liraglutide in combination with metformin [11]. The composite end-point of achieving $\text{HbA}_{1c} < 53 \text{ mmol/mol}$ ($< 7\%$), weight reduction of 1 kg and no severe hypoglycaemia, was achieved by significantly more patients in the liraglutide group compared with the sulfonylurea group (at 3 weeks' follow-up: 38% vs. 7%, $P = 0.001$; 12 weeks' follow-up: 27% vs. 8%, $P = 0.03$). There was a significant weight reduction in the liraglutide group. This is supported by recent data from the LIRA-Ramadan study [45], in which treatment with liraglutide in combination with metformin, from baseline to the end of Ramadan, saw significantly more patients achieving the composite end point of $\text{HbA}_{1c} < 53 \text{ mmol/mol}$ ($< 7\%$) and no confirmed hypoglycaemic episodes vs. sulfonylurea ($P < 0.001$). The proportion of patients experiencing adverse events during Ramadan was similar between groups (23.7% vs. 20.9%); the commonest side effects with GLP-1 agonists are gastrointestinal, including nausea, diarrhoea and abdominal pain. This aside, these studies suggest that GLP-1 agonists compared with sulfonylureas appear to be safe and well-tolerated during Ramadan, however, further studies investigating GLP-1 agonists in Ramadan are required.

Insulin

Patients with Type 2 diabetes on insulin, especially the elderly, are at higher risks of hypoglycaemia than those individuals on metformin [8]. Therefore, insulin doses should be adjusted and individualized during Ramadan.

Other studies in Ramadan have investigated the safety and use of mixed insulins. A randomized, open labelled, crossover study compared Humalog Mix25 (25% short-acting insulin lispro and 75% intermediate-acting neutral lispro protamine) and Humulin M3 (human insulin 30% soluble, 70% isophane) using identical doses. In those taking Humalog Mix25 (less short-acting insulin preparation) postprandial blood glucose was significantly better controlled, together with significantly better daily average glucose levels [46]. Although both preparations have similar weight gain and hypoglycaemic profiles, there is an increased cost associated with Humalog Mix25.

There are no studies to date investigating the safety and glycaemic control in fasting patients taking detemir, isophane insulin, such as insulatard, or the newer basal insulin analogues, such as degludec.

It is important to remember that changes to medications, particularly insulin regimes, should be individualized according to diet, exercise, baseline glycaemic control, blood glucose monitoring and occupation.

We recommend for patients well controlled on twice-daily mixed insulin that the morning dose should be taken instead with Iftar (at dusk) and half the evening dose taken with Suhoor (at dawn) [8,47].

Another strategy during Ramadan would be to use long-acting insulins, such as glargine, and short-acting insulins with the two meals of Ramadan. In this scenario, the basal insulin should be administered with the larger evening Iftar meal. Those already taking long-acting basal insulin should be advised to reduce the dose by 20% [7,47].

During fasting, human soluble insulin preparations may remain in the system for 8–12 h with a late long-lasting peak 2 h after administration. This could potentially put an individual at risk of late postprandial hypoglycaemia [49]. There is some evidence that using rapid-acting insulin analogues instead of human insulin before meals in patients with Type 2 diabetes

during Ramadan is associated with less hypoglycaemia and smaller postprandial glucose excursions [46,48].

Pregnancy

Most Muslims will agree that pregnant women with diabetes are exempt from fasting [14]. Recommendations strongly advise against fasting due to the clear maternal and fetal risks associated with poor glycaemic control in pregnancy [49]. There are no studies observing pregnant women with diabetes fasting in Ramadan.

When to break the fast

Many Muslims are resistant to the idea of breaking a fast. However, it is important to emphasize that the *Qur'an* exempts individuals when fasting adversely affects health. Patients should be made aware of the risks of fasting and the symptoms of hypoglycaemia, hyperglycaemia and dehydration, and advised on when to break their fast. Our recommendations, based on the American Diabetic Association's 2010 guidelines, are summarized in Table 3 [8]. Patients should carry on with their personal treatment for hypoglycaemia, as well as monitor blood glucose levels frequently and if they become unwell.

Smoking

Muslims must abstain from smoking during fasting hours. Therefore, Ramadan presents an opportune time for smoking cessation. A study looking at smoking cessation in British Pakistani and Bangladeshi adults, showed Ramadan had a positive impact on willingness to quit smoking [50].

Conclusion

In our experience, most people do not appreciate the implications of Ramadan fasting on their diabetes, and that these risks are greater when the fast is prolonged. If patients are provided

with good education and support, they will be able to make informed decisions about whether to fast. Central to this is the early assessment of patients with diabetes and individual risk stratification. This allows for those who are high risk to understand the hazards of fasting and the opportunity to abstain from fasting, as it is permissible from a religious point of view. Risk stratification will also aid religious authorities to appreciate those at risk of fasting. If an individual does choose to fast, they must be supported by healthcare professionals and advised how to fast safely, with adjustments made to medications as necessary.

There is still insufficient evidence available, with some data published on DPP-4 and GLP-1 analogues, but none to date on the use of SGLT2 inhibitors during Ramadan. More research, including randomized controlled trials, particularly with new and emerging therapies, is required for best medical management of diabetes during Ramadan (Table 6).

The current best practice is to ensure that patients are reviewed sufficiently well in advance, their risk of fasting is calculated and they have an individualized approach for best management. Ramadan is a great opportunity to address a healthy lifestyle with patients, by advising about healthy eating habits, smoking cessation and improving self-control, which is central to Ramadan.

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Competing interests

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Table 1 Topics to be covered in the pre-Ramadan medical assessment

Topic	Notes
Full annual review	This should include blood pressure, and checking for diabetic complications involving feet and eyes.
Investigations	Bloods (HbA _{1c} , lipid profile, renal function) and urinary albumin to creatinine ratio.
Risk stratification	Assess suitability to fast (see Table 2).
Risks of fasting	Advice about the potential risks of fasting and when to stop fasting.
Medication review	Review of all medications and alteration of medications should be made for safe fasting.
Blood glucose monitoring	Patients should be advised to monitor their blood glucose levels more frequently and be reminded that this does not break the fast.
Dietary advice	Advice regarding sensible eating and avoiding food high in fat and sugar (often eaten indulgently at Iftar). In hot climates and countries where fasting lengths are long, such as the UK, avoid dehydration, by advising that patients have good fluid intake during permissible hours. Fluids should be sugar- and caffeine-free drinks.
Exercise and Taraweeh prayers	Regular light and moderate exercise is generally considered safe. Rigorous exercise is not recommended, as this increases the risk of hypoglycaemia, especially if on insulin or oral hypoglycaemic agents. Many Muslims participate in Taraweeh prayers (nightly special prayers held in the month of Ramadan involving the repeated cycle of rising, kneeling and bowing). Often people will walk to the mosque for these prayers. These should be taken into consideration and accounted for in their exercise regime. Individuals should carry water and treatment for hypoglycaemic events, such as rapid-acting carbohydrate drinks [7].
Smoking cessation	Muslims must abstain from smoking during fasting hours and therefore Ramadan is an opportune time for smoking cessation.
Travel	It is generally accepted by most Muslims and religious scholars that an individual is exempt from fasting while travelling [5]. Should an individual choose to fast whilst travelling, general advice is the same as for not travelling. Greater care should be taken, with additional monitoring of blood glucose levels and caution of hotter climates.
Occupation and shift work	Manual work will need similar considerations as exercise.

Table 2 Categories of risk in patients with diabetes who fast during Ramadan (based on expert recommendations [7]).

High risk – advised not to fast	<p>Patients with:</p> <ul style="list-style-type: none"> • Type 1 diabetes • Poor glycaemic control, defined as $HbA_{1c} > 69$ mmol/mol ($> 8.5\%$) • Hypoglycaemic unawareness • Severe episodes of hypoglycaemia (loss of consciousness or requiring third-party assistance) in the 3 months prior to Ramadan • Recurrent episodes of hypoglycaemia in the 3 months prior to Ramadan • History of ketoacidosis in the 3 months prior to Ramadan • History of hyperosmolar hyperglycaemic coma in the 3 months prior to Ramadan • Comorbidities, including advanced macrovascular complications, renal disease, liver disease, cognitive dysfunction, uncontrolled epilepsy (particularly precipitated by hypoglycaemia) • Acute illness, including a diabetic foot infection or foot ulcer. • Pregnant women. • Those undertaking frequent intense physical labour.
Moderate risk – may fast if patient and healthcare professionals are happy, with collaboration of care between all involved	<ul style="list-style-type: none"> • Moderate glycaemic control, defined as $HbA_{1c} = 58–69$ mmol/mol ($7.5–8.5\%$) and no major complications of diabetes • Well-controlled diabetes, defined as $HbA_{1c} < 58$ mmol/mol ($< 7.5\%$) treated with sulfonylurea, short-acting insulin secretagogue, insulin or treated with a combination oral or oral and insulin treatment
Low risk – should be able to fast with advice	<ul style="list-style-type: none"> • Diet-controlled diabetes • Diabetes well-controlled with monotherapy (metformin, DPP-4 inhibitors, acarbose, glucagon-like peptide 1 agonists, sodium–glucose co-transporter 2 inhibitors or thiazolidinediones) and otherwise healthy

Table 3 Guidance on self-monitoring of blood glucose

<ul style="list-style-type: none"> • Blood glucose monitoring during fasting does not break the fast. • Monitor blood glucose levels at the beginning of the fast and then regularly every 4 h. • Blood glucose levels should be checked if any symptoms of hypoglycaemia or if the patient becomes unwell. • Patients should be aware and stop fasting if:

- there is hypoglycaemia with blood glucose < 3.9 mmol/l at any time during the fast [7];
- blood glucose levels are 3.9 mmol/l at the start of the fast and the patient is taking insulin or sulfonylureas [7];
- there is hyperglycaemia with blood glucose levels > 16.7 mmol/l [7].

Table 4 Recommendations for medical therapy changes during Ramadan (adapted from Karamat et al. [9])

Treatment prior to Ramadan	During Ramadan
Diet-controlled diabetes	Dietary advice and increase physical activity
Metformin	No change in total 24-h dose is required.
Standard preparation	
e.g. Metformin 1000 mg bd	No change is required.
e.g. Metformin 500 mg tds	If a lunch-time dose is usually taken, then this should be taken at sunset (Iftar) together with the evening dose, e.g. metformin 500 mg tds prior to Ramadan should be converted to 500 mg at predawn meal (Suhoor) and 1000 mg at sunset (Iftar).
Prolonged release preparation	
e.g. Metformin SR 1000 mg od	If patients are on metformin SR 1000 mg od, this dose should be taken at Iftar.
Thiazolidinediones	
e.g. Pioglitazone 30 mg od	No change required to dose. Caution should be to other oral hypoglycaemics taken in combination, e.g. sulfonylurea dose will need to be adjusted.
Sulfonylureas	
Short-acting sulfonylurea	Consider reducing dose of sulfonylurea for HbA _{1c} ≤ 58 mmol/mol (≤ 7.5%) or if have a history of hypoglycaemic episodes.

e.g. Gliclazide 80 mg bd	Morning dose should be halved and taken with Suhoor and evening dose can stay the same, e.g. gliclazide 80 mg at Iftar, 40 mg at Suhoor.
e.g. Gliclazide 80 mg a.m. + 40 mg p.m.	Doses should be reversed so the larger dose is taken with Iftar in the evening, e.g. gliclazide 80 mg at Iftar, 40 mg at Suhoor.
Long-acting sulfonylurea	Switch to repaglinide or short-acting sulfonylurea, if possible, otherwise dose should be taken with evening meal, Iftar, e.g. glimepiride 4 mg at Iftar.
e.g. Glimepiride 4 mg od	
Other insulin secretagogues	No change is required to dose of repaglinide and should be taken with meals.
e.g. Repaglinide 4 mg bd	
DPP-4 inhibitors	No change is required. If taken in combination with sulfonylurea, the sulfonylurea dose must be reduced and timings changed (as above)
e.g. vildagliptin 50 mg bd, sitagliptin 100 mg od, saxagliptin 5 mg od and linagliptin 5 mg od	
Sodium–glucose co-transporter 2 inhibitors	Patients should be well-established on these drugs. No change in dose is required but caution around dehydration and syncope in warm countries, as well as patients pay close attention for any signs of ketoacidosis and be provided with ketone testing kits.
e.g. dapagliflozin, canagliflozin	
Glucagon-like peptide 1 agonists	No change to doses is required. However, if there is severe nausea, reduce dose of glucagon-like peptide 1 agonist by 50%. If taken in combination with sulfonylurea, sulfonylurea dose should be reduced and timings adjusted (as above).
e.g. liraglutide 1.2 mg od, exenatide 10 µg bd, lixisenatide 20 mg od, exenatide qw.	With exenatide ensure that the duration between both the doses is > 6 h. This may be affected when duration of fast is > 18 h.
Insulin	
Long-acting (basal) insulin	Long-acting insulin dose to be reduced by 20% and taken at Iftar, e.g. glargine dose to reduce from 20 units to 16 units and take with evening Iftar meal.

e.g. Glargine 20 units od

Rapid-acting (meal-time) insulin

Omit lunch dose and take twice daily with meals at Suhoor and Iftar

e.g. Novorapid/Humalog 10 units tds with meals

e.g. Novorapid/ Humalog 10 units with Suhoor and Iftar.

Mixed insulin

Consider changing to basal bolus regime. Otherwise reverse doses so morning dose taken at Iftar and evening dose taken at Suhoor. Halve Suhoor dose.

e.g. Novomix 30 – 30 units a.m. and 20 units p.m.

e.g. Novomix 30 – 10 units at Suhoor and 30 units at Iftar.

e.g. Humalog Mix 25 – 20 units a.m. and 20 units p.m.

e.g. Humalog Mix 25 – 10 units a.m. and 20 units p.m.

e.g. Humulin M3 – 32 units a.m. and 24 units p.m.

e.g. Humulin M3 – 12 units a.m. and 32 units p.m.

Table 5 Characteristics of included studies

Author and year	Intervention		Type 1 or Type 2 diabetes	Study	N	Country	Summary of results
Hassanein 2014 [10]	Vildagliptin	Sulfonylurea	Type 2	RCT	557	Egypt, Lebanon, Tunisia, Russia, Indonesia, Germany, Jordan, Singapore, United Kingdom, Turkey, Spain, Malaysia, United Arab Emirates, Kuwait, Saudi Arabia, Denmark	Hypoglycaemia: 3% of patients taking vildagliptin reported hypoglycaemic events compared with 7% taking gliclazide (P = 0.039). Glycaemic control: There was no significant difference in HbA _{1c} . Weight: There was no difference in weight between groups.
Brady 2014 [11]	Liraglutide	Sulfonylurea	Type 2	RCT	99	United Kingdom	Hypoglycaemia: There were no episodes of severe hypoglycaemia in either group. Self-recorded episodes of blood glucose ≤ 3.9 mmol/l were significantly lower with liraglutide (P < 0.0001). Glycaemic control: More patients on liraglutide achieved a composite endpoint of HbA _{1c} 53 mmol/mol (< 7%) compared with those taking sulfonylurea. From a baseline HbA _{1c} of 61 mmol/mol (7.7%) at 12 weeks, there was no change in HbA _{1c} in the sulfonylurea group (+0.02%), whereas there was a 0.3% reduction in HbA _{1c} in the liraglutide group (P = 0.05). Weight: Significant reductions in weight were reported in patients on liraglutide compared with sulfonylureas.
Mafauzy 2002 [33]	Repaglinide	Sulfonylurea	Type 2	RCT	235	Malaysia, United Kingdom, France, Saudi Arabia,	Hypoglycaemia: The number of hypoglycaemic events was significantly lower in the repaglinide group (2.8%) than in the

						Morocco	<p>glibenclamide group (7.9%) (P = 0.001).</p> <p>Glycaemic control: Patients taking repaglinide had a significant reduction in mean serum fructosamine concentration from baseline (P < 0.05), but this was not seen with glibenclamide. There was no significant difference in HbA_{1c} between groups.</p> <p>Hypoglycaemia: There was no significant difference in hypoglycaemic events between the two groups.</p> <p>Glycaemic control: Blood glucose levels were significantly lower in the glimepiride group compared to the repaglinide group.</p> <p>Hypoglycaemia: There was no increase in hypoglycaemic events between patients taking pioglitazone compared with patients taking other oral hypoglycaemic agents.</p> <p>Hypoglycaemia: The risk of symptomatic hypoglycaemia was significantly lower in the sitagliptin group compared with the sulfonylurea group; P < 0.001.</p> <p>Hypoglycaemia: No hypoglycaemic events were reported with vildagliptin compared with 35 events (one severe) with sulfonylureas.</p> <p>Glycaemic control: Mean HbA_{1c} decreased in the vildagliptin group [from 60 mmol/mol (7.6%) to 55 mmol/mol (7.2%)] vs. no difference in sulfonylureas group; mean between-group difference P = 0.026.</p> <p>Weight: No significant difference reported.</p> <p>Other: Compliance was better with vildagliptin; mean number of missed doses 0.2 (SD 0.8) vs. 7.6 (SD 14.9).</p>
Anwar 2006 [35]	Repaglinide	Sulfonylurea	Type 2	RCT	41	Malaysia	
Vasan 2006 [37]	Pioglitazone	Placebo	Type 2	RCT	86	India	
Al-Sifri 2011 [40]	Sitagliptin	Sulfonylurea	Type 2	RCT	1021	Egypt, Israel, Jordan, Lebanon, Saudi Arabia, United Arab Emirates	
Hassanein 2011 [12]	Vildagliptin	Sulfonylurea	Type 2	OBS	59	United Kingdom	

Al-Arouj 2013 [13]	Vildagliptin	Sulfonylurea	Type 2	OBS	1315	Bangladesh, Egypt, India, Indonesia, Kuwait, Lebanon, Oman, Pakistan, Saudi Arabia, United Arab Emirates	<p>Hypoglycaemia: Significantly fewer patients experienced ≥ 1 hypoglycaemic event with vildagliptin compared with those on sulfonylureas (5.4% vs. 19.8%; $P < 0.001$); no vildagliptin-treated patients reported severe hypoglycaemia vs. 4 in sulfonylurea-treated patients ($P = 0.053$).</p> <p>Glycaemic control: Mean HbA_{1c} from baseline were improved in vildagliptin: -0.24%, SUs: $+0.02\%$ ($P < 0.001$).</p> <p>Weight: Mean body weight reductions from baseline were more significant with vildagliptin: -0.76 kg compared with SUs: -0.13 kg ($P < 0.001$).</p>
Bakiner 2009 [15]	Repaglinide plus glargine in fasting	Repaglinide plus glargine in non-fasting	Type 2	OBS	19	Turkey	<p>Hypoglycaemia: There were no reported hypoglycaemic events in either group.</p> <p>Glycaemic control: There was no difference in glycaemic control between the fasting and non-fasting groups.</p>
Mucha 2004 [27]	Glargine/rapid acting insulin in fasting	Glargine/rapid acting insulin in non-fasting	Type 1	OBS	15	United States of America	Hypoglycaemia: Only two episodes of hypoglycaemia were reported in fasting patients.
Azar 2008 [28]	Glargine/insulin lispro	Glargine/aspart	Type 1	Open- label	9	Libya	<p>Hypoglycaemia: There were no reported episodes of severe hypoglycaemia.</p> <p>Glycaemic control: HbA_{1c} remained stable.</p> <p>Other: There were no reports of ketoacidosis.</p>
Kadiri 2001 [29]	Isophane insulin (Humulin I) plus insulin lispro	Isophane insulin (Humulin I) plus short- acting human insulin	Type 1	Open- label, crossover study	64	Morocco, Kuwait, Egypt, Pakistan, Austria, United Kingdom	<p>Hypoglycaemia: The incidence and frequency of hypoglycaemic events were significantly lower with use of insulin lispro [(incidence: 23.4% vs. 48.4%; $P = 0.004$) and (frequency: 0.70 ± 0.19 vs. 2.25 ± 0.36 episodes/patient/30 days; $P < 0.001$)].</p> <p>Glycaemic control: Significantly lower postprandial blood</p>

glucose levels were noted after Iftar ($P = 0.026$) in the group taking isophane insulin plus insulin lispro, compared with isophane insulin plus short-acting human insulin.

Benbarka 2009 [30]	Insulin pump in fasting	Insulin pump in non-fasting	Type 1	OBS	63	United Arab Emirates	<p>Hypoglycaemia: Approximately half of patients reduced basal insulin by 5–50% of their pre-fasting doses. Seventeen patients had hypoglycaemia requiring breaking the fast. No severe hypoglycaemia was reported.</p> <p>Glycaemic control: Hyperglycaemia was reported in nine patients (18.4%), with only one hospital visit. Only 12 patients had fructosamine levels measured both before and immediately after Ramadan; in these patients, a reduction in fructosamine levels was reported ($P = 0.007$).</p>
Sari 2004 [34]	Repaglinide	Sulfonylurea	Type 2	OBS	52	Turkey	<p>Hypoglycaemia: Only one hypoglycaemic event was reported in a patient on glimepiride.</p> <p>Glycaemic control: There was no change in fasting plasma glucose, fructosamine, HbA_{1c} between the two groups.</p> <p>Weight: There was no reported change in body weight between groups.</p>
GLIRA study group 2005 [36]	Glimepiride		Type 2	OBS	332	Algeria, Egypt, Indonesia, Jordan, Lebanon, Malaysia	<p>Hypoglycaemia: The incidence of hypoglycaemia during Ramadan was similar to pre- and post-Ramadan periods: 3% in newly diagnosed patients and 3.7% in previously treated patients.</p>
Hui 2009 [49]	Humalog Mix 50	Human Mixtard 30	Type 2	OBS	52	United Kingdom	<p>Glycaemic control: Patients taking Humalog Mix 50 had a mean HbA_{1c} reduction of 0.48% ($P = 0.0001$) pre- and post-Ramadan, compared with an increase of 0.28% in patients</p>

Azar S Liraglutide Sulfonylurea Type 2 RCT 343 Lebanon
2015 [46]

taking Human Mixtard 30 ($P = 0.007$).

Glycaemic control: Significantly more patients treated with liraglutide achieved the composite end point of an HbA_{1c} target < 53 mmol/mol ($< 7\%$) and no confirmed hypoglycaemic events compared with those taking a sulfonylurea (53.8% vs. 23.5%, $P < 0.0001$). Overall low incidence of severe adverse events observed in both groups (1.3% liraglutide and 0% sulfonylurea).

Table 6 Areas for further research and development in this field

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- Continuous glucose monitoring-based physiological studies in fasting patients.
 - Studies demonstrating the safety of sodium–glucose co-transporter 2 inhibitors.
 - Studies regarding the safety and tolerability with glucagon-like peptide 1 analogues.
 - Further observational data on complications of fasting.
 - Further research investigating the impact of patient education in Ramadan.
 - Patient satisfaction questionnaires.
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Table 7 Further resources

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- Diabetes UK: <https://www.diabetes.org.uk/ramadan>.
Factsheet available at <http://www.mcb.org.uk/wp-content/uploads/2014/07/Ramadan-and-Diabetes-MCB-DiabetesUK-leaflet.pdf>
 - Muslim Council of Britain: <http://www.mcb.org.uk/ramadan/ramadan-and-you/>.
Factsheet available at <http://www.mcb.org.uk/wp-content/uploads/2014/06/Ramadan-and-diabetes-A-guide-for-patients-2013.pdf>
 - Apnee Sehat: www.apneesehat.com
 - DESMOND BME: www.desmond-project.org.uk/bmefoundationnewlydiagnosed-279.html
 - Facts About Fasting: www.factsaboutfasting.com
 - South Asian Health Foundation: www.sahf.org.uk
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