

# **Guidelines for managing diabetes in Ramadan**

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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 Muslims constitute 23% of the world's population, some 1.6 billion people; this number is increasing at a rate of approximately 3% each year.[1] The International Diabetes Federation estimates that in 2013 there were 382 million people living with diabetes, predicted to rise to 592 million by 2035. If these figures are extrapolated globally there are approximately 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 suggests there are approximately 2.9 million Muslims living in the UK [4] thus approximately 0.4 million British Muslims have diabetes.[3]

The holy month of Ramadan forms one of the five pillars of 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 with approximately 13,000 patients. The EPIDIAR study reported that 43% of patients with Type 1 diabetes (T1DM) and 79% with Type 2 diabetes (T2DM) fast irrespective of advice given to them.[6]

Furthermore, approximately 80% of Muslims with diabetes fast for at least 15 days.[6] Extrapolating these figures suggests that approximately 0.32 million Muslims with diabetes in the UK and more than 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 daylight hours of dawn to sunset. There are no restrictions to intake outside of 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 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 shall 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 between 16-20 hours, compared to 7-11 hours 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 is no available

data regarding how many Muslims with diabetes fast in Ramadan during summer time or the associated physiological consequences, when the duration of fasting is much longer.

Two previous reviews and the American Diabetes Associations 2010 recommendations have provided guidance in 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 SGLT-2 inhibitors in Ramadan. With emergence of recent randomised 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 management of diabetes in 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 day-time 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-recognised that with a decrease in food intake, patients with diabetes are at a higher risk of hypoglycaemic events; in particular with patients on sulphonylureas, 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 the risk of severe hypoglycaemia, defined as hypoglycaemia leading to hospitalisation, increased by 4.7-fold in T1DM and 7.5-fold in T2DM under fasting conditions.

In contrast, smaller studies, including patients treated with oral hypoglycaemic medications or insulin have not shown a significant increase in hypoglycaemia.[15] 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 (DKA)**

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, hospitalisations due to severe hyperglycaemia DKA increased 5-fold in people with T2DM (from 1 to 5 events/100 people/month) and in T1DM, the incidence of severe hyperglycaemia with or without ketoacidosis increased 3-fold (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 T1DM were more prone to developing DKA, particularly if their glycaemic control was suboptimal prior to Ramadan.[6] There is limited data on DKA and Ramadan in those with T2DM, however, a recent study reported no significant increase in the incidence and mortality of DKA for those with T2DM fasting during Ramadan.[16] This suggests DKA may not present a risk for this patient population, however more evidence is required to substantiate this. Interestingly, the authors report the commonest triggers for DKA 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 to 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 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 largely 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 one to two 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 next opportune consultation, as is done routinely with preconception and diabetes.[8] Discussion should be made according to risk assessment of fasting, see below. [Table 1](#) summarises 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 health-care professionals (HCP), 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**

NICE advocates structured education integral in the management of people with diabetes. Diabetes in Ramadan is a situation where a structured education programme may be of great benefit.[20]

In an observational study (n=111), patients with T2DM 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 approximately 50% reduction in hypoglycaemia, whilst maintaining stable glycaemic control and lost a small amount of weight compared to 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 T2DM during Ramadan, and to help patients prepare for Ramadan.[22] It comprises of three individual educational components for the patient, the community and the HCP. The success of this programme, and any other alike, are 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, by

organising 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 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 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 timing of medications without seeking medical advice.[26] Doing so, patients believe 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 choice of glucose lowering medication, dosage and timing are essential issues to address prior to Ramadan. The classes of medications is discussed in more depth below and summarised in [Table 4](#), as it is important to bear in mind that certain classes are less likely to cause hypoglycaemia and require less 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](#) summarises the current studies investigating treatment regimes in Ramadan.

### **Managing patients with type 1 diabetes**

Although the general advice to patients with T1DM is that they should not fast, evidence from the EPIDIAR study suggests 43% of patients with T1DM do.[6] The safest way for these individuals to fast would be with a basal bolus regime, preferably with insulin analogues with frequent blood glucose monitoring or an insulin pump.

Glargine was reviewed in a small study (n=15) of relatively well-controlled patients with T1DM who fasted for 18 hours.[27] Only two episodes of hypoglycaemia and a minimal decline in mean plasma glucose (125 to 93mg/dl; equivalent 6.9 to 5.2mmol/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 entire Ramadan. No patients reported episodes of severe hypoglycaemia or diabetic ketoacidosis requiring admission to hospital, and glycaemic control measured by HbA1c 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 T1DM 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 patients with T1DM are generally discouraged from fasting owing to the risks of hypoglycaemia, hyperglycaemia and diabetic 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 hours with basal infusion rates programmed and individualised 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 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 are limited indicate no major problems with hypoglycaemia nor hyperglycaemia, exhibiting the feasibility of fasting safely in educated and well-controlled patients with T1DM.[30] Insulin pumps however, are not available to many patients, are costly and may not be recommended as specific method of managing diabetes during Ramadan, particularly as time and good preparation is required for patients to adjust pump therapy.

## **Managing patients with type 2 diabetes**

### **Diet-controlled diabetes**

In patients 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, since 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 hours can stay the same. Should patients take a lunch-time 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. As 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 to sulphonylurea treatment.[32] Two Ramadan studies showed when compared to sulphonylureas, repaglinide contributed towards improved glycaemic control with decreased hypoglycaemic events in fasting patients with T2DM.[33,34] We suggest meglitinides be taken with the two meals of Ramadan, but used with caution.

### **Sulphonylureas**

Sulphonylureas act by increasing insulin release from pancreatic beta cells and thereby have an inherent risk of hypoglycaemia.

Sari et al examined the effects of diet, sulphonylurea 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 6 countries, demonstrated 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 there was 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 sulphonylureas. We recommend sulphonylureas should be used with caution in Ramadan; particularly longer-acting sulphonylureas, such as glibenclamide and gliclazide MR, as these are more likely to induce hypoglycaemia than shorter-acting sulphonylureas. In the case of once daily sulphonylureas, patients should switch the timing to take with the evening Iftar. In patients with a history of hypoglycaemia on sulphonylureas the clinician should consider a switch to an alternative class of glucose lowering therapy with a lower risk of hypoglycaemia such as DPP-IV inhibitors. In those with an HbA1c <7.5% a significant reduction in the dosing of their sulphonylurea might be advantageous. With shorter-acting sulphonylureas, such as gliclazide, we recommend the morning dose with Suhoor should be reduced and the larger dose should be taken with Iftar.

### **Thiazolidenediones**

Overall the use of thiazolidenediones in Ramadan is thought to be safe, as 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 randomised controlled trial comparing pioglitazone 30mg to placebo in patients taking other oral hypoglycaemic agents or alone, however did not find an increase in hypoglycaemic episodes during Ramadan.[37] The glucose lowering benefits of thiazolidenediones take some 2-4 weeks to come into effect and hence are not an alternative as an immediate pre-Ramadan switch.[8]

### **Dipeptidyl peptidase-4 inhibitors**

Dipeptidylpeptidase-4 (DPP-4) inhibitors increase the sensitivity of both pancreatic  $\alpha$ - and  $\beta$ -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 increased risk of hypoglycaemia.[38] Therefore, they may constitute a sensible alternative for

sulphonylureas in Ramadan. Amongst the DPP-4 inhibitors, vildagliptin has been the most studied in Ramadan.

A multi-centred prospective observational cohort study (n=59), VECTOR (Vildagliptin Experience Compared To gliclazide Observed during Ramadan) assessed vildagliptin plus metformin or gliclazide plus metformin in fasting British Muslims with T2DM. Patients in the vildagliptin group were reported to have reduced HbA1c 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 randomised controlled trial comparing another DPP-4 inhibitor, sitagliptin with sulphonylurea treatment also confirmed the lower risk of hypoglycaemia with DPP-4 inhibitors in fasting patients with T2DM during Ramadan.[40] In this study, results were attributed to better adherence, less defensive eating, and/or higher baseline HbA1c in patients in this cohort [7.7% (61mmol/mol) vs. 7.2% (55mmol/mol)] than the sulphonylurea group.

In another, larger observational study conducted over 10 countries (n>1300), VIRTUE (Vildagliptin experience compared with sulphonylureas observed during Ramadan), significantly fewer patients had hypoglycaemic events with vildagliptin compared with those taking sulphonylureas [5.4% versus 19.8%; OR (95% CI) = 0.23 (0.16; 0.34),  $p < 0.001$ ], with improved glycaemic control (HbA1c change -0.24% versus +0.02%) and weight control (-0.76kg versus -0.13kg).[13]

Consistent with these findings are the results of a recent multi-centred, randomised controlled double-blind study in 16 countries, Study Evaluating vildagliptin compared to gliclazide in patients with type 2 diabetes FASTing during Ramadan (STEADFAST).[10] Patients (n=557) with well-controlled T2DM, previously treated with metformin and any sulphonylurea, were randomised to receive either vildagliptin or gliclazide, in addition to metformin. Patients in the vildagliptin group reported fewer hypoglycaemic events compared to the gliclazide group (3.0% vs. 7.0%). There was no significant difference in weight loss (-1.1kg), treatment adherence or glycaemic control (HbA1c +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 a large variability in incident hypoglycaemia with sulphonylureas 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 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 sulphonylureas. However, in those patients on dual therapy of DPP-4 inhibitors and a sulphonylurea, stopping the sulphonylurea or those with sub-optimal control (HbA1c <7.5%), may be challenging for glycaemic control, therefore we would recommend in these patients altering the medication dose and timings, as described in the sulphonylurea section.

### **SGLT2 Inhibitors**

SGLT2-inhibitors prevent glucose absorption from the kidney, independent of insulin.[41] The risk of hypoglycaemia is low as 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 caloric 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 given 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, randomised controlled trials for SGLT2 inhibitors in Ramadan are required. Certainly, we would recommend they are used with caution and patients drink at least two-litres of water/day to reduce the risk of dehydration. In addition, initiating a patient on an SGLT2 inhibitor just prior to Ramadan should be avoided.

### **DKA and SGLT2 inhibitors**

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

A recent study investigated all serious adverse events of DKA and related events (ketoacidosis, metabolic acidosis, and acidosis) in 17,596 patients from randomized studies of canagliflozin.[44] They reported a

similar incidence of DKA in those receiving canagliflozin compared to observational data from the general population with T2DM.

In the context of Ramadan fasting, it is not recommended that SGLT2 inhibitors are used in those with T1DM, indeed it is not currently licensed for use in this population.

In the current climate, it may be pertinent to test for ketones in patients with T2DM on SGLT2 inhibitors periodically throughout the fasting period. 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 in Ramadan, given they act in a glucose-dependent manner, thus have a low hypoglycaemic profile. As these are relatively novel therapies, few studies have reported the use of GLP-1 agonists in Ramadan.

A large randomised control trial conducted in two UK centres (n=99), compared sulphonylureas with liraglutide in combination with Metformin.[11] The composite end-point of achieving HbA1c <7% (<53mmol/mol), weight reduction of ≥1kg and no severe hypoglycaemia, was achieved by significantly more patients in the liraglutide compared to the sulphonylurea 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] where treatment with liraglutide in combination with metformin, from baseline to the end of Ramadan, saw significantly more patients achieving the composite end point of HbA1c <7% and no confirmed hypoglycaemic episodes versus. sulphonylurea (p<0.001). The proportion of patients experiencing adverse events during Ramadan was similar between groups (23.7% vs. 20.9%), the commonest side effect with this class of drug appears to be gastrointestinal and includes nausea, diarrhoea, abdominal pain. Aside these studies suggests that GLP-1 agonists compared to sulphonylureas appear to be safe and well-tolerated during Ramadan, however, further studies investigating GLP-1 agonists in Ramadan are required.

## **Insulin**

Patients with T2DM on insulin, especially the elderly, are at higher risks of hypoglycaemia than those individuals on metformin.[8] Therefore insulin doses should be adjusted and individualised during Ramadan.

Other studies in Ramadan have investigated the safety and use of mixed insulins. A randomised, 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 (PPBG) was significantly better controlled, together with significantly better daily average glucose levels.[46] Whilst 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 individualised, 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 hours with a late long-lasting peak 2 hours 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 T2DM 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 foetal 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 emphasise 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 ADA 2010 guidelines, are summarised in [Table 3](#). [8] Patients should carry on their person 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 assessments 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 health-care 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-IV and GLP-1 analogues but none to date on SGLT2 inhibitors during Ramadan, more research, including RCTs 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 patients are reviewed sufficiently well in advance, their risk of fasting is calculated and then they have an individualised approach for best management. Ramadan is a great opportunity to address healthy lifestyle with patients, by advising about healthy eating habits, smoking cessation and improving self-control, which is central to Ramadan.



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

Topics	Notes
Full annual review	This should include BP, and checking for diabetic complications involving feet and eyes.
Investigations	Bloods (HbA1c, lipid profile, renal function) and urinary ACR.
Risk stratification	Assess suitability to fast (see table 2).
Risks of fasting	Advice about 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 reminded that this does not break the fast.
Dietary advice	<p>Advice regarding sensible eating and avoiding food high in fat and sugar (often eaten indulgently at Iftar).</p> <p>In hot climates and countries where fasting lengths are long, such as the UK, avoid dehydration, by advising to have good fluid intake during permissible hours.</p> <p>Fluids should be sugar- and caffeine-free drinks.</p>
Exercise and Taraweeh prayers	<p>Regular light and moderate exercise is generally considered safe.</p> <p>Rigorous exercise is not recommended, as this increases the risk of hypoglycaemia, especially if on insulin or oral hypoglycaemic agents.</p> <p>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.</p> <p>Individuals should carry water and treatment for hypoglycaemic events, such as rapid acting carbohydrate drinks.[7]</p>
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 whilst travelling, an individual is exempt from fasting.[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	Labour 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]).**

<p><b>High Risk - Advised not to fast</b></p> <p><b>Patients with:</b></p> <ul style="list-style-type: none"> <li>• Type 1 diabetes</li> <li>• Poor glycaemic control, defined as HbA1c &gt; 69mmol/mol (&gt; 8.5%)</li> <li>• Hypoglycaemic unawareness</li> <li>• Severe episodes of hypoglycaemia (loss of consciousness or requiring third party assistance) in three months prior to Ramadan</li> <li>• Recurrent episodes of hypoglycaemia in three months prior to Ramadan</li> <li>• History of diabetic ketoacidosis in the three months prior to Ramadan</li> <li>• History of hyperosmolar hyperglycaemic coma in the three months prior to Ramadan</li> <li>• Comorbidities, including advanced macrovascular complications, renal disease, liver disease, cognitive dysfunction, uncontrolled epilepsy (particularly precipitated by hypoglycaemia)</li> <li>• Acute illness, including a diabetic foot infection or foot ulcer</li> <li>• Pregnant women</li> <li>• Frequent intense physical labour</li> </ul>
<p><b>Moderate Risk – May fast if patient and health-care professionals are happy, with collaboration of care between all involved</b></p> <p><b>Patients with:</b></p> <ul style="list-style-type: none"> <li>• Moderate glycaemic control, defined as HbA1c 58 to 69mmol/mol (7.5 to 8.5%) and no major complications of diabetes</li> <li>• Well-controlled diabetes, defined as HbA1c &lt;58mmol/mol (&lt; 7.5%) treated with sulphonylurea, short-acting insulin secretagogue, insulin, or treated with a combination oral or oral and insulin treatment</li> </ul>
<p><b>Low Risk - Should be able to fast with advice</b></p> <p><b>Patients with:</b></p> <ul style="list-style-type: none"> <li>• Diet-controlled diabetes</li> <li>• Diabetes well-controlled with monotherapy (Metformin, dipeptidyl peptidase-4 inhibitors, acarbose, GLP-1 agonists, SGLT 2 or thiazolidinediones) and otherwise healthy</li> </ul>

**Table 3: Guidance on self-monitoring of blood glucose**

<ul style="list-style-type: none"> <li>• Blood glucose monitoring during fasting does not break the fast</li> <li>• Monitor blood glucose levels at the beginning of the fast and then regularly every 4 hours</li> <li>• Blood glucose levels should be checked if any symptoms of hypoglycaemia or if patients become unwell</li> <li>• Patients should be aware to stop fasting if: <ul style="list-style-type: none"> <li>○ There is hypoglycaemia with blood glucose less than 3.9mmol/l at any time in the fast [7]</li> <li>○ Blood glucose levels are 3.9mmol/l at the start of the fast and the patient is taking insulin or sulphonylureas [7]</li> <li>○ Hyperglycaemia with blood glucose levels greater than 16.7mmol/l [7]</li> </ul> </li> </ul>
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**Table 4: Recommendations for medical therapy changes during Ramadan (adapted from Karamat et al. 2010 [9])**

Treatment prior to Ramadan	During Ramadan
Diet-controlled diabetes	Dietary advice and increase physical activity
Metformin Standard preparation e.g. Metformin 1000mg bd e.g. Metformin 500mg tds  Prolonged release preparation e.g. Metformin SR 1000mg od	No change in total 24 hour dose is required.  No change is required. If a lunch-time dose is usually taken, then this should be taken at sunset (Iftar) together with the evening dose, e.g. Metformin 500mg tds prior to Ramadan should be converted to 500mg at predawn meal (Suhoor) and 1000mg at sunset (Iftar).  If patients are on Metformin SR 1000mg od, this dose should be taken at Iftar.
Thiazolidinediones e.g. Pioglitazone 30mg od	No change required to dose. Caution should be to other oral hypoglycaemics taken in combination, e.g. sulphonylurea dose will need to be adjusted.
Sulphonyureas  Short-acting sulphonylurea e.g. Gliclazide 80mg bd  e.g. Gliclazide 80mg am + 40mg pm  Long-acting sulphonylurea e.g. Glimepiride 4mg od	Consider reducing dose of sulphonylurea for HbA1c $\geq 7.5\%$ or if have a history of hypoglycaemic episodes  Morning dose should be halved and taken with Suhoor and evening dose can stay the same, e.g. Gliclazide 80mg at Iftar, 40mg at Suhoor.  Doses should be reversed so the larger dose is taken with Iftar in the evening, e.g. Gliclazide 80mg at Iftar, 40mg at Suhoor.  Switch to repaglinide or short-acting sulphonylurea, if possible, otherwise dose should be taken with evening meal, Iftar, e.g. Glimepiride 4mg at Iftar.
Other insulin secretatogogues e.g. Repaglinide 4mg bd	No change is required to dose of Repaglinide and should be taken with meals.
DPP-4 inhibitors e.g. vildagliptin 50mg bd, sitagliptin 100mg od, saxagliptin 5mg od and Linagliptin 5mg od	No change is required. If taken in combination with sulphonylurea, the sulphonylurea dose must be reduced and timings changed (as above)
SGLT2 inhibitors e.g. Dapagliflozin, Canagliflozin	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.
GLP-1 agonists e.g. Liraglutide 1.2mg od, Exenatide 10mcg bd, Lixisenatide 20mg OD, Exenatide QW.	No change to doses are required. However, if there is severe nausea, reduce dose of GLP-1 agonist by 50%. If taken in combination with sulphonylurea, sulphonylurea dose should be reduced and timings adjusted (as above).

	With Exenatide ensure that the duration between both the doses is greater than 6 hrs. This may be affected when duration fast is greater than 18 hrs.
<p>Insulin</p> <p>Long-acting (basal) insulin</p> <p>e.g. Glargine 20 units od</p> <p>Rapid-acting (meal-time) insulin</p> <p>e.g. Novorapid/Humalog 10 units tds with meals</p> <p>Mixed insulin</p> <p>e.g. Novomix 30 – 30 units am and 20 units pm</p> <p>e.g. Humalog Mix 25 – 20 units am and 20 units pm</p> <p>e.g. Humulin M3 – 32 units am and 24 units pm</p>	<p>Long-acting insulin dose to be reduced by 20% and taken at Iftar, e.g. Glargine dose to reduce from 20 units dose to 16 units and take with evening Iftar meal.</p> <p>Omit lunch dose and take twice daily with meals at Suhoor and Iftar e.g. Novorapid/ Humalog 10 units with Suhoor and Iftar</p> <p>Consider changing to basal bolus regime. Otherwise reverse doses so morning dose taken at Iftar and evening dose taken at Suhoor. Halve Suhoor dose</p> <p>e.g. Novomix 30 – 10 units at Suhoor and 30 units at Iftar</p> <p>e.g. Humalog Mix 25 – 10 units am and 20 units pm</p> <p>e.g. Humulin M3 – 12 units am and 32 units pm</p>

**Table 5: Characteristics of included studies**

Author and Year	Interventions		T1DM or T2DM	Study	N	Country	Summary of results
Hassanein 2014 [10]	Vildagliptin	Sulphonylurea	T2DM	RCT	557	Egypt, Lebanon, Tunisia, Russia, Indonesia, Germany, Jordan, Singapore, United Kingdom, Turkey, Spain, Malaysia, United Arab Emirates, Kuwait, Saudi Arabia, Denmark	<i>Hypoglycaemia:</i> 3% of patients taking vildagliptin reported hypoglycaemic events compared with 7% taking gliclazide ( $p=0.039$ ). <i>Glycaemic control:</i> There was no significant difference in HbA1c. <i>Weight:</i> There was no difference in weight between groups.
Brady 2014 [11]	Liraglutide	Sulphonylurea	T2DM	RCT	99	United Kingdom	<i>Hypoglycaemia:</i> There were no episodes of severe hypoglycaemia in either group. Self-recorded episodes of blood glucose $\leq 3.9$ mmol/l were significantly lower with liraglutide ( $p<0.0001$ ). <i>Glycaemic control:</i> More patients on liraglutide achieved a composite endpoint of HbA1c $< 7\%$ (53mmol/mol) compared with those taking sulphonylurea. From a baseline HbA1c of 7.7% (61mmol/mol), at 12 weeks there was no change in HbA1c in the sulphonylurea group ( $+0.02\%$ ), whereas there was a 0.3% reduction of HbA1c in the liraglutide group ( $p = 0.05$ ). <i>Weight:</i> Significant reductions were reported in patients on liraglutide compared with sulphonylureas.
Mafauzy 2002 [33]	Repaglinide	Sulphonylurea	T2DM	RCT	235	Malaysia, United Kingdom, France, Saudi Arabia, Morocco	<i>Hypoglycaemia:</i> The number of hypoglycaemic events was significantly lower in the repaglinide group (2.8%) than the glibenclamide group (7.9%) ( $P=0.001$ ). <i>Glycaemic control:</i> Patients taking repaglinide had a significant reduction in mean serum fructosamine concentration from baseline ( $P<0.05$ ) but not with glibenclamide. There was no significant difference in HbA1c between groups.
Anwar 2006[35]	Repaglinide	Sulphonylurea	T2DM	RCT	41	Malaysia	<i>Hypoglycaemia:</i> There was no significant difference in hypoglycaemic events between the two groups. <i>Glycaemic control:</i> Blood glucose levels were significantly lower in the glimepiride group compared to the repaglinide group.
Vasan 2006 [37]	Pioglitazone	Placebo	T2DM	RCT	86	India	<i>Hypoglycaemia:</i> There was no increase in hypoglycaemic events between patients taking pioglitazone compared to patients taking other oral hypoglycaemic agents.

Al-Sifri 2011[40]	Sitagliptin	Sulphonylurea	T2DM	RCT	1021	Egypt, Israel, Jordan, Lebanon, Saudi Arabia, United Arab Emirates	<i>Hypoglycaemia:</i> The risk of symptomatic hypoglycaemia was significantly lower in the sitagliptin group compared with the sulphonylurea group; $p < 0.001$ .
Hassanein 2011 [12]	Vildagliptin	Sulphonylurea	T2DM	OBS	59	United Kingdom	<i>Hypoglycaemia:</i> No hypoglycaemic events were reported with vildagliptin compared with 35 events (one severe) with sulphonylureas. <i>Glycaemic control:</i> Mean HbA1c decreased in the vildagliptin group [from 7.6% (60mmol/mol) to 7.2% (55mmol/mol)] vs no difference in sulphonylureas group; mean between-group difference $p = 0.026$ . <i>Weight:</i> No significant difference reported. <i>Other:</i> Compliance was better with vildagliptin; mean number of missed doses 0.2 [SD 0.8] vs 7.6 [SD 14.9].
Al-Arouj 2013[13]	Vildagliptin	Sulphonylurea	T2DM	OBS	1315	Bangladesh, Egypt, India, Indonesia, Kuwait, Lebanon, Oman, Pakistan, Saudi Arabia, United Arab Emirates	<i>Hypoglycaemia:</i> Significantly fewer patients experienced $\geq 1$ hypoglycaemic event with vildagliptin compared with those on sulphonylureas (5.4% vs. 19.8%; $p < 0.001$ ); no vildagliptin-treated patients reported severe hypoglycaemia vs. 4 in sulphonylureas treated patients ( $p = 0.053$ ). <i>Glycaemic control:</i> Mean HbA1c from baseline were improved in vildagliptin: -0.24%, SUs: +0.02% ( $p < 0.001$ ). <i>Weight:</i> Mean body weight reductions from baseline were more significant with vildagliptin: -0.76 kg compared with SUs: -0.13 kg ( $p < 0.001$ ).
Bakiner 2009 [15]	Repaglinide plus glargine in fasting	Repaglinide plus glargine in non-fasting	T2DM	OBS	19	Turkey	<i>Hypoglycaemia:</i> There were no reported hypoglycaemic events in either group. <i>Glycaemic control:</i> There was no difference in glycaemic control between the fasting and non-fasting groups.
Mucha 2004 [27]	Glargine/ Rapid acting insulin in fasting	Glargine/ Rapid acting insulin in non-fasting	T1DM	OBS	15	United States of America	<i>Hypoglycaemia:</i> Only two episodes of hypoglycaemia were reported in fasting patients.
Azar 2008 [28]	Glargine/ insulin lispro	Glargine/ aspart	T1DM	Open- label	9	Libya	<i>Hypoglycaemia:</i> There were no reported episodes of severe hypoglycaemia. <i>Glycaemic control:</i> HbA1c remained stable. <i>Other:</i> There were no reports of DKA.

Kadiri 2001 [29]	Isophane insulin (Humulin I) plus insulin lispro	Isophane insulin (Humulin I) plus short-acting human insulin	T1DM	Open-label, crossover study	64	Morocco, Kuwait, Egypt, Pakistan, Austria, United Kingdom	<i>Hypoglycaemia:</i> The incidence and frequency of hypoglycaemic events were significantly lower with use of insulin lispro [(incidence: 23.4% vs 48.4%; $p=0.004$ ) & (frequency: 0.70 +/- 0.19 vs 2.25 +/- 0.36 episodes/patient/30 days; $p<0.001$ )]. <i>Glycaemic control:</i> Significantly lower postprandial blood 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	T1DM	OBS	63	United Arab Emirates	<i>Hypoglycaemia:</i> Approximately half of patients reduced basal insulin by 5-50% of their pre-fasting doses. 17 patients had hypoglycaemia requiring breaking the fast. No severe hypoglycaemia was reported. <i>Glycaemic control:</i> 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 ( $p = 0.007$ ).
Sari 2004 [34]	Repaglinide	Sulphonylurea	T2DM	OBS	52	Turkey	<i>Hypoglycaemia:</i> Only one hypoglycaemic event was reported in a patient on glimepiride . <i>Glycaemic control:</i> There was no change in fasting plasma glucose, fructosamine, HbA1c between the two groups. <i>Weight:</i> There was no reported change in body weight between groups.
GLIRA study group 2005 [36]	Glimepiride		T2DM	OBS	332	Algeria, Egypt, Indonesia, Jordan, Lebanon, Malaysia	<i>Hypoglycaemia:</i> 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.
Hui 2009 [49]	Humalog Mix 50	Human Mixtard 30	T2DM	OBS	52	United Kingdom	<i>Glycaemic control:</i> Patients taking Humalog Mix 50 had a mean HbA1c reduction of 0.48% ( $p = 0.0001$ ) pre- and post-Ramadan, compared to an increase of 0.28% in patients taking Human Mixtard 30 ( $p = 0.007$ ).
Azar S 2015 [46]	Liraglutide	Sulphonylurea	T2DM	RCT	343	Lebanon	<i>Glycaemic control:</i> Significantly more patients treated with liraglutide achieved the composite end point of an HbA1c target $<7\%$ and no confirmed hypoglycaemic events compared to those taking a sulphonylurea (53.8% vs. 23.5%, $p<0.0001$ ). overall low incidence of severe AEs observed in both groups (1.3% liraglutide and 0% sulphylurea).

**Table 6. Areas for further research and development in this field:**

- Continuous Glucose Monitoring (CGM) based physiological studies in fasting patients
- Studies demonstrating the safety of SGLT-2 inhibitors
- Studies regarding the safety and tolerability with GLP-1 analogues
- Further observational data on complications of fasting
- Further research investigating the impact of patient education in Ramadan
- Patient satisfaction questionnaires.

**Table 7. Further resources**

- 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](http://www.apneesehat.com)
- DESMOND BME: [www.desmond-project.org.uk/bmefoundationnewlydiagnosed-279.html](http://www.desmond-project.org.uk/bmefoundationnewlydiagnosed-279.html)
- Facts About Fasting: [www.factsaboutfasting.com](http://www.factsaboutfasting.com)
- South Asian Health Foundation: [www.sahf.org.uk](http://www.sahf.org.uk)

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