

Treatment Options for Patients with Type 2 Diabetes Mellitus during the Fasting Month of Ramadan

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Abstract

During Ramadan, Muslims fast from sunrise (Sahur) to sunset (Iftar) and are required to abstain from food and fluids, including oral and injectable medications. Patients with diabetes who fast during Ramadan are at risk of developing hyperglycemia with increased risk of ketoacidosis, hypoglycemia, dehydration and thrombosis. Pre-Ramadan education and preparation of a fasting patient are essential to reduce severe complications. This review paper summarizes studies to date on oral and injectable medications available for patients with type 2 diabetes during Ramadan fasting, as well as recommendations on management of these patients during Ramadan. Although there is limited data on the use of Metformin, Acarbose and Thiazolidinedione in Ramadan, they appear to be safe. Sulphonylurea, especially Glibenclamide, is associated with higher risk of hypoglycemia during Ramadan fasting, hence may need adjustment in dosing and timing. The incretin group and SGLT2 inhibitor use during Ramadan fasting is associated with low risk of hypoglycemia with no increased adverse events. Insulin regimes need to be individualized for patients who fast during Ramadan.

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Key words: Anti-diabetic medication dose adjustment; Iftar (sunset), Muslims; Sahur (sunrise); Treatment modification

Case Study

A is a 49-year old gentleman who has type 2 diabetes (T2D), hypertension and dyslipidaemia for 8 years. His treatment for T2D are Metformin 1g b.d., Gliclazide 160mg b.d. and nocturnal s/c Insulatard 12u. His body mass index is 30.8kg/m². His latest blood results reveal HbA1c of 8.6%, fasting blood glucose 7.5mmol/L, creatinine 118umol/L. During the previous Ramadan, he experienced a few episodes of hypoglycaemia, requiring him to break his fast. He wishes to fast for this Ramadan.

Introduction

Ramadan fasting is one of the 5 pillars of Islam. The fast is between sunrise (Sahur) and sunset (Iftar), i.e.

the start of the fast is at sunrise and it ends at sunset; essentially during the period of daytime. During the fast, Muslims are required to abstain from food (including fluids), as well as oral and injectable medications. The estimated number of diabetic Muslims who choose to fast every year is close to 150 million worldwide,¹ which makes it one of the most challenging conditions to manage.

Prolonged fasting in a patient with T2D is associated with increased medical risks, especially hyperglycaemia, hypoglycaemia, dehydration and thrombosis. Nevertheless, despite these risks and the fact that patients with T2D are exempted from fasting, the majority of Muslim diabetic patients still choose to

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fast during Ramadan. The EPIDIAR and CREED studies indicated that 80–90% of Muslims with T2D fasted more than 15 days, with up to two-thirds of the participants fasting every day during Ramadan.^{2,3}

Pre-Ramadan preparations and education

Fasting during Ramadan is important to Muslims as it is a deeply spiritual experience, allowing them to devote themselves to their faith. Besides, it is also shown to confer metabolic and glycaemic benefits.⁴ It can be practised safely with early preparations, advice, guidance, and effective pre-Ramadan education.⁵ It has been shown that patients who did not receive adequate education prior to Ramadan had an increased risk of hypoglycaemia during fasting compared to those who did.⁶

One of the key components in a Ramadan-focused educational program is to quantify and stratify the patients' risks if they choose to fast (Table 1). In A's case, illustrated above, the experience of prior hypoglycaemia episodes during previous fasting and HbA1c of 8.6% put him in the high-risk category, and he should be advised against fasting. Generally, risk stratification is based on several factors. Among these are the presence of concomitant comorbidities or diabetes-related complications such as renal failure, and patient's hypoglycaemia risk. These factors may increase adverse events during Ramadan and high-risk patients are strongly advised against prolonged fasting.⁵

However, the patients' wish to fast must be respected, hence the importance of a more structured Ramadan-focused care and support for them. A should be advised to monitor his blood glucose more regularly, and to look out for hypoglycaemic symptoms, as illustrated in Table 2. He should be advised to take plenty of non-caloric fluids during the non-fasting period to avoid dehydration and thrombosis. He should also adhere to standard dietary advice, such as avoiding sugary desserts and not skipping meals during Sahur (sunrise). Light to moderate intensity exercises are encouraged on a regular basis, and should be performed preferably 1–2 hours post-Iftar (sunset).⁷ Very importantly, A should be educated on the symptoms of hypoglycaemia, hyperglycaemia, dehydration, when to break the fast, and the management of acute complications.

It is important to note that most medications that the patients are on, prior to Ramadan, can be continued with safely or have their dosages adjusted during Ramadan. Nevertheless, a few newer agents may have less potential for hypoglycaemia and be beneficial to patients during Ramadan. We present here a summary of studies, to date, on the available oral and injectable medications for patients with T2D.

Oral Anti-diabetic agents (OAD)

Metformin

Metformin, which reduces hepatic gluconeogenesis, is the first line agent for patients with T2D, and should

Table 1. Risk Stratification of Patients with Type 2 Diabetes Prior to Ramadan Fasting (Adapted with permission from Practical Guide to Diabetes Management in Ramadan⁷)

Risk category	Examples	Advice
Very high risk	History of severe diabetes complications (within 3 months of fasting) eg DKA, HHS, and severe hypoglycaemia, Hypoglycaemia unawareness Acute illness Sustained HbA1c > 9% Pregnant Advanced renal failure or on dialysis	Must not fast
High risk	HbA1c 7.5–9.0% Moderate renal failure or chronic kidney disease stage 3 Advanced macrovascular complications Living alone and treated with insulin or insulin secretagogue Presence of comorbid conditions that add on to risks Old age with ill health Treated with drugs that affect mentation	Should not fast
Moderate risk	Well-controlled diabetes on short-acting insulin secretagogues	Can fast but adhere to medical advice
Low risk	Well-controlled diabetes treated with lifestyle therapy or metformin, acarbose, thiazolidinediones, incretin-based therapies in otherwise healthy patients	Can fast but adhere to medical advice

Table 2. Home Glucose Monitoring Guide Among Patients with Type 2 Diabetes Who Fast During Ramadan (Adapted with permission from Practical Guide to Diabetes Management in Ramadan⁷)

Time	Reflection of insulin	Very high risk/high risk	Moderate/low risk
Pre-sahur (sunrise)	Pre-iftar (sunset)/pre-bed	√	√
2 hours post-sahur (sunrise)	Pre-sahur (sunrise)	√	
Mid-day	Pre-sahur (sunrise)	√	√
Pre-iftar (sunset)	Pre-sahur (sunrise)	√	√
2 hours post-iftar (sunset)	Pre-iftar (sunset)	√	
Hypoglycaemic symptoms		√	√

be duly prescribed, unless it is contraindicated. Unfortunately, there are no randomised controlled trials (RCT) looking at the effect of Metformin monotherapy during Ramadan. There are, however, studies of Metformin in combination with dipeptidyl peptidase 4 (DPP-4) inhibitors and sodium-glucose co-transporter 2 (SGLT2) inhibitors, which have shown low hypoglycaemic risks, good HbA1c reduction, no increased adverse events and better weight control, compared to the combination of Metformin with Sulphonylureas (SU).^{8–14}

Alpha-glucosidase Inhibitor (AGI)

AGI acts by reducing or delaying carbohydrate digestion by competitive alpha-glucosidase enzyme inhibition at the brush border of gut epithelium, without stimulating insulin release. There are no RCTs available on the effect of AGI during Ramadan. However, in a non-fasting group, it is associated with low hypoglycaemic risks with the added benefit of mild weight loss, absent cardiovascular sequelae with modest HbA1c reduction of 0.4–0.6%.^{15–19} It may, however, be limited by its gastrointestinal side effects, especially after a heavy carbohydrate intake seen during the breaking of fast.^{20–22} On the other hand, the twice-daily dosing during Ramadan (with the omission of lunch dose) may reduce its gastrointestinal side effects, which are dose-dependent.

Thiazolidinedione (TZD)

This class of drug is an insulin sensitiser, which acts by increasing glucose absorption into the adipose tissue and muscle, plus decreasing gluconeogenesis in the liver. Pioglitazone is the most widely-approved and used TZD in patients with T2D at the moment.²³ There is only

1 study that looked at the effect of this drug during Ramadan, which showed no significant difference in hypoglycaemic episodes between the 2 arms.²⁴ Pioglitazone showed better glycaemic control throughout the study period, as evidenced by the lower stable fructosamine values. However, pioglitazone users experienced more weight gain and oedema (mean weight gain 3.02 kg, $P = 0.001$), compared to those who received placebo.

Insulin Secretagogue

SU and Metglinides act by stimulating the pancreatic β -cells to produce insulin in a glucose-independent manner, and hence are associated with higher risks of hypoglycaemia. Despite that, SU is the most commonly prescribed OAD during Ramadan in most countries,³ probably owing to its affordability as well as glycaemic efficacy. Both drugs are estimated to reduce HbA1c by 1–2%, compared to placebo in non-fasting population.^{25,26}

When compared to Glibenclamide, Repaglinide showed better glycaemic efficacy with lower mid-day hypoglycaemic events.²⁷ However, shorter-acting SUs (Glimiperide and Gliclazide) showed comparable glycaemic control with minimal hypoglycaemic events, when compared with Repaglinide.²⁸ Indeed, in an observational study during Ramadan, SU users who were prescribed Glibenclamide reported the highest incidence of severe hypoglycaemia compared to those who were on Glimiperide or Gliclazide.²⁹ Lowering the dose of Glibenclamide did not seem to reduce hypoglycaemic events during Ramadan.³⁰ There were several other studies which compared other classes of drugs to SU, and these will be covered in the later sections.

DPP-4 Inhibitor

DPP-4 inhibitor acts by inhibiting the DPP-4 enzyme which inactivates the incretin hormones, thereby prolonging the effects of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) in stimulating the pancreatic β -cells to secrete insulin, and suppressing α -cells from producing glucagon. As DPP-4 inhibitor acts in a glucose-dependent manner, the risk of hypoglycaemia is low.

There are currently 4 RCTs and 6 observational studies examining the effects of DPP-4 inhibitor during Ramadan. The majority used Vildagliptin and 2 of them used Sitagliptin as the choice of DPP-4 inhibitor. The comparator group for all the studies was SU. In one of the larger RCTs examining Vildagliptin versus Gliclazide in patients on a background of Metformin therapy, there was no significant difference in glycaemic control in both arms ($P = 0.165$ for between-group difference).¹² Those prescribed with Vildagliptin had significantly lower confirmed hypoglycaemic events compared to the Gliclazide group (3.0% versus 7.0%, $P = 0.039$). Overall, no severe hypoglycaemic events were reported. Even patients with longer duration of T2D (mean 7.1 years \pm 3.1 years) with suboptimal control (mean HbA1c 8.98% \pm 0.37%) prescribed with Vildagliptin during Ramadan showed significantly lower hypoglycaemic events compared to the Gliclazide group (7.7% versus 61.5%, $P < 0.001$).³¹ In a multi-centre observational study examining Vildagliptin versus SUs, which included Glibenclamide, significantly fewer patients from the Vildagliptin arm experienced hypoglycaemic events compared to the SU arm (5.4% versus 19.8%, $P < 0.001$).³² While there were no reports of severe hypoglycaemic events from those receiving Vildagliptin, 4 patients receiving SU reported such events, although it only achieved borderline significance ($P = 0.053$). A sub-analysis showed Glibenclamide contributed to the highest proportion (31.8%) of hypoglycaemic events, followed by Gliclazide (19.2%), Glimepiride (17.9%), and Glipizide (12.5%). In this study, Vildagliptin arm achieved better HbA1c reduction compared to SU (between-treatment difference -0.26% , $P < 0.001$) and more weight loss (between treatment difference -0.63kg , $P < 0.001$). As Vildagliptin is associated with a lower risk of hypoglycaemia, treatment adherence was higher when compared to insulin secretagogue. The proportion of patients missing more than 5 doses during Ramadan was lower in Vildagliptin arm (8.5%) than in the SU arm (15.4%).¹⁰

In the largest RCT available, comparing Sitagliptin ($n = 507$) and SU ($n = 514$), a lower proportion of Sitagliptin users developed hypoglycaemia compared to those on SU (6.7% versus 13.2%, $P < 0.001$).³³ However, in the sub-group analysis, the highest proportion of hypoglycaemic events occurred in subjects who were on Glibenclamide (19.7%). On the other hand, among those who were put on Gliclazide, the proportion who experienced hypoglycaemic events was similar to those in the Sitagliptin arm (6.6% versus 6.7%).

Other reported adverse events associated with Vildagliptin and Sitagliptin are fever, infection and gastrointestinal disturbances, but the numbers are relatively small.^{12,14,29,32–34}

SGLT2 Inhibitors

This is the newest class of OAD for T2D, and is gaining popularity owing to the recently discovered cardiovascular and renal protection.^{35–41} It acts by inhibiting the SGLT2 receptors found mainly on the S1 segment of the proximal glomerular tubules, which are responsible for the reabsorption of glucose filtered through the kidneys back into the circulation. This inhibition leads to a loss of glucose in the urine, hence contributing to significant weight loss among SGLT2 inhibitor users. However, along with the glycosuria, other concerns arise, such as (i) dehydration due to osmotic diuresis, which may become a major concern in Ramadan fasting, (ii) infection, especially of the genitourinary tract, and (iii) euglycaemic ketoacidosis, brought about mainly by the subsequent reduction of insulin doses to prevent hypoglycaemia once SGLT2 inhibitor is started.

There are only 3 studies examining this class of drug during Ramadan. In an open-label study, by one of the authors, comparing Dapagliflozin versus SU, both comprising patients on background Metformin therapy, fewer patients in the Dapagliflozin arm experienced symptomatic (3.4% versus 19.2%, $P = 0.008$) or documented hypoglycaemia (7.3% versus 27.1%, $P = 0.007$) compared to SU users.⁹ Although there was a tendency for Dapagliflozin subjects to end up with adverse events such as genitourinary tract infection (10.3% versus 3.8%, $P = 0.277$) and postural hypotension (13.8% versus 5.8%, $P = 0.210$), there was no statistically significant difference when compared to the SU arm. There was comparable glycaemic control, assessed using serum fructosamine, fasting plasma glucose and HbA1c between pre- and post-Ramadan for both arms. In this study, the subjects

who were randomised to SGLT2 inhibitor were specifically instructed to take the drug at the break of fast (Iftar) to avoid dehydration during the daytime fast.

In addition, Canagliflozin or Empagliflozin users, who have been on stable doses for at least 3 months prior to the study, did not exhibit a significant rise in β -hydroxybutyrate levels post-Ramadan. This translates to a minimal risk of developing ketosis with the use of these anti-diabetic agents during Ramadan fasting.⁴² In this study, there was also no statistically significant difference in the secondary end points between the SGLT2 inhibitor and the non-SGLT2 inhibitor arm, with respect to weight changes, systolic and diastolic blood pressures, fasting plasma glucose and estimated glomerular filtration rates. There were no increased hypoglycaemic events pre- and post-Ramadan in both arms, with no severe hypoglycaemic events reported.

In a real-world observational trial of 417 subjects treated with either Dapagliflozin or Canagliflozin on top of insulin or other OAD, 27.0% of SGLT2 inhibitor users developed hypoglycaemic events and 9.3% had symptoms of dehydration during Ramadan, both seen among those who were concurrently treated with insulin.⁴³

GLP-1 Receptor Analogue (GLP-1RA)

GLP-1RA is an attractive option in patients with T2D, owing to its extra benefit of weight loss by delaying gastric emptying. It is given at a supra-physiological dose and mimics incretin hormone GLP-1, which stimulates pancreatic β -cells to produce insulin and suppresses α -cells from secreting glucagon in a glucose-dependent manner, and hence is associated with a low risk of hypoglycaemia.

There are 2 available RCTs and one observational study examining the effects of GLP-1RA during Ramadan. TREAT 4 Ramadan is a 12-week trial where patients with T2D were randomised to receive either Liraglutide 1.2mg/day or SU, in addition to Metformin.⁴⁴ The primary outcome was a composite endpoint of HbA1c < 7.0% with no weight gain and no severe hypoglycaemic events. Although not statistically significant, more subjects in the Liraglutide arm tended to achieve the composite endpoints compared to SU users (26.7% versus 10.3%, $P = 0.06$) at 12 weeks post-Ramadan. When individual components were analysed, subjects who received Liraglutide achieved better HbA1c reduction ($-0.54\% \pm 0.87\%$ versus $-0.27\% \pm 0.60\%$, $P = 0.03$) and weight loss (-2.23 ± 2.96 versus

-0.42 ± 1.57 , $P = 0.02$) at 3 weeks post-Ramadan compared to the SU arm. Liraglutide users also had a lower risk of hypoglycaemic events compared to SU users.⁴⁵ There were, however, significantly more patients experiencing gastrointestinal discomfort prior to Ramadan, especially during the dose escalation period, leading to withdrawal from the study. Hence, it is recommended that dose titration should be completed 6–8 weeks prior to Ramadan to reduce these adverse events. The sole observational study revealed 16.2% of hypoglycaemic events when Liraglutide of at least 1.2 mg daily was added to on-going anti-diabetic agents among 111 participants during Ramadan.⁴⁶ There were, however, no severe hypoglycaemic events requiring hospital admission. In this study, 94.6% of the participants were on either insulin or SU therapy.

A dose adjustment guide for non-insulin therapies in Ramadan is summarised in Table 3.

Insulin

For insulin-requiring patients with T2D, the commonly prescribed regimes are (i) once daily basal insulin with or without addition of prandial insulin, and (ii) pre-mixed insulin given twice daily. There is no guide on the ideal insulin regime for patients with T2D who fast during Ramadan, as the insulin regime ideally should be individualised according to the patient's profile. Suffice to say, analogue insulin differs from human soluble insulin in terms of the onset and duration of action, and hence is associated with a lower risk of hypoglycaemia, especially nocturnal hypoglycaemia.⁴⁷ Unfortunately, there is no large RCT on insulin use in Ramadan.

There is no head-to-head trial comparing basal analogue insulin with human insulin. Observational studies of Glargine showed glycaemic efficacy and hypoglycaemic event rates to be comparable to those of Glimpiride and Repaglinide.⁴⁸ This basal analogue insulin also appears to be safe when added to Repaglinide with no increased risk of hypoglycaemic events when studied in non-fasting population. However, this study is limited by its small sample size of 7 subjects per arm.⁴⁹ When Glargine or Glimpiride was added to either insulin-naïve or subjects already receiving insulin prior to Ramadan in an observational study, glycaemic control improved and was maintained throughout Ramadan, with no significant difference in the risk of hypoglycaemia between the 2 arms.⁵⁰ The predictive factors for developing hypoglycaemia during Ramadan were found to be geographical area, weight < 70 kg, waist

Table 3. Dose and Timing Adjustment of Non-Insulin Treatment Options During Ramadan (Adapted with permission from Practical Guide to Diabetes Management in Ramadan⁷)

Anti-diabetic agent		Dose change
Biguanides	IR twice daily	No change
	IR thrice daily	2/3 of dose pre-iftar (sunset), 1/3 of dose pre-sahur (sunrise)
	XR once daily	No change
Alpha glucosidase inhibitor		No change
Thiazolidinediones		No change
Sulphonylurea	Glibenclamide	Avoid
	Gliclazide twice daily	Reduce/omit pre-sahur (sunrise) dose, maintain pre-iftar (sunset) dose
	Gliclazide MR once daily	Take at pre-iftar (sunset)
	Glimepiride once daily	Take at pre-iftar (sunset)
Glinides		No change
DPP-4 inhibitor		No change
SGLT2 inhibitor		No change
GLP-1 receptor analogue		No change

circumference < 90 cm and well-controlled blood sugar levels prior to Ramadan.

In a recent study comparing 2 insulin analogues, IDegAsp and BIAsp 30, those who were given the ultra-long insulin basal analogue IDegAsp had 74% and 83% reduction in the rate of overall and nocturnal hypoglycaemia, respectively, compared with those given BIAsp 30, despite comparable glycaemic efficacy.⁵¹

When premixed analogue insulin was compared with premixed human insulin 30/70 in an open-label crossover study involving 151 participants, those who received analogue insulin had lower post-Iftar (sunset) blood sugar despite the use of identical mean doses of insulin for both arms.⁵² There was, however, no significant difference in hypoglycaemic events between the 2 groups.

In a non-inferiority trial evaluating a new insulin regime combining Levemir given pre-Sahur (sunrise) and Novomix 70 pre-Iftar (sunset) compared to the standard insulin regime, the pre-Iftar (sunset) blood sugar levels were lower in the control arm ($P = 0.006$), whereas the post-Iftar (sunset) blood sugar levels were lower in the intervention arm ($P < 0.001$).⁵³ This translates to lower blood sugar excursion between pre- and post-Iftar (sunset) in the intervention arm. There were also significantly fewer subjects in the intervention arm who developed hypoglycaemia (4.8% versus 21.4%, $P < 0.001$).

Similarly, in another study, subjects given rapid acting insulin pre-Iftar (sunset) showed lower 1 hour and 2 hour post-prandial blood glucose rise compared to when they were given short acting human insulin ($P < 0.001$) in a cross-over study involving 57 out patients.⁵⁴

A summary of recommendations for insulin adjustments and dosing is shown in Tables 4 and 5.

Conclusion

In summary, Muslim diabetic patients who belong to the high-risk and very high-risk categories should be advised against fasting during Ramadan to prevent severe acute diabetic complications. Nevertheless, for those who choose to fast, pre-Ramadan preparations and education are essential to reduce the risks of these complications. This group of patients should be advised on the timing and dose adjustments necessary during this crucial month.⁵⁵ There is limited data on the use of Metformin, Acarbose and TZD during Ramadan. However, they are associated with low risks of hypoglycaemia. SU, although widely used during Ramadan, is associated with higher risks of hypoglycaemia especially with Glibenclamide, which should be avoided, if possible, during Ramadan fasting. Shorter-acting SUs may need adjustments in terms of dosing and timing. Incretin therapies are associated with low risks of hypoglycaemia as they work in a glucose-dependent manner. Patients on DPP-4 inhibitors

Table 4 Insulin Dose and Timing Changes during Ramadan (Adapted with permission from Practical Guide to Diabetes Management in Ramadan^{7,55})

Pre-Ramadan	During Ramadan	Note	
Prandial insulin	Pre-breakfast	Pre-sahur (sunrise)	May need dose reduction
	Pre-lunch	Omit	
	Pre-dinner	Pre-iftar (sunset)	May need dose increment
Basal insulin	Same time as pre-Ramadan		
Pre-mixed insulin	Pre-breakfast given at pre-iftar (sunset) Pre-dinner given at pre-sahur (sunrise)	Reduce pre-sahur (sunrise) dose by 20–50% Alternative: switch to basal bolus	

Table 5 Insulin Dose Changes Every 3 Days Based on Home Glucose Monitoring during Ramadan (adapted with permission from Hassanein 2017⁵)

Fasting or pre-meals blood glucose, mmol/L	Action (applies to prandial, basal or pre-mixed insulin)
<3.9 or symptomatic	Break fast, hypoglycaemia management, reduce by 4u subsequently
4.0–<5	Reduce by 2u
5.0–7.0	Maintain same dose
>7.0	Increase by 2u
>16.6	Break fast, check for ketones, increase by 4u subsequently

have lower risks of hypoglycaemia, with similar glycaemic efficacy, compared to SU during Ramadan. Hence, DPP-4 inhibitors may be a more suitable and attractive treatment option among patients with higher risks of hypoglycaemia, especially elderly patients, those with renal impairment, those with periods of erratic food intake and those with history of hypoglycaemia during fasting while on SU. SGLT2 inhibitor is associated with low risks of hypoglycaemia with no increased adverse events. Insulin analogue is generally associated with a lower risk of hypoglycaemia compared to human soluble insulin with comparable glycaemic efficacies. However, the insulin regime for patients who fast during Ramadan needs to be individualised.

In the case of A, diabetes treatment modification is necessary during Ramadan. Metformin can be safely continued as it is associated with low risks of hypoglycaemia. Basal insulin dose may need adjustments based on his fasting blood glucose levels. Gliclazide dose pre-Sahur (sunrise) needs to be reduced especially since he had experienced hypoglycaemic events during previous fasting. Alternatively, Gliclazide can be replaced with a DPP-4 inhibitor during Ramadan to avoid the risk of hypoglycaemia.

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