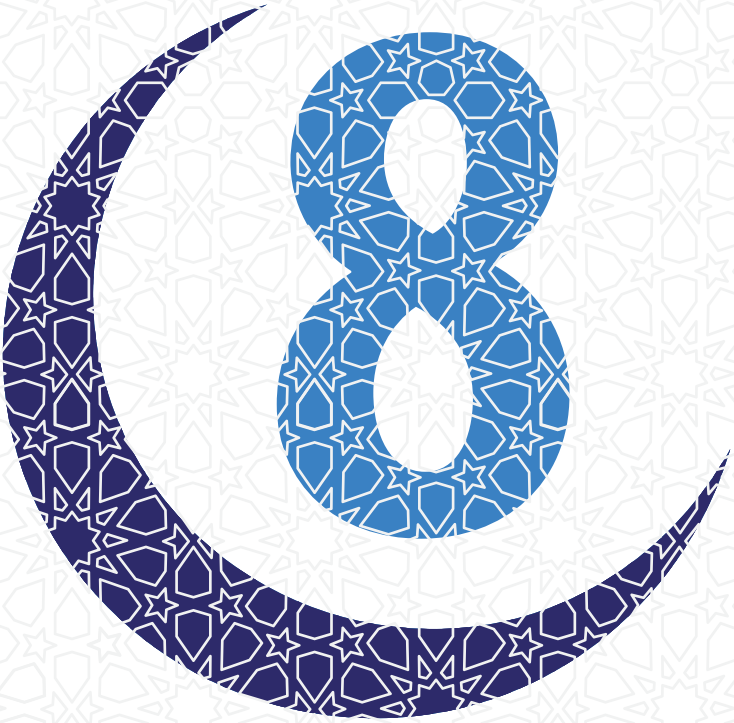

Chapter 8.
Management of Diabetes during Ramadan

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8.1 Introduction

Due to the metabolic instability and change in lifestyle during the fasting and feasting hours, management of diabetes during Ramadan presents several challenges. One of the main concerns is the increased risk of hypoglycaemia. In general, anti-diabetic drugs that act by increasing insulin sensitivity and have extra-pancreatic effects have a significantly lower risk of hypoglycaemia than drugs that act by increasing insulin secretion [1]. Despite the risks, many people with diabetes will fast during this month. The majority of patients with type 2 diabetes mellitus (T2DM) can fast safely as long as appropriate medical advice is sought and followed prior to and during fasting. People with type 1 diabetes mellitus (T1DM) and pregnant women need special attention. Individualisation of treatment options is the proper approach for the management of diabetes during Ramadan [2, 3]. This process can be broken down into a number of steps involving pre-Ramadan patient assessment, medication adjustment during Ramadan and post-Ramadan follow-up.

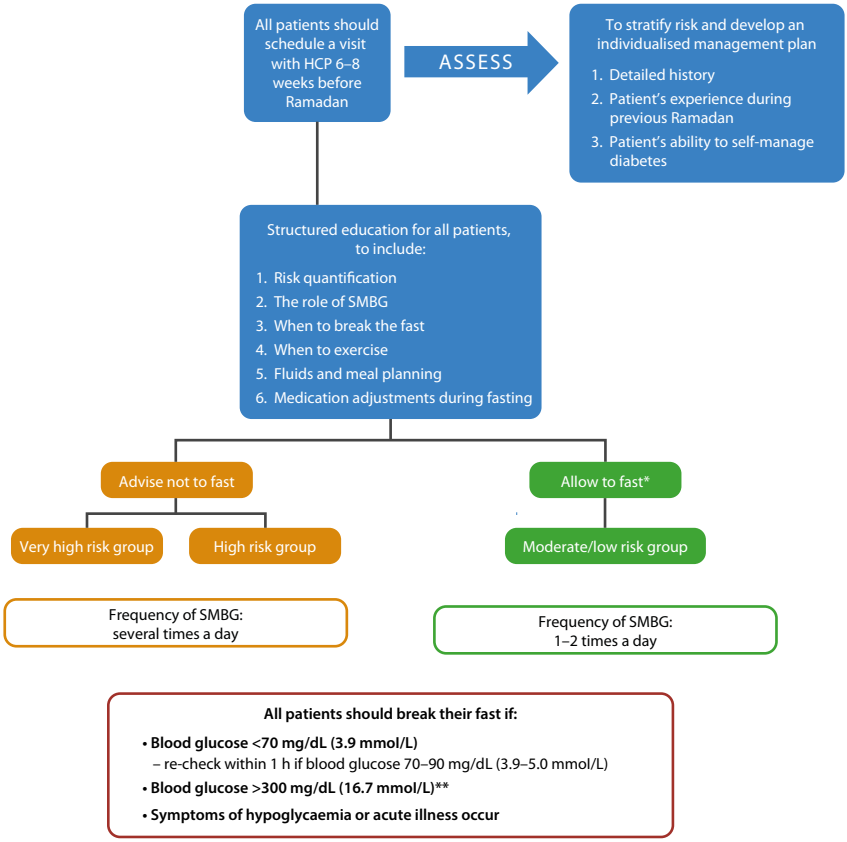
8.2 Pre-Ramadan patient assessment

All patients with diabetes wishing to fast should have a pre-Ramadan assessment with a healthcare professional (HCP), ideally 6–8 weeks before the start of Ramadan. By taking a detailed medical history and reviewing the patient's glycaemic control, risk of hypoglycaemia and self-management capabilities, as well as other factors, the HCP can categorise the risk to the patient as very high, high or moderate/low and advise the patient to fast or not (***Figure 1***). Chapter 4 describes the risk stratification process in more detail. If the patient decides to fast, which may be against the advice of the HCP, an individualised management plan must be produced. An integral part of this is Ramadan-focused education (see Chapter 6), which should include information on diet, exercise, the frequency of self-monitoring of blood glucose (SMBG) levels and critically when to break the fast to avoid harm. Very high/high risk patients, such as those with T1DM, should perform SMBG multiple times during the day and further details can be found later in this chapter. Dietary information must be provided as Ramadan changes not only the timings of meals but often the types of food consumed. Chapter 7 describes the use of a Ramadan Nutrition Plan as a way to educate patients on the importance of diet during the holy month.

8.3 Medication adjustment

The type of medication the patient is taking for diabetes management influences the potential risks that fasting may cause and needs careful attention within the treatment plan. The following sections review the available evidence for the use of non-insulin and insulin anti-diabetic therapies during Ramadan in patients with T2DM and in those considered very high risk, for example people with T1DM and pregnant women, and uses it to generate evidence-based recommendations regarding treatment and any dose adjustments that may be required.

Figure 1. Patient assessment flowchart



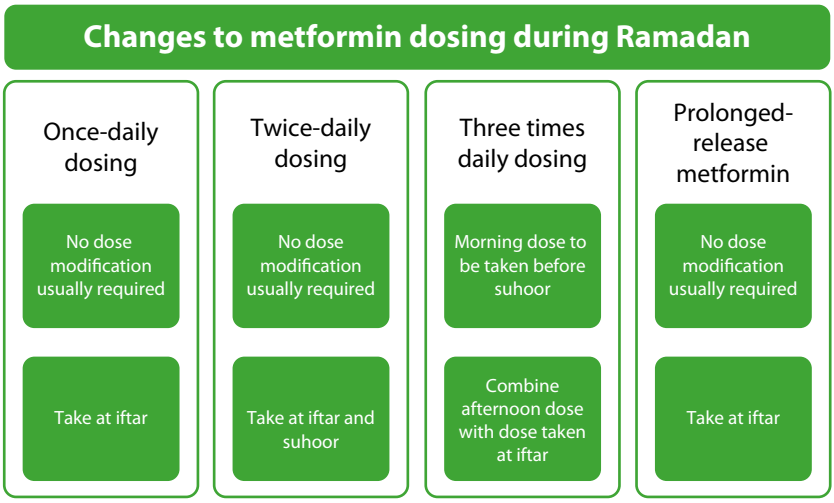
*Decision to fast based on medical opinion and ability of the individual to tolerate fast; **Consider individualisation of care
HCP, healthcare professional; SMBG, self-monitoring of blood glucose

8.3.1 Pharmacological management of people with T2DM

Metformin

Metformin is the most commonly used first-line oral anti-diabetic drug (OAD) and works by preventing the liver from producing new glucose. It comes in an immediate-release preparation which may be taken up to three times a day and a prolonged-release formulation which is typically taken just once a day. Severe hypoglycaemia in non-fasting patients receiving metformin is rare and while there are no randomised controlled trials (RCTs) on metformin use in patients with T2DM during Ramadan, it is considered safe for individuals on metformin to fast because the likelihood of hypoglycaemia is low. Ramadan dose adjustments are shown in ***Figure 2***.

Figure 2. Ramadan fasting dose adjustments for metformin in people with T2DM



Acarbose

Acarbose inhibits the actions of alpha-glucosidase, an enzyme that breaks down carbohydrates into glucose in the intestinal brush border, thereby slowing down the absorption of glucose and modifying insulin secretion. Like metformin, acarbose is typically introduced into treatment when healthy diet and exercise is not adequate for disease control. No dose adjustment of acarbose is needed during Ramadan as the risk of hypoglycaemia is low.

While no RCTs have been conducted on ACARBOSE in fasting patients with diabetes, NO DOSE MODIFICATION is considered necessary as the risk of hypoglycaemia is low

Thiazolidinediones

Thiazolidinediones (TZDs) improve insulin sensitivity of fat, muscle, liver and peripheral tissue cells by specifically activating the peroxisome proliferator-activated receptor-γ. This receptor is involved in glucose metabolism and activation by TZDs can increase glucose uptake, particularly in adipose tissue, subsequently lowering glucose in the blood [4]. As TZDs function without increasing insulin secretion, the risk of hypoglycaemia on TZD monotherapy in non-fasting individuals is very low [5]. Pioglitazone is the only TZD widely approved for use in T2DM but there are limited clinical data on its use during Ramadan. One study has evaluated the effects of

pioglitazone in addition to background OADs in 86 fasting Muslims during Ramadan (***Table 1***). Compared with placebo, pioglitazone significantly improved glycaemic control during the early, mid- and post-Ramadan periods. There was no difference in the number of hypoglycaemic events between the two treatment groups but a significant increase in weight of 3.02 kg was observed in the pioglitazone group compared with a non-significant loss in weight (-0.46 kg) in the placebo group [6].

Table 1. Studies evaluating TZD treatment in people with T2DM during Ramadan

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Pioglitazone	Vasan et al, 2006 [6]	n=86 *Study type:* Double-blind, randomised, controlled trial *Country:* India *Additional medication(s):* Oral anti-hyperglycaemic agents *Comparator:* Placebo	Events: Pioglitazone>placebo 39 vs 32 (p=0.21)	Fructosamine levels: Pioglitazone<placebo Early Ramadan: (p=0.003) Mid-Ramadan: (p=0.01) Post-Ramadan: (p=0.04)	Body weight: Pioglitazone: ↑3.02 kg (p=0.001) Placebo: ↓0.46 kg (p=0.37)

n, number of patients included in study

Due to the low risk of hypoglycaemia with PIOGLITAZONE, NO DOSE MODIFICATION is required during Ramadan and doses can be taken with iftar or suhoor

No adjustment to TZD medication is needed during Ramadan and doses can be taken with iftar or suhoor.

Short-acting insulin secretagogues

Short-acting insulin secretagogues such as repaglinide and nateglinide stimulate pancreatic β cells to secrete more insulin, and are usually taken before meals. In two small observational studies, no hypoglycaemic events were reported in patients treated with repaglinide during Ramadan [7, 8], while a third demonstrated no difference in hypoglycaemia when compared with insulin glargine or glimepiride, a sulphonylurea (SU) therapy [9]. Similarly, in two randomised parallel-group trials, a low incidence of hypoglycaemic events was associated with repaglinide treatment during Ramadan, occurring in similar proportions of patients treated with glibenclamide and glimepiride [10, 11].

Details of all studies are in ***Table 2***. Nateglinide use during Ramadan has not been reported, but as it has a faster onset and shorter duration of action than repaglinide, the risk of fasting hypoglycaemia is expected to be low [2].

Table 2. Studies evaluating repaglinide treatment in people with T2DM during Ramadan

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Repaglinide	Anwar et al, 2006 [10]	n=41 *Study type:* Open-label, parallel-group, randomised trial *Country:* Malaysia *Additional medication(s):* NR *Comparator:* SU (glimepiride)	Events: No significant difference between groups Symptomatic events during Ramadan: Repaglinide: 2.9%, Glimepiride: 3.5%	BG levels: Glimepiride <repaglinide	
	Bakiner et al, 2009 [7]	n=19 *Study type:* Observational *Country:* Turkey *Additional medication(s):* Insulin glargine *Comparator:* Non-fasting control group	Events: None reported in either group	No difference between the two groups	No significant weight changes in either group
	Cesur et al, 2007 [9]	n=65 *Study type:* Observational *Country:* Turkey *Additional medication(s):* Metformin *Comparators:* SU (glimepiride), insulin glargine, non-fasting control group	Patients experiencing event: No significant difference between fasting groups Glimepiride >repaglinide>insulin glargine 14.3% vs 11.1% vs 10.0% No severe episodes	No significant difference between fasting groups	No change in BMI in any fasting group Fasting did not adversely affect plasma lipids
	Mafauzy, 2002 [11]	n=235 *Study type:* Open-label, parallel-group, randomised trial *Countries:* France, Malaysia, Morocco, Saudi Arabia, UK *Additional medication(s):* None *Comparators:* SU (glibenclamide)	Patients experiencing event during Ramadan: Repaglinide: 7% Glibenclamide: 8% Ramadan midday BG <4.5 mmol/L: Repaglinide <glibenclamide 2.8% vs 7.9% (p=0.001)	Fructosamine levels: Repaglinide: significant ↓ from BL (p<0.05) Glibenclamide: no significant change No significant change in HbA1c in either group	

Table 2. Studies evaluating repaglinide treatment in people with T2DM during Ramadan *(cont.)*

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Repaglinide	Sari et al, 2004 [8]	n=52 *Study type:* Observational *Country:* Turkey *Additional medication(s):* NR *Comparators:* SU (glimepiride or gliclazide); diet only	Events: None reported in repaglinide or diet-only groups 1 reported in SU group (glimepiride)	No significant change in repaglinide or SU groups Significant ↑ β-hydroxybutyric acid from BL: Diet only (p=0.034)	Significant ↓ triglyceride levels from BL: Repaglinide (p=0.024) SU (p=0.002) Significant ↑ HDL-cholesterol from BL: Repaglinide (p=0.022)

BG, blood glucose; BL, baseline; BMI, body mass index; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; n, number of patients included in study; NR, not reported; SU, sulphonylurea; UK, United Kingdom

The short duration of action of these agents make them appealing for use during Ramadan as they can be taken before iftar and suhoor and carry a low risk of hypoglycaemia.

The daily dose of SHORT-ACTING INSULIN SECRETAGOGUES (based on a three-meal dosing) may be REDUCED or REDISTRIBUTED to two doses during Ramadan according to meal size

Sulphonylureas

SUs are widely used as second-line treatment for T2DM after metformin and so there is a wealth of evidence and experience with this low cost efficacious drug class. SUs stimulate insulin secretion from pancreatic β cells in a glucose-independent process. Because of this, SUs are associated with a higher risk of hypoglycaemia compared with other OADs, which has raised some concerns about their use during Ramadan. However, this risk varies across medications within this class due to differing receptor interactions, binding affinities and durations of action. Studies that have evaluated SU treatment during Ramadan are outlined in ***Table 3***.

In a multinational observational study of 1,378 patients with T2DM treated with SUs, approximately one fifth of patients experienced a symptomatic hypoglycaemic event during Ramadan. When this was broken down by drug, the highest incidence was associated with glibenclamide (25.6%) followed by glimepiride (16.8%) and gliclazide (14.0%) [12]. A similar outcome was observed in a large observational

Table 3. Studies evaluating SU treatment in people with T2DM during Ramadan

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
≥1 SUs ***(glibenclamide, gliclazide, glimepiride and/or glipizide)***	Aravind et al, 2011 [12]	n=1,378 *Study type:* Observational *Countries:* India, Israel, Malaysia, UAE, Saudi Arabia *Additional medication(s):* Metformin (not all patients) *Comparators:* NR	Symptomatic patients: Gliclazide <glimepiride <glibenclamide 14.0% vs 16.8% vs 25.6% Severe events: Gliclazide <glimepiride <glibenclamide 2.6% vs 5.1% vs 10.8%	NR	
	Aravind et al, 2012 [13]	n=870 *Study type:* Open-label, randomised, controlled trial *Countries:* India, Malaysia *Additional medication(s):* Metformin (not all patients) *Comparator:* DPP-4 inhibitor (sitagliptin)	Risk of symptomatic: Sitagliptin<SU (p=0.028) Patients experiencing symptomatic event: Sitagliptin<SU 3.8% vs 7.3% Breakdown of SU group: Gliclazide <glimepiride <glibenclamide 1.8% vs 5.2% vs 9.1%	NR	
	Al-Arouj et al, 2013 [14]	n=1,315 *Study type:* Observational *Countries:* Bangladesh, Egypt, India, Indonesia, Kuwait, Lebanon, Oman, Pakistan, Saudi Arabia, UAE *Additional medication(s):* Metformin (not all patients) *Comparator:* DPP-4 inhibitor (vildagliptin)	Patients experiencing ≥1 symptomatic event: Vildagliptin<SU 5.4% vs 19.8% (p<0.001) Breakdown of SU group: Glipizide<glimepiride <gliclazide <glibenclamide 12.5% vs 17.9% vs 19.2% vs 31.8% Confirmed by BG level (<3.9 mmol/L): Vildagliptin<SU 2.7% vs 12.9% Patients experiencing severe events: Vildagliptin<SU 0 vs 4 (p=0.053)	HbA1c change from BL: SU: ↑0.02% Vildagliptin: ↓0.24% (p<0.001 between treatments)	Body weight ↓: Vildagliptin>SU 0.76 kg vs 0.13 kg (p<0.001)

Table 3. Studies evaluating SU treatment in people with T2DM during Ramadan *(cont.)*

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
≥1 SUs ***(glibenclamide, gliclazide, glimepiride and/or glipizide)***	Al Sifri et al, 2011 [15]	n=1,066 *Study type:* Open-label, randomised, controlled trial *Countries:* Egypt, Israel, Jordan, Lebanon, Saudi Arabia, UAE *Additional medication(s):* Metformin (not all patients) *Comparator:* DPP-4 inhibitor (sitagliptin)	Risk of symptomatic: Sitagliptin<SU (p<0.001) Patients experiencing symptomatic event: Sitagliptin<SU 6.7% vs 13.2% Breakdown of SU group: Gliclazide<glimepiride <glibenclamide 6.6% vs 12.4% vs 19.7%	NR	
Glibenclamide	Belkhadir et al, 1993 [16]	n=591 *Study type:* Randomised, controlled trial *Country:* Morocco *Additional medication(s):* NR *Comparators:* Reduced dose of usual glibenclamide; non-randomised, non-fasting control group	Events: No significant difference between groups	Fructosamine levels: No significant difference between groups HbA1c levels: No significant difference between groups	
	Mafauzy, 2002 [11]	n=235 *Study type:* Open-label, parallel-group, randomised trial *Countries:* France, Malaysia, Morocco, Saudi Arabia, UK *Additional medication(s):* None *Comparators:* Insulin secretagogue (repaglinide)	Patients experiencing event during Ramadan: Repaglinide: 7% Glibenclamide: 8% Ramadan midday BG <4.5 mmol/L: Repaglinide <glibenclamide 2.8% vs 7.9% (p=0.001)	Fructosamine levels: Repaglinide: significant ↓ from BL (p<0.05) Glibenclamide: no significant change No significant change in HbA1c in either group	
Glimepiride	Anwar et al, 2006 [10]	n=41 *Study type:* Open-label, parallel-group, randomised trial *Country:* Malaysia *Additional medication(s):* NR *Comparator:* Insulin secretagogue (repaglinide)	Events: No significant difference between groups Symptomatic events during Ramadan: Repaglinide: 2.9% Glimepiride: 3.5%	BG levels: Glimepiride <repaglinide	

Table 3. Studies evaluating SU treatment in people with T2DM during Ramadan *(cont.)*

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Glimepiride	GLIRA Study Group, 2005 [17]	n=332 *Study type:* Observational *Countries:* Algeria, Egypt, Indonesia, Jordan, Lebanon, Malaysia *Additional medication(s):* NR *Comparator:* NR	Patients experiencing events during Ramadan: Newly-diagnosed: 3% Previously-treated: 3.7% Similar incidence in pre- and post-Ramadan periods	HbA1c pre-, at the start of and post-Ramadan: Newly-diagnosed: 9.2%, 7.7%, 7.1% Previously treated: 8.4%, 7.7%, 7.3%	
	Cesur et al, 2007 [9]	n=65 *Study type:* Observational *Country:* Turkey *Additional medication(s):* Metformin *Comparators:* Insulin secretagogue (repaglinide), insulin glargine; non-fasting control group	Patients experiencing event: No significant difference between fasting groups Glimepiride >repaglinide >insulin glargine 14.3% vs 11.1% vs 10.0% No severe episodes	No significant difference between fasting groups	No change in BMI in any fasting group Fasting did not adversely affect plasma lipids
Gliclazide	Hassanein et al, 2014 [18]	n=557 *Study type:* Double-blind, randomised controlled trial *Countries:* Denmark, Egypt, Germany, Indonesia, Jordan, Kuwait, Lebanon, Malaysia, Russia, Saudi Arabia, Singapore, Spain, Tunisia, Turkey, UAE, UK *Additional medication(s):* Metformin *Comparator:* DPP-4 inhibitor (vildagliptin)	Symptomatic: Vildagliptin<gliclazide 6.0% vs 8.7% (p=0.173) Confirmed events: Vildagliptin<gliclazide 3.0% vs 7.0% (p=0.039)	No significant change in either group	No significant difference in weight change between groups

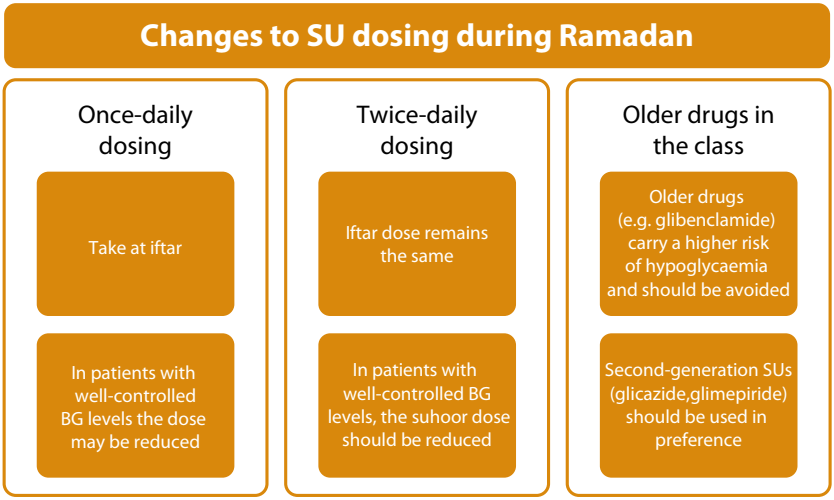
BG, blood glucose; BL, baseline; BMI, body mass index; DPP-4, dipeptidyl peptidase-4 inhibitor; HbA1c, glycated haemoglobin; n, number of patients included in study; NR, not reported; SU, sulphonylurea; UAE, United Arab Emirates; UK, United Kingdom

study comparing vildagliptin with SU treatment during Ramadan. Symptomatic hypoglycaemic events occurred in 31.8% of patients on glibenclamide but in fewer patients treated with gliclazide (19.2%), glimepiride (17.9%) or glipizide (12.5%) [14]. In addition, glibenclamide demonstrated significantly more hypoglycaemic events with midday blood glucose <4.5 mmol/L when compared to repaglinide (7.9% vs 2.8%, respectively; p=0.001) [11]. Lowering the dose of glibenclamide did not affect the

incidence of hypoglycaemic events [16]. More recent SUs such as glimepiride, glipizide and gliclazide are therefore preferred over conventional SUs, such as glibenclamide, because of their more favourable safety profile in terms of hypoglycaemia. In the large randomised trials comparing sitagliptin with SU treatment during Ramadan mentioned above, within the subgroups of patients that remained on gliclazide, the proportion of patients who experienced a hypoglycaemic event was comparable to the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin in the Al Sifri et al study (6.6% vs 6.7%, respectively) and less than sitagliptin in the Aravind et al study (1.8% vs 3.8%, respectively) [13, 15]. Similarly, no significant differences were observed in the proportions of patients reporting hypoglycaemic events treated with vildagliptin or gliclazide in the STEADFAST trial (6.0% vs 8.7%, respectively; p=0.173) [18].
To date, no trials have been conducted looking at the modified-release formulation of gliclazide during Ramadan. Incidence of hypoglycaemia is also low during Ramadan for glimepiride as shown in an open-label observational study where the incidence was just 3% in newly-diagnosed patients and 3.7% in previously treated patients, and was comparable to that observed before and after fasting [17]. Similarly, no significant differences in hypoglycaemic events were observed when glimepiride treatment was compared with either repaglinide or insulin glargine therapy [9, 10].

These studies demonstrate that patients with T2DM may continue to use second-generation SUs and fast safely during Ramadan. The use of older drugs within this class such as glibenclamide should be avoided in favour of gliclazide and glimepiride, which carry a much lower risk of hypoglycaemia. The use of these drugs should be individualised following clinician guidance and medication adjustments are outlined in ***Figure 3***.

Figure 3. Ramadan fasting dose adjustments for SUs in people with T2DM



BG, blood glucose; SU, sulphonylurea

Sodium-glucose co-transporter-2 (SGLT2) inhibitors

SGLT2 inhibitors including dapagliflozin, canagliflozin and empagliflozin, are the newest class of OADs. SGLT2 inhibitors have a unique mode of action whereby they increase excretion of glucose by the kidneys by reducing reabsorption in the proximal tubule, consequently decreasing blood glucose [19]. SGLT2 inhibitors have demonstrated effective improvements in glycaemic control and weight loss, and are associated with a low risk of hypoglycaemia. Because of this, it has been proposed that they provide a safe treatment option for patients with T2DM during Ramadan. However, certain safety concerns have been raised, such as an increase in some infections (urinary tract infections and genital mycotic infections) and a risk of ketoacidosis [19, 20]. An increased risk of dehydration in vulnerable patients has also been described, which may be a particularly pertinent issue during Ramadan. Currently, only one study has published data on the effectiveness of SGLT2 inhibitors during Ramadan (***Table 4***) [21].

Table 4. Studies evaluating SGLT2 inhibitor treatment in people with T2DM during Ramadan

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Dapagliflozin	Wan Juani et al, 2016 [21]	n=110 *Study type:* Open-label, randomised, 2-arm parallel-group study *Country:* Malaysia *Additional medication(s):* metformin *Comparator:* SU (glimepiride, gliclazide, or glibenclamide)	Events: Dapagliflozin<SU 6.9% vs 28.8% (p=0.002)	No significant differences in HbA1c, fasting BG, or fructosamine levels were observed between the groups	Postural hypotension: Dapagliflozin >SU 13.8% vs 5.8% (p=0.210) UTIs: Dapagliflozin >SU 10.3% vs 3.8% (p=0.277)

BG, blood glucose; HbA1c, glycated haemoglobin; n, number of patients included in study; SU, sulphonylurea; UTI, urinary tract infection

Patients with T2DM were randomised, in an open-label study, to receive either dapagliflozin or to continue with SU therapy. Significantly fewer patients in the dapagliflozin group reported hypoglycaemia than in the SU arm (6.9% vs 28.8%, respectively; p=0.002). Incidences of postural hypotension and urinary tract infections were greater in the dapagliflozin group than in the SU group, but did not reach significance [21]. Also, no increased risk of dehydration was evident with dapagliflozin treatment [22]. Further studies are warranted in order to prove the efficacy and safety

of SGLT2 inhibitors during Ramadan. A recent survey of physicians' views on the use of SGLT2 inhibitors during Ramadan for the treatment of patients with T2DM reported that the majority (70.6%) considered them suitable and safe for some patients [23]. Those that are deemed more at risk of complications such as the elderly, patients with renal impairment, hypotensive individuals, those at risk of dehydration or those taking diuretics should not be treated with SGLT2 inhibitors. Most of the physicians agreed that SGLT2 inhibitors should be taken with iftar and the importance of taking on extra fluids during the evening after a fast was highlighted [23].

SGLT2 inhibitors can be used with CAUTION in SOME patients. During Ramadan NO DOSE ADJUSTMENT is required and it is advised that the dose be taken with iftar

Dipeptidyl peptidase-4 (DPP-4) inhibitors

DPP-4 is an enzyme that rapidly metabolises glucagon-like peptide-1 (GLP-1), thereby regulating the activity of the hormone. By blocking this action, DPP-4 inhibitors effectively increase the circulating levels of GLP-1, which in turn stimulates insulin secretion in a glucose-dependent manner [24]. Currently available DPP-4 inhibitors include sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin, which are administered orally once or twice a day and are considered one of the best-tolerated OADs with low risk of hypoglycaemia in non-fasting patients [2]. Four RCTs [13, 15, 18, 25] and five observational studies [14, 26-29] have examined the efficacy and safety of DPP-4 inhibitor treatment during Ramadan and are detailed in ***Table 5***.

Table 5. Studies evaluating DPP-4 inhibitor treatment in people with T2DM during Ramadan

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Sitagliptin	Al Sifri et al, 2011 [15]	n=1,066 *Study type:* Open-label, randomised, controlled trial *Countries:* Egypt, Israel, Jordan, Lebanon, Saudi Arabia, UAE *Additional medication(s):* Metformin (not all patients) *Comparator:* SU (glimepiride, gliclazide or glibenclamide)	Risk of symptomatic: Sitagliptin<SU (p<0.001) Patients experiencing symptomatic event: Sitagliptin<SU 6.7% vs 13.2% Breakdown of SU group: Gliclazide<glimepiride <glibenclamide 6.6% vs 12.4% vs 19.7%	NR	

Table 5. Studies evaluating DPP-4 inhibitor treatment in people with T2DM during Ramadan *(cont.)*

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Sitagliptin	Aravind et al, 2012 [13]	n=870 *Study type:* Open-label, randomised, controlled trial *Countries:* India, Malaysia *Additional medication(s):* Metformin (not all patients) *Comparator:* SU (glimepiride, gliclazide or glibenclamide)	Risk of symptomatic: Sitagliptin<SU (p=0.028) Patients experiencing symptomatic event: Sitagliptin<SU 3.8% vs 7.3% Breakdown of SU group: Gliclazide<glimepiride <glibenclamide 1.8% vs 5.2% vs 9.1%	NR	
Vildagliptin	Al-Arouj et al, 2013 [14]	n=1,315 *Study type:* Observational *Countries:* Bangladesh, Egypt, India, Indonesia, Kuwait, Lebanon, Oman, Pakistan, Saudi Arabia, UAE *Additional medication(s):* Metformin (not all patients) *Comparator:* SU (glimepiride, gliclazide, glibenclamide or glipizide)	Patients experiencing ≥1 symptomatic event: Vildagliptin<SU 5.4% vs 19.8% (p<0.001) Breakdown of SU group: Glipizide <glimepiride<gliclazide <glibenclamide 12.5% vs 17.9% vs 19.2% vs 31.8% Confirmed by BG level (<3.9 mmol/L): Vildagliptin<SU 2.7% vs 12.9% Patients experiencing severe events: Vildagliptin<SU 0 vs 4 (p=0.053)	HbA1c change from BL: SU: ↑0.02% Vildagliptin: ↓0.24% (p<0.001 between treatments)	Body weight ↓: Vildagliptin>SU 0.76 kg vs 0.13 kg (p<0.001)
	Devendra et al, 2009 [26]	n=52 *Study type:* Observational *Country:* UK *Additional medication(s):* Metformin *Comparator:* SU (gliclazide)	Patients experiencing ≥1 event: Vildagliptin<gliclazide 7.7% vs 61.5% (p<0.001) Change in event incidence during Ramadan: Vildagliptin vs gliclazide: ↓0.24 vs ↑0.42 (p=0.0168)	HbA1c change: similar between groups	Between-treatment weight ↑: Vildagliptin: 0.34 kg (p=0.08) Gliclazide: 0.8 kg (p<0.001)

Table 5. Studies evaluating DPP-4 inhibitor treatment in people with T2DM during Ramadan *(cont.)*

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Vildagliptin	Halimi et al, 2013 [27]	n=198 *Study type:* Observational *Country:* France *Additional medication(s):* Metformin *Comparators:* SU or glinide	Patients experiencing ≥1 symptomatic event: Vildagliptin<comparators 34.2% vs 37.2% (p=0.665) Vildagliptin<comparators 34.2% vs 37.2% (p=0.665) Confirmed by BG level: Vildagliptin<comparators 23.5% vs 30.8% (p=0.260) Patients experiencing ≥1 severe event and/or medical visit: Vildagliptin<comparators 2.6% vs 10.4% (p=0.029)	Stable and similar in both treatment groups	Weight was stable in both treatment groups Treatment modifications: Vildagliptin< comparators 28.3% vs 66.7% (p<0.001)
	Hassanein et al, 2011 [28]	n=59 *Study type:* Observational *Country:* UK *Additional medication(s):* Metformin *Comparator:* SU (gliclazide)	Events: Vildagliptin< gliclazide 0 vs 35 Patients experiencing events: Between-group difference: -41.7% (p=0.0002)	HbA1c: Between-group difference: -0.5% (p=0.0262) Gliclazide: ↑0.1% (p=0.540) Vildagliptin: ↓0.4% (p=0.059)	No significant changes in weight in either group Mean number of missed doses: Vildagliptin < gliclazide 0.2 vs 7.6
	Hassanein et al, 2014 [18]	n=557 *Study type:* Double-blind, randomised, controlled trial *Countries:* Denmark, Egypt, Germany, Indonesia, Jordan, Kuwait, Lebanon, Malaysia, Russia, Saudi Arabia, Singapore, Spain, Tunisia, Turkey, UAE, UK *Additional medication(s):* Metformin *Comparator:* SU (gliclazide)	Symptomatic: Vildagliptin <gliclazide 6.0% vs 8.7% (p=0.173) Confirmed events: Vildagliptin <gliclazide 3.0% vs 7.0% (p=0.039)	No significant change in either group	No significant difference in weight change between groups
	Malha et al, 2014 [25]	n=69 *Study type:* Open-label, randomised, controlled trial *Country:* Lebanon *Additional medication(s):* Metformin *Comparator:* SU (glimepiride, gliclazide)	Events: Vildagliptin<SU 19 vs 26 (p=0.334)	HbA1c change: similar between groups Vildagliptin: ↓ 0.83 % SU: ↓ 0.96%	Post-Ramadan BMI: Vildagliptin: ↓ from BL 28.8 vs 29.5 kg/m^2 SU: ↑from BL 29.8 vs 28.9 kg/m^2

Table 5. Studies evaluating DPP-4 inhibitor treatment in people with T2DM during Ramadan *(cont.)*

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Vildagliptin	Shete et al, 2013 [29]	n=97 *Study type:* Observational *Country:* India *Additional medication(s):* Metformin (not all patients) *Comparator:* SU (glimepiride, gliclazide, glibenclamide or glipizide)	Patients experiencing events: Vildagliptin<SU 0% vs 4.8% (p=0.104)	HbA1c change from BL: SU: ↑0.01% (p=0.958) Vildagliptin: ↓0.43% (p=0.009) Patients achieving HbA1c <7.0%: Vildagliptin>SU 16.4% vs 4.8% (p=0.055)	Between-group weight ↓: Vildagliptin>SU 1.2 kg vs 0.03 kg (p<0.001)

BG, blood glucose; BL, baseline; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; HbA1c, glycated haemoglobin; n, number of patients included in study; NR, not reported; SU, sulphonylurea; UAE, United Arab Emirates; UK, United Kingdom; USA, United States of America

Specifically, the four RCTs examined the effects of switching from SU therapy to either vildagliptin or sitagliptin prior to Ramadan compared with continuing on SU. The largest of these studies compared the incidence of self-reported hypoglycaemic events in 1,066 patients with T2DM treated with sitagliptin or SUs during Ramadan. Overall, the risk of hypoglycaemia significantly decreased on the sitagliptin-based regimen compared to continuing with SU treatment (relative risk ratio [95% CI] = 0.51 [0.34, 0.75]; p<0.001) [15]. A study in India and Malaysia reported similar results when the risk of experiencing hypoglycaemic symptoms was almost halved on a sitagliptin regimen compared with SUs (risk ratio [95% CI] = 0.52 [0.29, 0.94]; p=0.028) [13]. In both studies the incidence of hypoglycaemia with sitagliptin was similar to that of the SU gliclazide. In the multinational STEADFAST study, patients with T2DM were randomised to receive either vildagliptin or gliclazide (plus metformin) during Ramadan. Patients were switched to study drug at least 8 weeks prior to fasting and continued treatment for up to four weeks after Ramadan [18]. No significant difference in the reporting of any hypoglycaemic event was observed between the two groups. However, the proportion of patients experiencing at least one confirmed hypoglycaemic event during Ramadan was lower on vildagliptin versus gliclazide (3.0% vs 7.0%; p=0.039). Both glycaemic control and body weight remained stable throughout the study in both treatment arms.

A number of observational studies have demonstrated significantly lower incidences of hypoglycaemia with vildagliptin treatment versus SU during Ramadan (***Table 5***). One small study in the UK investigated the addition of vildagliptin or gliclazide to treatment regimens for the fasting period. Compared with before

Ramadan, vildagliptin treatment was associated with a reduction in the number of hypoglycaemic events during Ramadan while gliclazide was associated with an increase. Two patients (7.7%) in the vildagliptin group experienced hypoglycaemic events during Ramadan compared with 16 (61.5%) in the gliclazide group ($p<0.001$) [26]. Similar results were recorded in the VECTOR study; no self-reported hypoglycaemic events were reported in the vildagliptin group compared with 35 events in 15 patients (41.7%) in the gliclazide arm (including one severe event). In addition, the change in glycated haemoglobin (HbA1c) from baseline to post-Ramadan was significantly better in the vildagliptin group compared with the gliclazide group ($p=0.0262$) while body weight remained unchanged in both groups [28]. The French VERDI study compared the incidence of hypoglycaemic events during Ramadan in patients who received vildagliptin or an insulin secretagogue in addition to metformin. It found no significant difference in the number of patients experiencing at least one hypoglycaemic event [27]. However, the proportion of patients experiencing a severe hypoglycaemic event and/or an unscheduled medical visit due to hypoglycaemia was significantly lower in the vildagliptin group compared with the insulin secretagogue group ($p=0.029$) [27]. In India, a study found a significant reduction in HbA1c (-0.43%; $p=0.009$) and a higher proportion of patients achieving HbA1c <7.0% in patients treated with vildagliptin during Ramadan compared with a SU treated group. No hypoglycaemic events occurred in the vildagliptin group [29]. The VIRTUE study, conducted in the Middle East and Asia, is the largest of the observational studies to date and enrolled >1,300 patients with T2DM. Like the smaller studies, DPP-4 inhibitor treatment (vildagliptin) demonstrated significantly fewer patients with at least one hypoglycaemic event during Ramadan compared with those on SUs (5.4% vs 19.8%, respectively; $p<0.001$). Patients on vildagliptin also demonstrated significant reductions in HbA1c and body weight from baseline compared with those on SUs [14]. A recent meta-analysis of 16 RCTs and 13 observational studies in patients with T2DM who fasted during Ramadan has suggested that, when all relevant studies were taken into account, DPP-4 inhibitors were associated with the lowest incidence and rate of hypoglycaemic events compared with SUs [30]. Other more recently approved DPP-4 inhibitors (alogliptin, saxagliptin, and linagliptin) have yet to be studied during Ramadan.

The results of the studies described above indicate that vildagliptin is effective in improving glycaemic control and that both vildagliptin and sitagliptin are associated with low rates of hypoglycaemia during fasting, making them attractive treatment options during Ramadan. These drugs do not require any treatment modifications during Ramadan.

DPP-4 inhibitors do NOT REQUIRE TREATMENT MODIFICATIONS during Ramadan

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs)

GLP-1 RAs mimic the incretin hormone and decrease glucose in the blood by increasing insulin secretion in a glucose-dependent manner. Like endogenous GLP-1, drugs in this class reduce glucagon secretion, increase glucose uptake and storage in muscle, decrease glucose production by the liver, reduce appetite and retard gastric emptying [24, 31]. As they act in a glucose-dependent manner, the risk of severe hypoglycaemia is low when used as monotherapy, but may still be an issue when given with SUs, glinides or insulin [2, 32]. A number of studies on the use of GLP-1 RAs during Ramadan have been published recently and details can be found in ***Table 6***.

Table 6. Studies evaluating GLP-1 RA treatment in people with T2DM during Ramadan

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Exenatide	Bravis et al, 2010 [33]	n=43 *Study type:* Observational *Country*: UK *Additional medication(s):* Metformin *Comparator:* SU (gliclazide)	Change in frequency of events: Exenatide: ↓0.08% (p=0.43) Gliclazide: ↑53.0% (p=0.03)	NR	Weight change: Exenatide: ↑0.12 kg (p=0.55) Gliclazide: ↑0.68 kg (p=0.01)
Liraglutide	Azar et al, 2015 [34]	n=343 *Study type:* Open-label, randomised, controlled trial *Countries:* Algeria, India, Israel, Lebanon, Malaysia, South Africa, UAE *Additional medication(s):* Metformin *Comparator:* SU	Symptomatic events during Ramadan: Liraglutide<SU (p=0.0009) Symptomatic events from BL to end of Ramadan: Liraglutide<SU (p<0.0001)	Fructosamine ↓ during Ramadan: Liraglutide similar to SU (despite better glycaemic control in liraglutide group at start of Ramadan) Fructosamine ↓ from BL to end of Ramadan: Liraglutide>SU (p<0.05) HbA1c (%) ↓ from BL to end of Ramadan: Liraglutide>SU (p<0.0001)	Body weight ↓ during Ramadan: Liraglutide>SU (p=0.0091) Body weight ↓: from BL to end of Ramadan: Liraglutide>SU (p<0.0001)
	Brady et al, 2014 [35]	n=99 *Study type:* Open-label, randomised, controlled trial *Country:* UK *Additional medication(s):* Metformin *Comparator:* SU (gliclazide, glipizide or glibenclamide)	Self-recorded episodes of BG ≤3.9 mmol/L: Liraglutide<SU (p<0.0001) No severe episodes	Change in HbA1c: 3 weeks post-Ramadan: Liraglutide>SU ↓0.54% vs ↓0.27% (p=0.03) 12 weeks post-Ramadan: Liraglutide>SU ↓0.32% vs ↑0.02% (p=0.05)	Body weight: 3 weeks post-Ramadan: Liraglutide>SU ↓2.23 kg vs ↓0.42 kg (p=0.02) 12 weeks post-Ramadan: Liraglutide>SU ↓2.57 kg vs ↑0.25 kg (p=0.002)

Table 6. Studies evaluating GLP-1 RA treatment in people with T2DM during Ramadan *(cont.)*

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Liraglutide	Khalifa et al, 2015 [36]	n=111 *Study type:* Observational *Country:* UAE *Additional medication(s):* Insulin, SU, none *Comparator:* None	Patients experiencing events: 16.2% No severe hypoglycaemia	HbA1c post-Ramadan vs BL: 8.0% vs 7.4% (p=0.000)	

BG, blood glucose; BL, baseline; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; n, number of patients included in study; NR, not reported; SU, sulphonylurea; UAE, United Arab Emirates; UK, United Kingdom

The TREAT4 Ramadan trial examined the safety and efficacy of liraglutide compared to SU as add-on to metformin treatment in patients with T2DM in the UK during Ramadan [35]. The primary outcome was the proportion of patients who achieved a composite endpoint of HbA1c <7%, no weight gain and no severe hypoglycaemia 12 weeks post-Ramadan. While more patients achieved this endpoint in the liraglutide group compared with the SU group (26.7% vs 10.3%, respectively), this did not reach statistical significance. However, there was a significant reduction in HbA1c levels and body weight at both three and 12 weeks post-Ramadan in the liraglutide group compared with the SU group (***Table 6***) [35]. The incidence rate of self-recorded hypoglycaemic events was also significantly lower in the liraglutide group (p<0.0001) [35]. In the open-label LIRA-Ramadan study conducted in Africa and Asia, patients with T2DM were randomised to switch to once-daily liraglutide or continue on SU [34]. The primary endpoint was change in fructosamine from the beginning to end of Ramadan. Similar fructosamine reductions were observed in both cohorts despite better glycaemic control at the beginning of Ramadan in the liraglutide group. Significantly more patients in the liraglutide group reached the composite endpoint (HbA1c <7%, no weight gain, no hypoglycaemia) than in the SU group at the end of Ramadan (51.3% vs 17.7%; p<0.0001). Patients in the liraglutide arm also demonstrated better weight control and fewer confirmed hypoglycaemic episodes compared with the SU group [34]. The effects of adding liraglutide to pre-existing anti-diabetic regimens (including SU and insulin) during Ramadan was investigated in an observational trial in the United Arab Emirates [36]. No participants – 94.6% of whom were on SU, insulin or both – experienced a severe hypoglycaemic event during Ramadan, although 16.2% did develop symptoms of hypoglycaemia. A small but significant increase in HbA1c was observed following Ramadan [36]. A small observational study in patients with T2DM treated with exenatide in addition to metformin reported no significant differences in weight or hypoglycaemic episodes [33].

Data relating to the use of newer GLP-1 RAs (lixisenatide, dulaglutide and albiglutide) during Ramadan are lacking.

These studies demonstrate that liraglutide is safe as an add-on treatment to metformin and can be effective in reducing weight and HbA1c levels during Ramadan. Data on exenatide is limited to one study but the short duration of action and dosing of exenatide suggest that, like liraglutide, the risk of hypoglycaemia during Ramadan is low.

As long as GLP-1 RAs have been appropriately DOSE-TITRATED prior to Ramadan (6 weeks before), NO FURTHER TREATMENT MODIFICATIONS are required

Insulin treatment for T2DM

Insulin treatment for T2DM may include the use of a long/intermediate-acting basal insulin (insulin glargine, insulin detemir or neutral protamine Hagedorn [NPH] insulin), possibly with a rapid or short-acting bolus/pre-meal insulin (lispro, aspart or regular human insulin) [37], and may be used in conjunction with OADs. Insulin use during prolonged fasting carries an increased risk of hypoglycaemia, particularly for those with T1DM but also for those with T2DM. The use of insulin analogues is recommended over regular human insulin due to a number of advantages that include less hypoglycaemia [38]. Although a number of small randomised trials and observational studies (***Table 7***) have been conducted to assess some insulin regimens during Ramadan, large RCT data in this area are lacking.

Table 7. Studies evaluating insulin treatment in people with T2DM during Ramadan

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Basal insulin: glargine	Bakiner et al, 2009 [7]	n=19 *Study type:* Observational *Country:* Turkey *Additional medication(s):* insulin secretagogue (repaglinide) *Comparator:* Non-fasting control group	Events: None reported in either group	No difference between the two groups	No significant weight changes in either group

Table 7. Studies evaluating insulin treatment in people with T2DM during Ramadan *(cont.)*

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Basal insulin: glargine	Cesur et al, 2007 [9]	n=65 *Study type:* Observational *Country:* Turkey *Additional medication(s):* Metformin *Comparators:* insulin secretagogue (repaglinide), SU (glimepiride), non-fasting control group	Patients experiencing event: No significant difference between fasting groups Glimepiride >repaglinide >insulin glargine 14.3% vs 11.1% vs 10.0% No severe episodes	No significant difference between fasting groups	No change in BMI in any fasting group Fasting did not adversely affect plasma lipids
	Salti et al, 2009 [39]	n=412 *Study type:* Observational *Countries:* Bangladesh, China, Egypt, India, Indonesia, Kuwait, Jordan, Lebanon, Malaysia, Morocco, Oman, Saudi Arabia, Tunisia, UAE *Additional medication(s):* SU (glimepiride), metformin/TZD (not all patients) *Comparator:* None	Events pre-, during and post-Ramadan: 156 vs 346 vs 153 Pre- vs. during Ramadan (p<0.001) Post- vs during Ramadan (p=0.0002)	No major change during Ramadan	Lower weight <70.0 kg (p=0.001) and waist circumference <90 cm (p=0.001) increased the risk of hypoglycaemia FBG >6.7 mmol/L (p<0.0001) decreased the risk of hypoglycaemia
Prandial insulin: lispro	Akram et al, 1999 [40]	n=68 *Study type:* Open-label, crossover, randomised trial *Countries:* Egypt, Kuwait, Pakistan, Saudi Arabia, UAE *Additional medication(s):* Humulin NPH (basal) *Comparator:* Soluble insulin (Humulin R)	Patients experiencing event: Similar for both treatment groups Events per patient per 14 days: Insulin lispro<soluble insulin 1.3% vs 2.6% (p<0.002) Total episodes in study: Insulin lispro<soluble insulin 22 vs 51 No severe episodes	↑ post-prandial BG (mmol/L): Insulin lispro <soluble insulin 1h: 3.0 vs 4.3 (p<0.01) 2h: 2.6 vs 4.0 (p=0.008)	

Table 7. Studies evaluating insulin treatment in people with T2DM during Ramadan *(cont.)*

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Premixed insulin regimens					
Insulin lispro Mix 50 (evening) and human insulin Mix 30 (morning)	Hui et al, 2009 [41]	n=52 *Study type:* Observational *Country:* UK *Additional medication(s):* NR *Comparator:* Human insulin Mix 30 (twice-daily dosing)	Events: Insulin lispro Mix 50 and human insulin Mix 30: ↓0.04 (p=0.81) Human insulin Mix 30: ↑0.15 (p=0.43) Between-group difference not significant (p=0.36)	HbA1c change: Insulin lispro Mix 50 and human insulin Mix 30: ↓ 0.48% (p=0.0001) Human insulin Mix 30: ↑ 0.28% (p=0.007). Between-group difference (p=0.0004)	No significant difference in weight changes between groups
Insulin lispro Mix25	Mattoo et al, 2003 [42]	n=151 *Study type:* Open-label, crossover, randomised trial *Countries:* Egypt, India, Malaysia, Morocco, Pakistan, Singapore, South Africa *Additional medication(s):* NR *Comparator:* Soluble insulin 30/70	Events per patient per 14 days: Similar for both treatment groups	Daily glycaemia (BG, mmol/L): Overall: Insulin lispro<soluble insulin 9.5 vs 10.1 (p=0.004) Pre-evening meal: Insulin lispro<soluble insulin 7.1 vs 7.5 (p=0.034) 2 hrs post-evening meal: Insulin lispro<soluble insulin 10.5 vs 11.6 (p=0.0001)	No significant change in body weight in any patient
Insulin detemir and biphasic insulin aspart	Shehadeh et al, 2015 [43]	n=245 *Study type:* Open-label, prospective, randomised controlled trial *Country:* Israel *Additional medication(s):* Metformin, SU (not all patients) *Comparator:* Standard care	Patients experiencing event: Intervention <standard care 4.8% vs 21.4% (p≤0.001)	Intervention was non-inferior to standard care	

Table 7. Studies evaluating insulin treatment in people with T2DM during Ramadan *(cont.)*

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Biphasic insulin aspart	Soewondo et al, 2009 [44]	n=152 *Study type:* Observational *Country:* Indonesia *Additional medication(s):* Oral hypoglycaemic agents (not all patients) *Comparator:* None	Events: End of study<BL (not significant)	Biphasic aspart significantly reduced all glycaemic indices	No significant changes in body weight or BMI

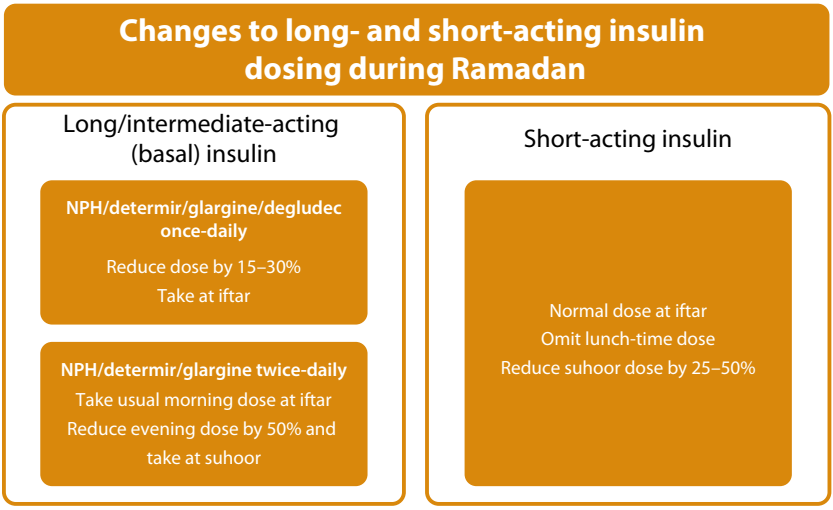
BG, blood glucose; BL, baseline; BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; n, number of patients included in study; NPH, Neutral Protamine Hagedorn; NR, not reported; SU, sulphonylurea; TZD, thiazolidinediones, UAE, United Arab Emirates; UK, United Kingdom

An observational study in patients with T2DM across 14 countries treated with insulin glargine plus glimepiride saw a significant increase in mild hypoglycaemic events during Ramadan compared with the pre-Ramadan period, and found that a lower weight and smaller waist circumference was associated with an increased risk [39]. Two smaller observational studies found insulin glargine safe to use during Ramadan with no significant increases in hypoglycaemia when compared with non-fasting individuals or when compared with those taking other OADs [7, 9]. Pre-meal administration of rapid or short-acting insulins may be required, in addition to long-acting basal insulin, to better control postprandial blood glucose. An open-label randomised trial by Akram et al compared the effects of two such insulins, rapid-acting analogue insulin lispro and short-acting soluble human insulin, taken before iftar during Ramadan. The postprandial rise in blood glucose levels after iftar and the rate of hypoglycaemia were both significantly lower in the lispro group [40]. Premixed insulins that combine short- and intermediate-acting insulins can be more convenient for patients with diabetes, as they require fewer injections than basal-bolus regimens, but may be associated with a higher risk of hypoglycaemia in non-fasting individuals [45, 46]. In an open-label randomised trial, the effects of two premixed insulin formulations (analogue insulin lispro Mix25 [25% short-acting lispro/75% intermediate-acting lispro protamine] and human insulin 30/70 [30% short-acting soluble human insulin/70% intermediate-acting NPH]) on glycaemic control were compared during Ramadan. Overall glycaemia was significantly lower for patients on insulin lispro Mix25 compared with patients on human insulin 30/70, with the greatest between-treatment difference evident before and after iftar. There was no difference in the number of hypoglycaemic episodes between treatments [42]. A regimen of premixed insulin lispro Mix50 (50% lispro/50% lispro protamine) in the evening and regular human insulin with NPH (30:70) in the morning was compared with regular human insulin with NPH (30:70) given twice daily during Ramadan in a small observational study. Switching the evening meal dose to insulin lispro Mix50 significantly improved glycaemic control without increasing the incidence of hypoglycaemic events [41]. A new regimen in which 40% of the daily

insulin dose was given as insulin detemir at suhoor and 60% was given as NovoMix70, a biphasic insulin aspart, before iftar was assessed in a recent randomised study. The new regimen was found to be non-inferior to standard care with a significantly lower hypoglycaemic event rate [43]. In addition, a prospective observational study in Indonesia found that compared to pre-Ramadan baseline levels, biphasic insulin aspart significantly reduced all glycaemic indices following Ramadan without an increase in body weight or risk of hypoglycaemia [44].

There are limited data available regarding the optimal insulin type or regimen for patients with T2DM during Ramadan but results from the studies described above indicate it may be safe to fast while on insulin, however treatment must be appropriately individualised. Recommended medication adjustments and SMBG-guided dose titrations for long/intermediate or short-acting insulin and premixed insulin can be found in ***Figures 4*** and ***5***, respectively.

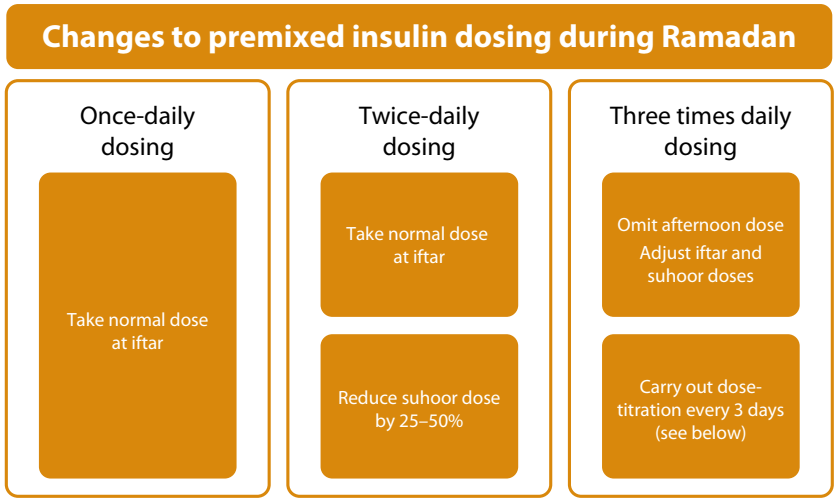
Figure 4. Ramadan fasting dose adjustments for long- or short-acting insulins in people with T2DM[a]



Fasting/pre-iftar/ pre-suhoor blood glucose	Pre-iftar*	Post-iftar*/ post-suhoor**
	Basal insulin	Short-acting insulin
<70 mg/dL (3.9 mmol/L) or symptoms	Reduce by 4 units	Reduce by 4 units
70–90 mg/dL (3.9–5.0 mmol/L)	Reduce by 2 units	Reduce by 2 units
90–130 mg/dL (5.0–7.2 mmol/L)	No change required	No change required
130–200 mg/dL (7.2–11.1 mmol/L)	Increase by 2 units	Increase by 2 units
>200 mg/dL (11.1 mmol/L)	Increase by 4 units	Increase by 4 units

[a]These recommendations also apply to patients with T1DM
*Adjust the insulin dose taken before suhoor; **Adjust the insulin dose taken before iftar
NPH, neutral protamine Hagedorn

Figure 5. Ramadan fasting dose adjustments for premixed insulin in people with T2DM[a]



Fasting/pre-iftar/pre-suhoor blood glucose	Premixed insulin modification
<70 mg/dL (3.9 mmol/L) or symptoms	Reduce by 4 units
70–90 mg/dL (3.9–5.0 mmol/L)	Reduce by 2 units
90–126 mg/dL (5.0–7.0 mmol/L)	No change required
126–200 mg/dL (7.0–11.1 mmol/L)	Increase by 2 units
>200 mg/dL (11.1 mmol/L)	Increase by 4 units

Table modified from [47]. [a]These recommendations also apply to patients with T1DM

Patients with T2DM and poor glycaemic control despite multiple daily injections (MDI) of insulin can possibly benefit from an insulin pump system with continuous subcutaneous insulin secretion [48]. While there are no data for insulin pump use during Ramadan for T2DM, studies have demonstrated that adults and adolescents with T1DM can fast safely using insulin pumps.

Many patients with T2DM can fast safely during Ramadan but it is important for both HCPs and patients to understand and implement appropriate medication adjustments

8.3.2 Pharmacological management of high risk populations

Adults with T1DM

People with T1DM who fast can be at high risk of developing serious health problems [49]. Indeed, religious leaders, in unification with many diabetes experts, do not recommend fasting in individuals with T1DM, and such patients are categorised as very high risk (see Chapter 4) [50]. However, many patients with T1DM will choose to fast, especially those living in Muslim countries where the majority of the population is fasting; this unintentional peer pressure may make them want to behave similarly to their community.

A study assessing the incidence of diabetic ketoacidosis (DKA)-related hospital admissions during Ramadan and the month after (Shawal) found that DKA admission rates were higher in Ramadan compared to pre-Ramadan but the authors noted that a majority of the patients had poor glycaemic control before the start of fasting [51]. Although the risk of severe hypoglycaemic events seems to be low in fasting individuals, a study involving continuous glucose monitoring noted variable blood glucose levels and significant periods of hypoglycaemia that went unnoticed [52].

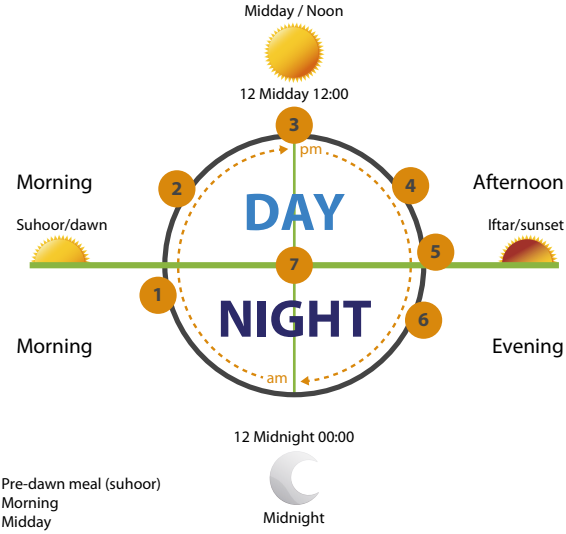
In general, patients with T1DM who have any of the following conditions are strongly advised not to fast [2, 49, 53]:

- History of recurrent hypoglycaemia
- Hypoglycaemia unawareness
- Poor diabetes control
- Brittle diabetes
- Non-compliance with medical treatment
- Patients who are 'unwilling' or 'unable' to monitor and manage their blood glucose levels.

Those who insist on fasting must be aware of all the potential risks associated with Ramadan fasting and be under close medical supervision [53]. Patients are advised to monitor their blood glucose several times during the day (***Figure 6***) and most importantly, levels should be checked at any time when symptoms of hypoglycaemia are recognised [47]. The post-meal test reduces the risk of postprandial hyperglycaemia [54]. The regularity of the blood glucose checks is dependent on the frequency of insulin treatment and/or the risk of hypo- or hyperglycaemia. To get a true understanding of how blood glucose changes while fasting, patients should be encouraged to keep a Ramadan logbook detailing the measurements [54]. All patients should comprehend the dangers of low and high blood glucose levels and

know to break the fast if blood glucose is <70 mg/dL (3.9 mmol/L) or >300 mg/dL (16.7 mmol/L) [2]. They should also be advised not to fast if they are unwell [2]. It must be stressed that performing a glucose blood test during the day does not violate the fast [54]. A study in Pakistan in 2010 involving 1,050 patients revealed that 28% thought a needle prick test was not allowed during fasting and 55% were unaware they should break the fast if glucose levels were low (60–70 mg/dL [3.3–3.9 mmol/L]), indicating that patient education is critical [55].

Figure 6. Recommended timings to check blood glucose levels during Ramadan fasting



1. Pre-dawn meal (suhoor)
2. Morning
3. Midday
4. Mid-afternoon
5. Pre-sunset meal (iftar)
6. 2-hours after iftar
7. At any time when there are symptoms of hypoglycaemia/hyperglycaemia or feeling unwell

Studies have shown that some patients with T1DM can tolerate fasting with no added risks of severe hypoglycaemia or DKA (***Table 8***) although adjustments to medication and/or dosing regimen may be required; however, it should be noted that periods of hypoglycaemia may go unrecognised [52].

Table 8. Studies evaluating insulin treatment in adults with T1DM during Ramadan

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Insulin lispro	Kadiri et al, 2001 [56]	n=67 *Study type*: Open-label, randomised, crossover study *Countries:* Saudi Arabia, Kuwait, Pakistan, Egypt, Morocco *Additional medication(s):* intermediate-acting insulin (Humulin N) *Comparator:* Human insulin (Humulin R)	Events: Insulin lispro<human insulin 23.4% vs 48.4% (p=0.004)	↑ postprandial BG (mmol/L): Insulin lispro<human insulin 2h: 2.5 vs 3.5 (p=0.026)	
Ultralente	Kassem et al, 2005 [57]	n=17 *Study type:* Observational *Country:* Lebanon *Additional medication(s):* Regular insulin *Comparator:* None	No severe episodes	HbA1c: no change from before to after fasting	By end of Ramadan Ultralente dose was 70% of total insulin dose
Glargine	Mucha et al, 2004 [58]	n=15 *Study type:* Observational, non-Ramadan study *Country:* USA *Additional medication(s):* Rapid-acting insulin *Comparator:* None	Events: Fasting days<control days 2 vs 8 No severe episodes	Mean BG (mg/dL) on fasting day declined from 125±16 at 0700 to 93±11 at 1700 (p=0.055)	
Insulin pump therapy	Benbarka et al, 2010 [59]	n=49 *Study type:* Observational *Country:* UAE *Additional medication(s):* NR *Comparator:* None	Events: 17 patients had to break fast No severe episodes	↓ basal insulin rate: 47% by 5–50% Median reduction 14% ↓ serum fructosamine (mmol/L): pre-Ramadan 4.0±0.6 post-Ramadan 3.6±0.6 (p=0.007)	61.2% fasted the whole month 18.4% fasted 27–28 days 16.3% fasted 24–25 days 4.1% fasted 23 days

Table 8. Studies evaluating insulin treatment in adults with T1DM during Ramadan *(cont.)*

Study drug	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Insulin pump therapy	Khalil et al, 2012 [60]	n=21 *Study type:* Observational *Country:* UAE *Additional medication(s):* NR *Comparator:* None	No severe episodes	↓ basal insulin rate: During the day by 5–20% from before Ramadan ↑ basal insulin rate: During the night mean change in the overall amount of basal insulin was not significant A larger than usual amount of insulin bolus was given at meals	

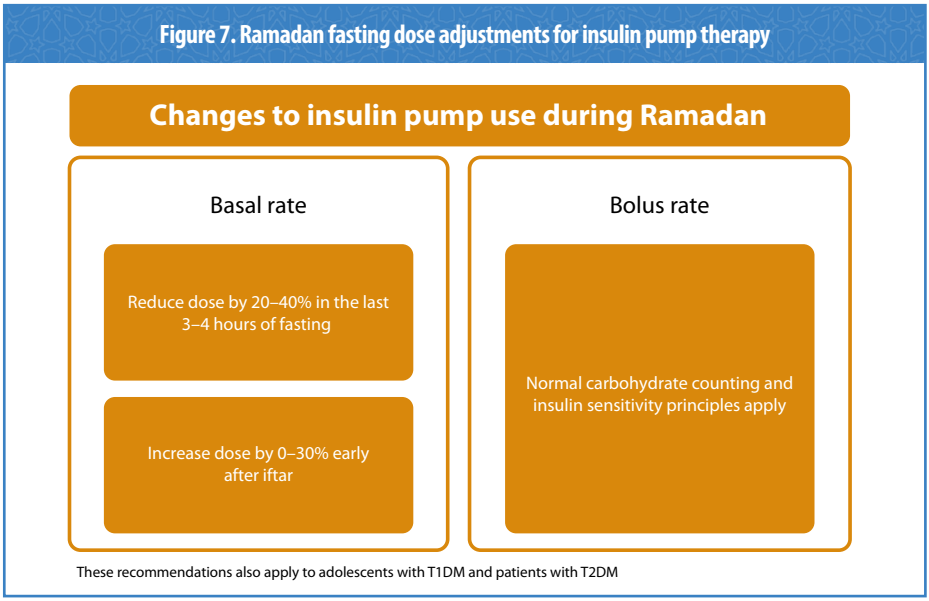
BG, blood glucose; HbA1c, glycated haemoglobin; n, number of patients included in study; NR, not reported; UAE, United Arab Emirates

In a non-Ramadan study, patients taking the long-acting insulin, glargine, could fast safely for 18 hours with only mild hypoglycaemic episodes reported [58] and another study found that patients taking ultralente during Ramadan could fast without experiencing severe hypoglycaemic episodes [57]. Insulin lispro provided better glycaemic control and a lower incidence of hypoglycaemia than regular human insulin in a small randomised study [56]. The *South Asian Consensus Guideline: Use of insulin in diabetes during Ramadan* states that 'Once- or twice-daily injections of intermediate- or long-acting insulin along with pre-meal rapid-acting insulin is the management of choice' [61]. If patients with T1DM decide to fast then adjustments to insulin dose are recommended and can be found in ***Figures 4*** and ***5***.

More recent studies in patients using insulin pumps reported no cases of severe hypoglycaemia although some episodes of hypoglycaemia required the fast to be broken and adjustments to the basal rate were needed [59, 60]. Recommended dose adjustments for insulin pump therapy during Ramadan are outlined in ***Figure 7***.

The decision by an individual with T1DM to fast during Ramadan must be respected. There is some evidence to suggest that, as long as they are otherwise stable and healthy, they can do so safely. However, strict medical supervision and focused education on how to control their glycaemic levels is essential

Figure 7. Ramadan fasting dose adjustments for insulin pump therapy



Young adults/adolescents with T1DM

Once a child reaches puberty they are expected to fast during Ramadan. Care for adolescents with T1DM, particularly in Ramadan, should be restricted to experts in the management of diabetes in this age group. There have been a number of studies, albeit with a limited number of patients, that have investigated fasting in adolescents with T1DM (***Table 9***) and the general consensus is that only some can fast safely if they have good hypoglycaemia awareness, good glycaemic control pre-Ramadan, have the knowledge and willingness to SMBG levels, are able to adjust medication as needed and are carefully supervised by an expert physician. As with adults, adolescents with T1DM who decide to fast (and their parents) must be aware of all potential risks associated with Ramadan fasting. Frequent blood glucose monitoring, observing the breaking fasting rules and avoiding fasting on 'sick days' are all essential to avoid complications [62]. Children and adolescents on a conventional twice-a-day regimen should take their usual morning dose before iftar and short-acting insulin at suhoor [63, 64]. Recommended dose adjustments for adolescents on MDI are outlined in ***Figure 8***. For those using insulin pumps the changes to dose are the same as those for adults (***Figure 7***).

As with adults, adolescents with T1DM who decide to fast (and their parents) must be aware of all potential risks associated with Ramadan fasting

Table 9. Studies evaluating insulin regimens in adolescents with T1DM during Ramadan

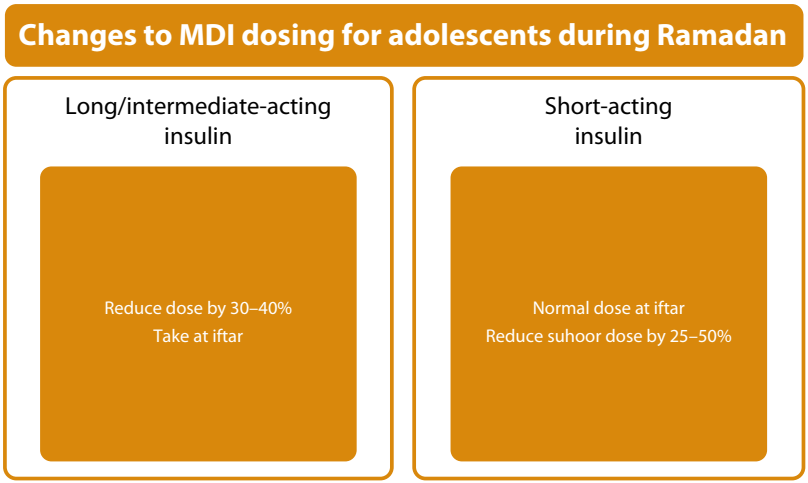
Insulin regimen	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Insulin (conventional BID regimen)	Zabeen et al, 2014 [64]	n=33 *Study type:* Observational *Country:* Bangladesh *Additional medication(s):* NR *Comparator:* None	Events: 2 patients from group I (those that completed fast; n=20) 3 patients from group II (those that broke fast; n=13) No severe episodes	Mean HbA1c pre-Ramadan vs post-Ramadan: Group I, 8.5% vs 8.1% Group II, 8.9% vs 9.4%	No significant change in body weight
	Al-Khawari et al, 2010 [63]	n=22 *Study type:* Observational *Countries:* UK, Kuwait *Additional medication(s):* NR *Comparator:* MDI	Events: BID<MDI 44% vs 61.5%	NR	↑ weight: 91% patients by 1–2 kg regardless of insulin regimen
Insulin (MDI)	AlAlwan et al, 2010 [65]	n=20 *Study type:* Observational *Country:* Saudi Arabia *Additional medication(s):* NR *Comparator:* Non-fasting group (n=8)	1 child in fasting group (n=12) withdrew due to hypoglycaemia	HbA1c pre-Ramadan vs post-Ramadan: Fasting group, 10.4% vs 10.4% Non-fasting group, 10.6% vs 10.4%	No significant change in body weight
Insulin pump	Bin-Abbas, 2008 [66]	n=9 *Study type:* Observational *Country:* Saudi Arabia *Additional medication(s):* NR *Comparator:* Conventional BID regimen	Events per patient per month: Pump<BID 16 vs 29 ($p<0.002$) No severe episodes	Mean HbA1c: Pump<BID 7.8% vs 9.1% ($p<0.001$)	

Table 9. Studies evaluating insulin regimens in adolescents with T1DM during Ramadan *(cont.)*

Insulin regimen	Authors	Study details	Hypoglycaemia	Glycaemic control	Additional observations
Insulin pump or glargine plus short-acting insulin	Kaplan & Afandi, 2015 [52]	n=21 *Study type:* Observational *Country:* UAE *Additional medication(s):* NR *Comparator:* None	Hypoglycemia (<70 mg/dL [3.9 mmol/L]) was observed in 14.2% of the fasting hours and 2.5% of the eating hours (p<0.05) Episodes of unreported hypoglycaemia observed	Large fluctuations in BG during fasting and eating hours were noted	Patients were able to fast for a majority (85%) of the days; 76% fasted ≥25 days Hyperglycemia (>300 mg/dL [16.7 mmol/L]) was observed in 12% of the fasting hours and 17% of the eating hours (p<0.05)

BG, blood glucose; BID, twice-a-day; CGM, continuous glucose monitor; HbA1c, glycated haemoglobin; MDI, multiple daily injections; n, number of patients included in study; NR, not reported; UAE, United Arab Emirates

Figure 8. Ramadan fasting dose adjustments for MDI therapy in adolescents with T1DM



MDI, multiple daily injections

Management in pregnancy

Fasting during pregnancy has always been a contentious issue. All pregnant women have the option not to fast if they are worried about either their health or that of their foetus. However, many do decide to participate as they feel guilty if they do not [67, 68]. If a pregnant woman elects not to fast she will be expected to make up missed days once the baby has been born, presumably at a time when others within the family are not

fasting. Fasting alone is challenging and this may deter pregnant women from obtaining the exemption [68, 69]. In fact, evidence from some countries suggests that the majority of pregnant women (70–90%) do observe the fast [70], although surveys suggest that they may not manage the full month [67, 71, 72]. This is despite the fact that pregnant women with diabetes are considered very high risk and are advised not to fast during Ramadan [2, 49, 50].

Pregnant women with diabetes are stratified as VERY HIGH RISK with a high probability of harm and are advised NOT to fast

Some studies in healthy pregnant women, with no diabetes, have shown no harmful effects of fasting on baby or mother [71, 73-75], although one study found that low birth weight was 1.5-times more likely in women who were in the first trimester when they fasted compared with non-fasting mothers [76]. Other studies have also demonstrated detrimental effects. Decreased placental weight was observed in women who were in second and third trimester when they fasted although birth weight was unaffected [77]. The authors suggested that this may have an effect on foetal programming with long-term health implications [77]. Data from Uganda and Iraq suggest a possible link between prenatal exposure to Ramadan and learning disabilities in adulthood [70]. With such discrepancies in the literature and the religious licence for women not to fast during pregnancy, it is perhaps not surprising to find that at present there is a consensus to categorise pregnant women as high risk, until further evidence is available. However, fasting during pregnancy is an important personal decision and a practical approach would be to explain the potential effects on mother and foetus, thereby empowering the patient with knowledge and education regarding self-management skills for good pregnancy outcomes. Women with gestational diabetes who are well-controlled pre-Ramadan on diet or metformin are at lower risk of hypoglycaemia. The risk of postprandial hyperglycaemia however still exists. If they insist on fasting then they should aim at achieving postprandial glucose targets and they should be managed by an expert team. However, patients on SU therapy and/or insulin should be strongly advised against fasting due to the higher risk of hypoglycaemia. Modifications to diet and insulin regimens such as those outlined for patients with T1DM will be required in conjunction with frequent blood glucose monitoring, focused education and strict medical supervision.

Fasting during pregnancy is an important personal decision. A practical approach would be to explain the potential effects on mother and foetus thereby empowering the patient with knowledge and education regarding self-management skills for good pregnancy outcomes

8.4 Post-Ramadan follow-up

Eid ul-Fitr, a 3-day festival, marks the end of Ramadan and patients with diabetes should be made aware of the risks of overindulgence during this time. A post-Ramadan follow-up meeting with HCPs is advisable in order to discuss medication and regimen readjustments and assess how the patient handled the fasting. It should be stressed to the patient that a safe fast one year does not automatically make them a low risk for the next year due to the progressive nature of the disease.

Summary

- A pre-Ramadan assessment is vital for any patient with diabetes who intends to fast in order to evaluate the risks, educate the patient in self-management of the condition during Ramadan and to produce a patient-specific treatment plan.
- With the correct advice and support from HCPs most people with T2DM can fast safely during Ramadan.
- Patients taking metformin, short-acting insulin secretagogues, SUs or insulin will need to make adjustments to dose and or timings to reduce the risk of hypoglycaemia while maintaining good glycaemic control.
- Newer OADs including incretin-based therapies are associated with a lower risk of hypoglycaemia and may be preferable for use during Ramadan.
- SGLT2 inhibitors are probably safe but should be used with caution in some patients. More data regarding the use of SGLT2 inhibitors during Ramadan are required.
- Patients classified as very high/high risk including T1DM and pregnant women with diabetes need close medical supervision and focused Ramadan-specific education if they insist on fasting.
- A post-Ramadan follow-up consultation is recommended.

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