

CHAPTER 10

Management of Type 2 diabetes when fasting during Ramadan

Chapter lead:

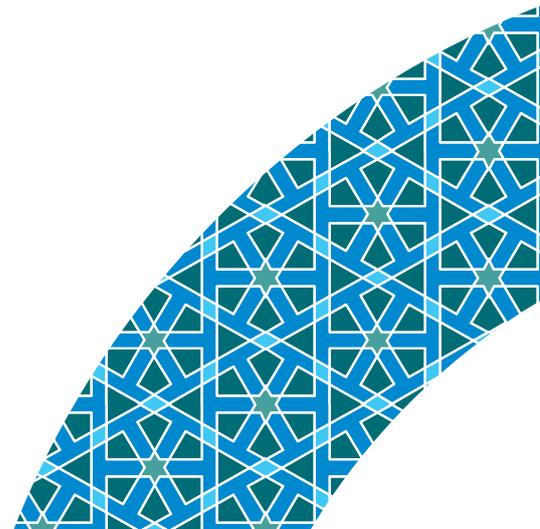
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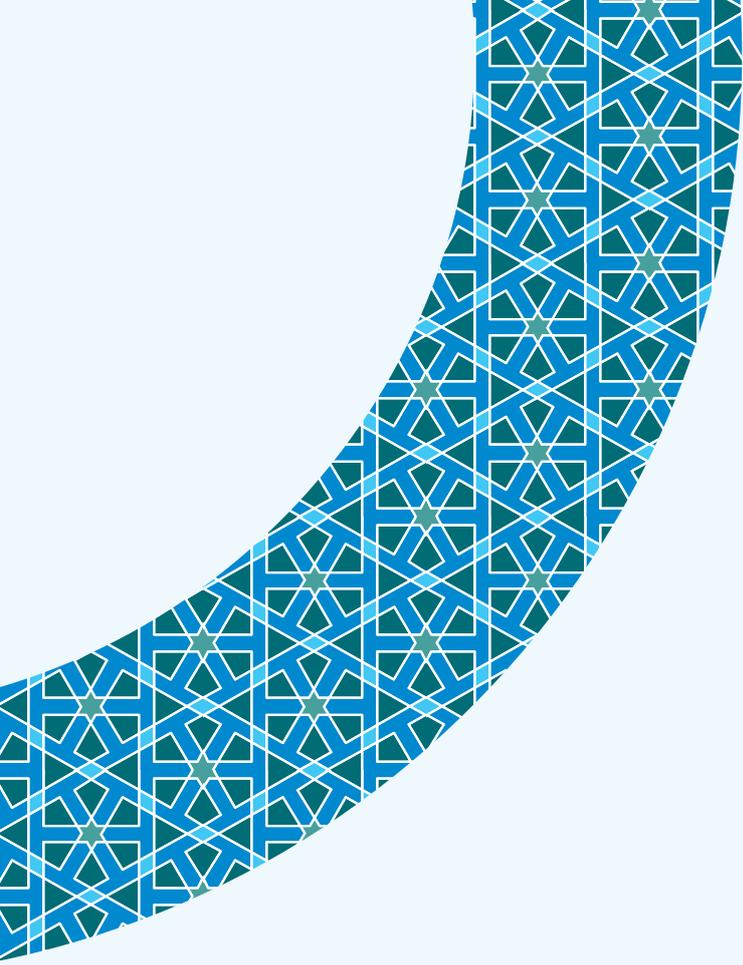
Authors:

Mohamed Hassanein

Tarik A. Elhadd

Nazeer Ahmed Mohamed







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WHAT IS KNOWN?

- A pre-Ramadan assessment is very important for all individuals seeking to fast during Ramadan.
- The majority of people with type 2 diabetes mellitus (T2DM) can safely fast during Ramadan.
- Individuals taking metformin, sulphonylureas (SUs), insulin secretagogues or insulin will need to make treatment adjustments to reduce the risk of hypoglycaemia.
- A post-Ramadan Assessment is recommended.

WHAT IS NEW?

- New studies on certain SUs highlight efficacy and ensure safe fasting for people with T2DM that wish to fast during Ramadan.
- New studies on Sodium-glucose co-transporter-2 (SGLT2) inhibitors provide more confidence on the use of specific drugs of this class during Ramadan fasting
- New studies have been published that provide stronger evidence regarding the use of different types of insulin and or Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in people with T2DM that fast during Ramadan
 - Dose modifications alongside stricter schedules of self-monitoring of blood glucose (SMBG) are important tools to ensure safe fasting with good glycaemic control during Ramadan.
- Individuals on multiple antidiabetic therapies need individualised dose reductions to avoid additional risks of hypoglycaemia or hyperglycaemia when fasting during Ramadan.

WHAT IS MISSING?

- Further randomised controlled trials for different antidiabetic therapies are required to provide more specific treatment recommendations.

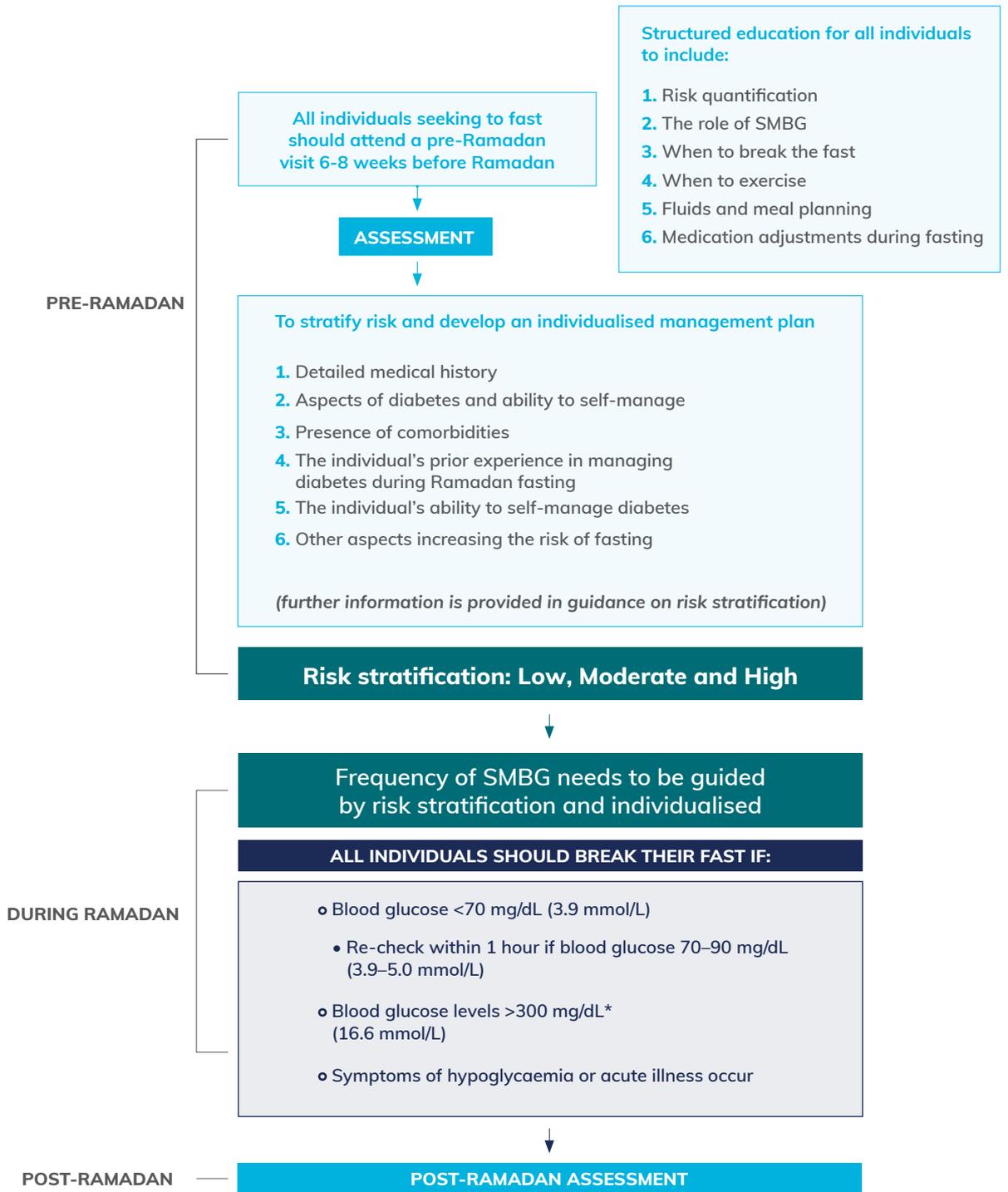
1. INTRODUCTION

Fasting during Ramadan can lead to metabolic changes during the fasting and eating hours and managing type 2 diabetes mellitus (T2DM) can present several challenges. One of the main risks is having uncontrolled blood glucose levels which can lead to hyperglycaemia and/or hypoglycaemia and measures need to be taken to minimise these risks. These measures include increasing self-monitoring of blood glucose (SMBG) and adjusting antidiabetic medications, which indirectly affect insulin effectivity [1], and insulin regimens. Many people with diabetes fast during Ramadan and the majority can do so safely if they follow expert advice and guidance. Existing guidelines and treatment algorithms recommend the individualisation of guidance as the best approach for the management of T2DM during Ramadan [2, 3]. This process can be broken down into a number of steps including a pre-Ramadan assessment, medication adjustments during Ramadan and a post-Ramadan follow-up.

2. STEP 1: PRE-RAMADAN ASSESSMENT

All people with diabetes seeking to fast during Ramadan should have a pre-Ramadan assessment with their healthcare provider, ideally, 6–8 weeks before the start of Ramadan. Healthcare professionals (HCP) can obtain a detailed medical history on individuals seeking to fast and review their glycaemic control and capability to self-manage their diabetes. Among other things, the HCP can apply the new risk scoring process to stratify the individual seeking to fast as “high”, “moderate” or “low” and provide advice on whether fasting is safe (see **Figure 1**). Information on risk stratification is described in detail, please see **chapter 5: Risk stratification of people with diabetes before Ramadan**.

If the individual decides to fast, which may be against the advice of the HCP, an individualised management plan must be provided. An integral part of management plan is Ramadan-focused education which should include information on diet, exercise, the frequency of SMBG and, critically, when to break the fast to avoid harm, (further information is provided in **chapter 7: Pre-Ramadan Assessment and Education**). Those individuals that wish to fast need to increase their frequency of SMBG to reduce risk of hypoglycaemia and/or hyperglycaemia. The use of continuous glucose monitoring (CGM) or flash glucose monitoring (FGM) systems can provide more detailed information especially for those treated with multiple insulin doses. Users of such devices are advised to increase the frequency of downloading and review of their glucose data. Moreover, dietary information must also be provided as Ramadan changes not only the timing of meals but often the types of food consumed. **Chapter 8: The Ramadan Nutrition Plan (RNP) for people with diabetes** describes the Ramadan Nutrition Plan as a way to educate individuals on the importance of diet during the holy month of Ramadan.



SMBG, self-monitoring blood glucose

*This applies for those with sudden rise in blood glucose level, individualisation of care is advisable

FIGURE 1
Assessment flowchart

3. STEP 2: MEDICATION ADJUSTMENTS

The type of medication the individual is taking for the management of their diabetes influences the potential risks that fasting during Ramadan may lead to and, therefore, needs careful attention when formulating the treatment plan. The following sections review the available evidence for the use of insulin and non-insulin antidiabetic therapies when fasting during Ramadan and provide medication dose adjustments where applicable.

3.1 Metformin

Metformin is the most commonly used, first-line, oral antidiabetic 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 per day, and a prolonged release formulation which is typically taken just once a day.

Severe hypoglycaemia in non-fasting individuals receiving metformin is rare, and while there are no randomised controlled trials (RCTs) on the use of metformin in people with T2DM that fast during Ramadan, it is considered safe for individuals on metformin monotherapy to fast. Dose adjustments are shown in **Figure 2**.

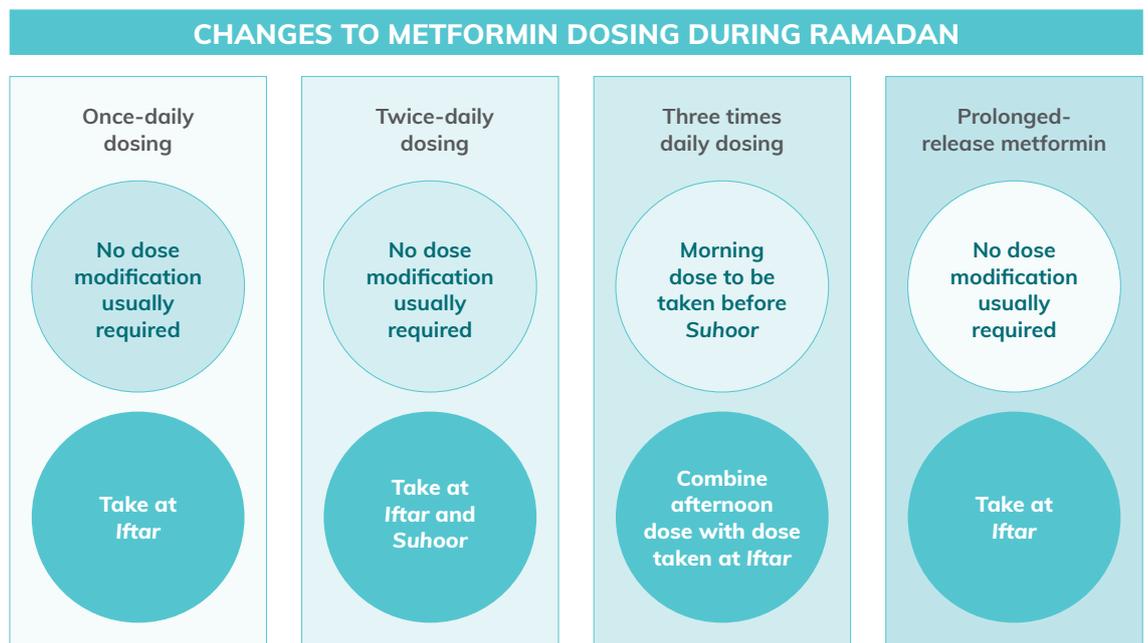


FIGURE 2
Dose adjustments for metformin

3.2 Acarbose

Acarbose is a drug that inhibits the actions of alpha-glucosidase, an enzyme that breaks down carbohydrates into glucose within 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 diabetes control. However, due to its lower efficacy when compared with metformin, and the occurrence of side effects such as flatulence, its clinical use has been limited.

While no RCTs have been conducted on acarbose in people with T2DM that fast during Ramadan, NO DOSE MODIFICATION is considered necessary as the risk of hypoglycaemia is low.

3.3 Thiazolidinediones

Thiazolidinediones (TZDs) improve the insulin sensitivity of fat, muscle, liver and peripheral tissue cells by specifically activating the peroxisome proliferator-activated receptor (PPAR)- γ . This receptor controls the level of proteins involved in glucose regulation and uptake; activation of PPAR γ via TZDs can increase glucose uptake and utilisation, particularly in adipose tissue. An increase in glucose uptake will subsequently lower glucose levels in the blood [4]. As TZDs function without increasing insulin secretion, the risk of hypoglycaemia in non-fasting people on TZD monotherapy is very low [5].

Pioglitazone is the only TZD widely approved for use in T2DM but there is limited clinical data on its use during Ramadan. One study 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 associated with the pioglitazone group compared with a non-significant loss in weight (-0.46 kg) in the placebo group [6].

TABLE 1: STUDIES OF TZDS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
Pioglitazone	Vasan et al., (2006) [6]	N=86 Study type: Double-blind, randomised, controlled trial Country: India Additional medication(s): Oral antihyperglycaemic agents Comparator: Placebo	A non-significant increase in the number of hypoglycaemic events was associated with Pioglitazone, when compared with placebo (39 vs 32, respectively; p=0.21)	Fructosamine levels were higher in the placebo group when compared with the Pioglitazone group: Early Ramadan: (p=0.003) Mid-Ramadan: (p=0.01) Post-Ramadan: (p=0.04)	The pioglitazone group saw an increase in weight 3.02kg (p=0.001) The placebo group saw a non-significant decrease in weight 0.46 kg (p=0.37)

N, total number of participants included in study

Due to the low risk of hypoglycaemia with pioglitazone, NO DOSE MODIFICATION is required during Ramadan, but dose should be taken with *Iftar*.

TZD medication should be taken with *iftar* rather than *Suhoor* and individuals should not be switched onto to this class of medications close to Ramadan as it can take up to three months for an optimal antihyperglycaemic effect of these drugs to be reached [3].

3.4 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 among individuals treated with Repaglinide during Ramadan [7, 8], while a third demonstrated no difference in rates of hypoglycaemia when compared with insulin glargine or glimepiride — a sulfonylurea (SU) based therapy [9]. Similarly, in two randomised trials, a low incidence of hypoglycaemic events was associated with repaglinide use during Ramadan, occurring in similar proportions to individuals 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 a shorter duration of action than repaglinide, the risk of hypoglycaemia occurring when fasting during Ramadan is expected to be low [2].

TABLE 2: STUDIES OF REPAGLINIDE IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
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 statistically significant differences observed between groups Symptomatic events during Ramadan: • Repaglinide: 2.9%, • Glimepiride: 3.5%	BG levels: Glimepiride was associated with lower BG levels than repaglinide	NR
	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

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TABLE 2: STUDIES OF REPAGLINIDE IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
Repaglinide	Cesur et al., (2007) [9]	N=65 Study type: Observational Country: Turkey Additional medication(s): NR Comparators: SU (glimepiride), insulin glargine	Individuals experiencing event: No significant difference between treatment groups of glimepiride, repaglinide or insulin glargine (14.3%, 11.1%, 10.0%, respectively) No severe episodes were noted	No significant difference between groups in terms of glycaemic control	No change in BMI in any group was identified
	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)	Ramadan at midday with BG levels below 4.5 mmol/L (%): Repaglinide showed fewer cases when compared with glibenclamide (2.8% and 7.9%, respectively; p=0.001)	Fructosamine levels: Repaglinide led to a statistically significant decrease from baseline (p<0.05) Glibenclamide: did not lead to any statistically significant changes No statistically significant change in HbA1c in either group	NR
	Sari et al., (2004) [8]	N=52 Study type: Observational Country: Turkey Additional medication(s): NR Comparator: SU (glimepiride or gliclazide)	Events: No events reported in repaglinide group and 1 reported in glimepiride group	No statistically significant changes identified in either treatment group	No statistically significant changes in weight were identified in either treatment group

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

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 sizes.

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

GLP-1 RAs mimic the incretin hormone and decrease glucose levels 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 [12, 13]. As they act in a glucose-dependent manner, the risk of severe hypoglycaemia is low when used as monotherapy, but this risk may be higher when given with sulphonylureas (SUs) or insulin [14].

A few studies on the use of GLP-1 RAs during Ramadan have been published and details can be found in **Table 3**.

TABLE 3: STUDIES OF GLP-1 RAS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
Exenatide	Bravis et al., 2010 [15]	N=43 Study type: Observational Country: UK Additional medication(s): Metformin Comparator: SU (gliclazide)	Events: Exenatide led to a non-significant decrease (0.08%) in the number of events of hypoglycaemia (p=0.43) Gliclazide led to a statistically significant 53.0% increase in the number of events of hypoglycaemia (p=0.03)	NR	Weight change: Exenatide led to a non-significant increase of 0.12 kg (p=0.55) Gliclazide led to a statistically significant increase of 0.68 kg (p=0.01)
Liraglutide	Azar et al., (2015) [16]	N=343 Study type: Open-label, randomised controlled trial Countries: Algeria, India, Israel, Lebanon, Malaysia, South Africa, UAE Additional medication(s): Metformin Comparator: SU (gliclazide, glipizide or glibenclamide)	Symptomatic events during Ramadan: Liraglutide led to fewer events than SU (p=0.0009) Symptomatic events from baseline to end of Ramadan: Liraglutide led to fewer events than SU (p<0.0001)	Fructosamine levels during Ramadan were similar among Liraglutide and SU treated individuals (despite better glycaemic control in liraglutide group at start of Ramadan) Fructosamine levels decreased from baseline to end of Ramadan: Liraglutide led to a greater decrease than SU (p<0.05) HbA1c (%) levels decreased from baseline to end of Ramadan: Liraglutide led to a greater decrease than SU (p<0.0001)	Body weight decreased during Ramadan: Liraglutide led to a greater decrease than SU (p=0.0091) Body weight decreased from baseline to end of Ramadan: Liraglutide led to a greater decrease than SU (p<0.0001)

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TABLE 3: STUDIES OF GLP-1 RAS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
Liraglutide	Brady et al., (2014) [17]	N=99 Study type: Open-label, randomised controlled trial Country: UK Additional medication(s): Metformin Comparator: SU	Self-recorded episodes of BG ≤ 3.9 mmol/l: Liraglutide led to fewer events than SU ($p < 0.0001$) No severe episodes were noted	Change in HbA1c (%): 3 weeks post-Ramadan Liraglutide led to a greater decrease than SU (0.54 and 0.27, respectively; $p = 0.03$) 12 weeks post-Ramadan Liraglutide showed some evidence of a greater decrease than SU (0.32 and 0.02, respectively; $p = 0.05$)	Body weight (kg): 3 weeks post-Ramadan Liraglutide led to a greater decrease than SU (2.23 and 0.42, respectively; $p = 0.02$) 12 weeks post-Ramadan Liraglutide led to a greater decrease than SU (2.57 and 0.25, respectively; $p = 0.002$)
	Khalifa et al., (2015) [18]	N=111 Study type: Observational Country: UAE Additional medication(s): Insulin, SU, none Comparator: None	No severe hypoglycaemia	HbA1c post-Ramadan compared with baseline: 8.0% and 7.4%, respectively ($p < 0.001$)	NR

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TABLE 3: STUDIES OF GLP-1 RAS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
Lixisenatide	Hassanein et al., (2019) [19]	<p>N=184</p> <p>Study type: Open label randomised controlled trial</p> <p>Countries: Kuwait, India, Israel, Lebanon, Turkey</p> <p>Additional medication(s): Basal insulin (BI), Metformin</p> <p>Comparator: SU (glibenclamide, gliclazide, glimepiride, glipizide)</p>	<p>Individuals experiencing documented events:</p> <p>In the pre-Ramadan period Lixisenatide and BI was associated with fewer events than SU and BI (Odds Ratio 0.20; 95% CI 0.04-0.99)</p> <p>During the whole treatment period of pre-Ramadan, during Ramadan and after Ramadan</p> <p>Lixisenatide and BI was associated with fewer events than SU and BI (Odds Ratio 0.22; 95% CI 0.07-0.70)</p> <p>No hypoglycaemic events occurred during the Fasting hours for those on Lixisenatide and BI while 9 events occurred for those on BI and SUs.</p> <p>Only one episode of severe hypoglycaemia occurred during the whole study and within the BI + SU arm</p>	<p>There were reductions from baseline in HbA1c (%) seen in both treatment groups from baseline and the post-Ramadan period.</p> <p>However, there were no observed differences between treatment groups</p>	<p>There were reductions from baseline in body weight seen in both treatment groups from baseline and the post-Ramadan period.</p> <p>There were no observed differences between treatment groups</p>
	Sahay et al., (2020) [20]	<p>N=150</p> <p>Study type: Open label randomised controlled trial</p> <p>Countries: India</p> <p>Additional medication(s): Basal insulin (BI)</p> <p>Comparator: SU</p>	<p>Individuals experiencing documented events:</p> <p>During the Ramadan fasting period the number of events for those treated with Lixienatide and BI was 1 while for those treated with BI and SU were 5 (Odds Ratio 0.22; 95% CI 0.02-1.93)</p> <p>Any hypoglycaemic event:</p> <p>During the whole treatment period of pre-Ramadan, during Ramadan and after Ramadan, Lixienatide and BI was associated with fewer events than SU and BI (Odds Ratio 0.06; 95% CI 0.01-0.46)</p> <p>Only 1 severe event in the study among those with SU and BI</p>	<p>There were reductions from baseline in HbA1c (%) seen in both treatment groups from baseline and the post-Ramadan period.</p> <p>However, there were no observed differences between treatment groups</p>	<p>There were reductions from baseline in body weight seen in both treatment groups from baseline and the post-Ramadan period.</p>

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



The TREAT4 Ramadan trial examined the safety and efficacy of liraglutide compared to SU as add-on to metformin treatment among people with T2DM in the UK during Ramadan [17]. The primary outcome was the proportion of individuals who achieved a composite endpoint of HbA1c <7% (8.6 mmol/L), no weight gain and no severe events of hypoglycaemia noted by 12 weeks post-Ramadan. While more individuals achieved this primary outcome in the liraglutide group compared with the SU group (26.7% and 10.3%, respectively), this did not reach statistical significance. However, there was a statistically significant reduction in HbA1c levels and body weight at both 3 and 12 weeks post-Ramadan in the liraglutide group compared with the SU group (**Table 3**) [17]. The incidence rate of self-reported hypoglycaemic events was also significantly lower in the liraglutide group ($p < 0.0001$) [17].

In the open-label LIRA-Ramadan study conducted in Africa and Asia, participants with T2DM were randomised to switch to once-daily liraglutide or continue on SU, both in combination with metformin [16]. The primary endpoint was a change in fructosamine from the beginning to the end of Ramadan. Similar fructosamine reductions were observed in both cohorts despite there being a better glycaemic control at the beginning of Ramadan in the liraglutide group. More individuals in the liraglutide group reached the composite endpoint (HbA1c <7% or 8.6 mmol/L, no weight gain, no hypoglycaemia) than in the SU group at the end of Ramadan (51.3% vs 17.7%; $p < 0.0001$). Individuals in the liraglutide arm also demonstrated better weight control and fewer confirmed hypoglycaemic episodes compared with the SU group [16].

The effects of adding liraglutide to pre-existing antidiabetic regimens (including SU and insulin) during Ramadan was investigated in an observational trial in the UAE. 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 [18].

The recent LixiRam study was a phase IV, randomised, open-label, 12–22 week study conducted in people with insufficiently controlled T2DM that intended to fast during Ramadan. Individuals were treated with lixisenatide, as an add-on to basal insulin or with SUs together with basal insulin and one oral glucose-lowering agent. Those that took lixisenatide had fewer documented symptomatic hypoglycaemic events than those on SUs (3.3% and 8.9%; OR, 0.34; 95% CI, 0.09–1.35; proportion difference, -0.06; 95% CI, -0.13 – 0.01). The difference was statistically significant for ‘any hypoglycaemia’ (lixisenatide and basal insulin (4.3%) compared to SUs and basal insulin (17.4%); OR, 0.22; 95% CI, 0.07–0.68; proportion difference -0.13, 95% CI -0.22 to -0.04) [19].

A sub-group analyses [20] of the full study [19] was performed on 150 participants from India with T2DM who were randomised to receive either lixisenatide and basal insulin or SUs and basal insulin during Ramadan. The incidence of any hypoglycaemic event was lower among those treated with lixisenatide and basal insulin compared to those on SUs and basal insulin during Ramadan fasting (1.3% and 14.7%, respectively; OR: 0.09; 95% CI: 0.01–0.69). However, the differences in the documented events of hypoglycaemia between those treated with lixisenatide and basal insulin and those treated with SUs and basal insulin was not statistically significant (odds ratio (OR): 0.22; 95% CI, 0.02–1.93) [20].

A small observational study in people with T2DM that were treated with exenatide in addition to metformin reported no significant changes to weight or hypoglycaemic episodes during Ramadan [15]. There is yet more research needed into the use of newer GLP-1 Ras during Ramadan (such as dulaglutide and albiglutide).

These studies demonstrate that liraglutide and Lixisenatide are safe as an add-on treatment to pre-existing antidiabetic regimens including metformin and insulin. 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 liraglutide, lixisenatide, exenatide have been appropriately DOSE-TITRATED prior to Ramadan (at least 2–4 weeks), NO FURTHER TREATMENT MODIFICATIONS are required.

3.6 Dipeptidyl peptidase-4 (DPP-4) inhibitors

DPP-4 is an enzyme that rapidly metabolises 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 [13]. 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 antidiabetic drugs with low risk of hypoglycaemia in non-fasting patients [2]. Four RCTs [21–24] and five observational studies [25–29] have examined the efficacy and safety of DPP-4 inhibitor treatment during Ramadan and are detailed in **Table 4**.

TABLE 4: STUDIES OF DPP-4 INHIBITORS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
Sitagliptin	Al Sifri et al., (2011) [21]	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 events: Those treated with Sitagliptin had a lower risk of events than those treated with SU (p<0.001) Individuals experiencing symptomatic events: Sitagliptin was associated with fewer events than SU (6.7% and 13.2%) Breakdown of the events in the SU treated group: in ascending order the proportion of events in each group were Gliclazide 6.6%, glimepiride 12.4% and glibenclamide 19.7%	NR	NR

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TABLE 4: STUDIES OF DPP-4 INHIBITORS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
Sitagliptin	Aravind et al., (2012) [22]	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 events: Sitagliptin was associated with a lower risk of events than SU (p=0.028) Individuals experiencing symptomatic events: Sitagliptin was associated with a lower risk of symptomatic events than SU (3.8% and 7.3%) Breakdown of the events in the SU group: in ascending order the proportion of events in each group were Gliclazide 1.8%, glimepiride 5.2% and glibenclamide 9.1%	NR	NR
Vildagliptin	Al-Arouj et al., (2013) [25]	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)	Individuals experiencing ≥ 1 symptomatic event: Vildagliptin was associated with fewer events than SU (5.4% and 19.8%, respectively; p< 0.001) Among those treated with SU: Glipizide 12.5%, glimepiride 17.9%, gliclazide 19.2% glibenclamide 31.8% Events confirmed by BG level: Vildagliptin was associated with a lower risk than SU (2.7% and 12.9%, respectively) Individuals experiencing severe events: there was weak evidence that Vildagliptin was associated with a lower risk of severe events than SU (0 and 4, respectively; p=0.053)	HbA1c change from baseline: SU was associated with a small increase of 0.02% Vildagliptin was associated with a decrease of 0.24% (p<0.001)	Body weight decrease: Vildagliptin was associated with a greater decrease than SU (0.76 kg and 0.13 kg, respectively; p<0.001)
	Devendra et al., (2009) [26]	N=52 Study type: Observational Country: UK Additional medication(s): Metformin Comparator: SU (gliclazide)	Individuals experiencing ≥ 1 event: Vildagliptin was associated with a lower risk gliclazide (7.7% and 61.5%, respectively; p< 0.001) Change in the number of events during Ramadan: Vildagliptin caused a greater decrease in the number of events when compared to gliclazide (p=0.0168)	HbA1c change: similar between both treatment groups	Both treatment groups were associated with a decrease in weight during Ramadan

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TABLE 4: STUDIES OF DPP-4 INHIBITORS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
Vildagliptin	Halimi et al., (2013) [27]	N=198 Study type: Observational Country: France Additional medication(s): Metformin Comparators: SU or glinide	Individuals experiencing ≥ 1 symptomatic event: the rates of symptomatic events were similar between all groups (34.2% Vildagliptin and 37.2% comparators; $p=0.665$) Confirmed by BG level: events among those treated with Vildagliptin was similar to those treated with comparators (23.5% and 30.8%, respectively; $p=0.260$) Individuals experiencing ≥ 1 severe event and/or medical visit: There was evidence that Vildagliptin treatment led to fewer severe events when compared to comparators (2.6 % and 10.4%, respectively; $p=0.029$)	Levels were stable and similar in both groups	Weight was stable in both treatment groups
	Hassanein et al., (2011) [28]	N=59 Study type: Observational Country: UK Additional medication(s): Metformin Comparator: SU (gliclazide)	Individuals experiencing events: Vildagliptin was associated with fewer events than SU (-41.7% decrease; $p=0.0002$)	HbA1c: Vildagliptin was associated with lower levels when compared to SU (-0.5%; $p=0.0262$)	No significant changes in weight in either group were observed No significant difference between groups were observed
	Hassanein et al., (2014) [23]	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 events: Vildagliptin and gliclazide showed no clear differences (6.0% and 8.7%, respectively; $p=0.173$) Confirmed events: Vildagliptin was associated with fewer events when compared to gliclazide (3.0% and 7.0%, respectively; $p=0.039$)	No significant changes were observed in either group	No significant difference between groups were observed

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TABLE 4: STUDIES OF DPP-4 INHIBITORS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
Vildagliptin	Malha et al., (2014) [24]	N=69 Study type: Open-label, randomised, controlled trial Country: Lebanon Additional medication(s): Metformin Comparator: SU (glimepiride, gliclazide)	Events: the number of events in those treated with Vildagliptin was similar to those treated with SU (19 and 26, respectively; p=0.334)	HbA1c change: reductions were seen in both groups during Ramadan but no differences in this reduction were observed between treatments groups	Post-Ramadan BMI: Vildagliptin was associated with a decrease in weight at post-Ramadan from baseline (-0.7 kg/m ²) SU was associated with an increase in weight post-Ramadan from baseline (+0.9 kg/m ²)
	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)	Individuals experiencing events: No clear differences were seen between Vildagliptin and SU (0% and 4.8%, respectively; p=0.104)	HbA1c change from baseline: SU was not associated with any changes in HbA1c levels from baseline (p=0.958) Vildagliptin was associated with a decrease in HbA1c levels from baseline -0.43% (p= 0.009) Individuals achieving HbA1c <7.0% (8.6 mmol/L): There was weak evidence that Vildagliptin leads to a greater number of individuals achieving target levels than those treated with SU (16.4% and 4.8%, respectively; p=0.055)	Between-group weight decrease in weight (kg): Vildagliptin was associated with a greater decrease in weight than those treated with SU (1.2 and 0.03, respectively; 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; UAE, United Arab Emirates; UK, United Kingdom; USA, United States of America; SU, sulphonylurea

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 participants with T2DM treated with sitagliptin or SUs (with or without concomitant metformin) that fasted during Ramadan. Overall, the risk of hypoglycaemia significantly decreased on the sitagliptin-based regimen compared to continuing with SU treatment (relative risk ratio = 0.51 95% CI 0.34 to 0.75; p<0.001) [21].

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 = 0.52 95% CI 0.29 to 0.94; $p=0.028$) [22]. In both studies the risk of hypoglycaemia with sitagliptin was equivalent to that of the SU gliclazide.

In the STEADFAST study, 557 individuals with T2DM in the Middle East, Europe and Asia, were randomised to receive either vildagliptin or gliclazide (plus metformin) while fasting during Ramadan. Participants in the study were switched to the study drug at least 8 weeks prior to fasting and continued treatment for up to four weeks after [23]. No statistically significant difference in the reporting of any hypoglycaemic event was observed between the two groups. However, the proportion of individuals experiencing at least one confirmed hypoglycaemic event during Ramadan was lower on vildagliptin when compared with gliclazide (3.0% and 7.0%, respectively $p=0.039$). 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 when compared to SU during Ramadan (Table 4). One small study in the UK investigated the addition of vildagliptin or gliclazide to treatment regimens during the fasting period. Compared with the period 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 individuals (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 where no self-reported hypoglycaemic events were reported in the vildagliptin group compared with 35 events in 15 (41.7%) individuals in the gliclazide arm (including one severe event). In addition, the change in HbA1c from baseline to post-Ramadan was statistically 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 that compared the incidence of hypoglycaemic events during Ramadan in individuals who received vildagliptin or an insulin secretagogue in addition to metformin did not find a statistically significant difference in the number of individuals experiencing at least one hypoglycaemic event [27]. However, the proportion of individuals 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 individuals achieving HbA1c $<7.0\%$ (8.6 mmol/L) among individuals treated with vildagliptin while fasting during Ramadan compared with those treated with SU. No hypoglycaemic events occurred in the vildagliptin group [29].

The VIRTUE study, conducted in the Middle East and Asia, enrolled 1,315 individuals with T2DM. Similarly, it was found that DPP-4 inhibitor treatment (vildagliptin) led to significantly hypoglycaemic events during Ramadan compared with those on SUs (5.4% and 19.8%,



respectively; $p < 0.001$). Individuals on vildagliptin also demonstrated significant reductions in HbA1c and body weight from baseline compared with those on SUs [25].

A recent meta-analysis of 16 RCTs and 13 observational studies in people with T2DM who fasted during Ramadan suggested, in a pooled analysis, DPP-4 inhibitors were associated with the lowest incidence of hypoglycaemic events compared with SU [30]. Other more recently approved DPP-4 inhibitors (alogliptin, saxagliptin, and linagliptin) have not yet been studied during Ramadan and further research is needed.

Moreover, Loh HH *et al.* performed a systematic review and a meta-analysis on studies comparing the use of DPP4 inhibitors against SUs among Muslim individuals with T2DM who fast in Ramadan (N=4,276). DPP4 inhibitors showed similar efficacy to SUs in reducing HbA1c levels and weight change. Compared to insulin secretagogue, individuals on DPP4 inhibitors had a lower risk of hypoglycaemia; among those treated with DPP4 inhibitors the risk of symptomatic hypoglycaemia reduced by nearly 50%, and severe hypoglycaemia by almost 80%. The authors advocated DPP4 inhibitors to be more suitable to individuals deemed to be at high risk of hypoglycaemia (including the elderly, those with renal impairment, erratic food intake or those with history of hypoglycaemia while on SU treatments [31].

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

DPP4-I do NOT REQUIRE TREATMENT MODIFICATIONS during Ramadan.

3.7 Sulphonylureas (SUs)

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 in individuals that fasted during Ramadan are outline in **Table 5**.

TABLE 5: STUDIES OF SULPHONYLUREAS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
≥ 1 SUs (glibenclamide, gliclazide, glimepiride and/or glipizide)	Aravind et al., (2011) [32]	N=1,378 Study type: Observational Countries: India, Israel, Malaysia, UAE, Saudi Arabia Additional medication(s): Metformin (not all patients) Comparators: NR	Symptomatic individuals: in ascending order the proportion of events in each group were Gliclazide 14.0%, glimepiride 16.8% and glibenclamide 25.6% Severe events: in ascending order the proportion of severe events were Gliclazide 2.6%, glimepiride 5.1% and glibenclamide 10.8%	NR	NR
	Aravind et al., (2012) [22]	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 events: Sitagliptin was associated with a lower risk of symptomatic events than SU (p=0.028) Breakdown of SU group: In ascending order, the proportion of severe events were Gliclazide 1.8%, glimepiride 5.2% and glibenclamide 9.1%	NR	NR

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TABLE 5: STUDIES OF SULPHONYLUREAS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
≥1 SUs (glibenclamide, gliclazide, glimepiride and/or glipizide)	Al Sifri et al., (2011) [21]	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 events: Those treated with Sitagliptin had a lower risk of events than those treated with SU (p<0.001) Individuals experiencing symptomatic events: Sitagliptin was associated with fewer events than SU (6.7% and 13.2%) Breakdown of the events in the SU treated group: in ascending order the proportion of events in each group were Gliclazide 6.6%, glimepiride 12.4% and glibenclamide 19.7%	NR	NR
Glibenclamide	Belkhadir et al., (1993) [33]	N=591 Study type: Randomised, controlled trial Country: Morocco Additional medication(s): NR Comparators: Reduced dose of usual glibenclamide	Events: No significant differences were observed between groups	Fructosamine levels: No significant difference between groups were observed HbA1c levels: No significant difference between groups were observed	No significant difference in weight between groups were observed
	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)	Ramadan at midday with BG levels below 4.5 mmol/L (%): Repaglinide showed fewer cases when compared with glibenclamide (2.8% and 7.9%, respectively; p=0.001)	Fructosamine levels: Repaglinide led to a statistically significant decrease from baseline (p<0.05) Glibenclamide: did not lead to any statistically significant changes No statistically significant change in HbA1c identified in either group	NR

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TABLE 5: STUDIES OF SULPHONYLUREAS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
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 statistically significant differences observed between groups Symptomatic events during Ramadan: • Repaglinide: 2.9%, • Glimepiride: 3.5%	BG levels: Glimepiride was associated with lower BG levels than repaglinide	NR
	GLIRA Study Group (2005) [34]	N=332 Study type: Observational – newly diagnosed individuals and previously treated individuals Countries: Algeria, Egypt, Indonesia, Jordan, Lebanon, Malaysia Additional medication(s): NR Comparator: NR	Individuals experiencing events: Similar proportions of events were observed pre-Ramadan, during Ramadan and post-Ramadan Newly diagnosed: 3% Previously treated: 3.7%	HbA1c levels pre-Ramadan, during Ramadan and post-Ramadan were: 9.2%, 7.7%, 7.1%, respectively, among those newly diagnosed And 8.4%, 7.7%, 7.3%, respectively, among those previously treated	NR
	Cesur et al., (2007) [9]	N=65 Study type: Observational Country: Turkey Additional medication(s): NR Comparators: Insulin secretagogue (repaglinide), insulin glargine	Individuals experiencing event: No significant difference between treatment groups of glimepiride, repaglinide or insulin glargine (14.3%, 11.1%, 10.0%, respectively) No severe episodes were noted	No significant difference between groups in terms of glycaemic control	No change in BMI in any group was identified

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TABLE 5: STUDIES OF SULPHONYLUREAS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

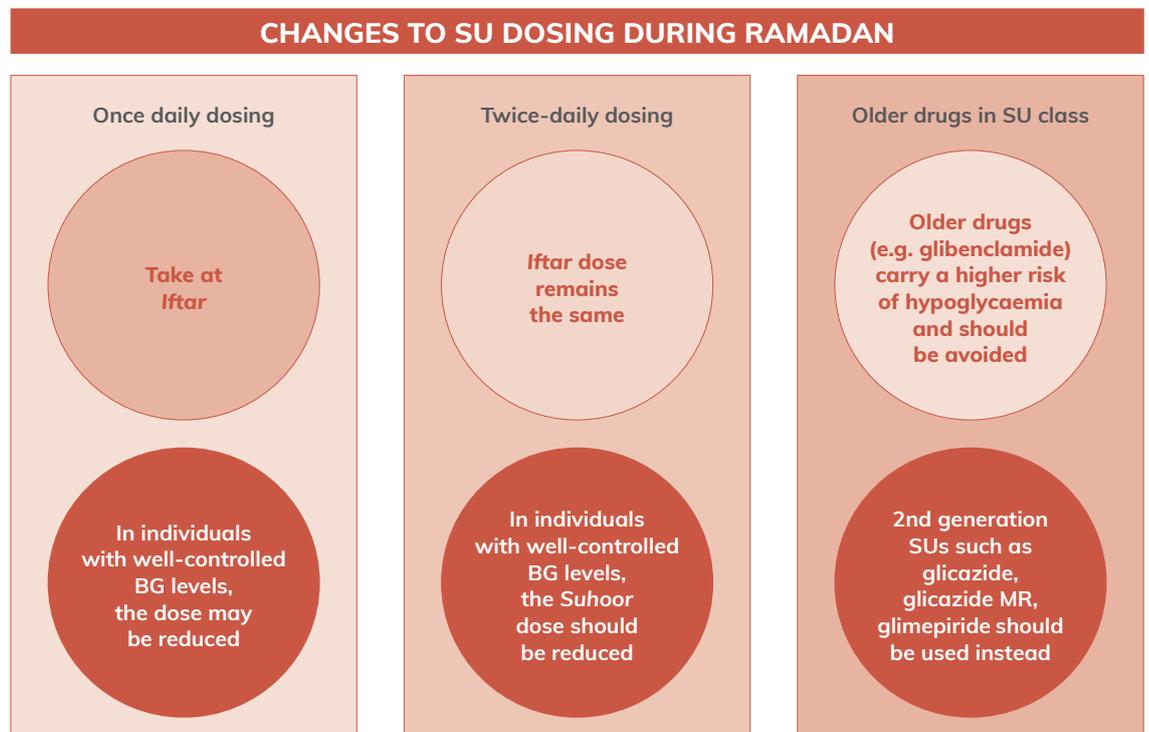
Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
Gliclazide	Hassanein et al., (2014) [23]	N=557 Study type: Double-blind, randomised controlled trial Countries: Bangladesh, Egypt, India, Indonesia, Kuwait, Malaysia, Pakistan, Saudi Arabia and UAE. , UK Additional medication(s): Metformin, DPP-4 inhibitor	Symptomatic events: Vildagliptin and gliclazide showed no clear differences (6.0% and 8.7%, respectively; p=0.173) Confirmed events: Vildagliptin was associated with fewer events when compared to gliclazide (3.0% and 7.0%, respectively; p=0.039)	No significant changes were observed in either group	No significant difference between groups were observed
Gliclazide MR	Hassanein et al., (2020) [35]	N=1214 Study type: Real-world observational trial Countries: Bangladesh, Egypt, Indonesia, India, Kuwait, Malaysia, Saudi Arabia, UAE Additional medication(s): any other OAD or GLP1RA	The proportion of individuals with confirmed hypoglycaemia during Ramadan was 1.6% (total cases in all assessment periods before, during and after Ramadan 1.7%) There were no severe cases of hypoglycaemia during or after Ramadan	HbA1c levels were 7.5% (9.4 mmol/L) pre-Ramadan and 7.2% (8.9 mmol/L) post Ramadan; change of -0.3% p<0.001 Fasting Plasma Glucose reduced by 9.7 mg/dL at post-Ramadan compared to pre-Ramadan; p<0.001	Body weight was seen to decrease by 0.5 kg; p<0.001

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; UAE, United Arab Emirates; UK, United Kingdom; SU, sulphonylurea

In a multinational observational study of 1,378 people with T2DM treated with SUs that fasted during Ramadan, approximately one fifth experienced a symptomatic hypoglycaemic event. When this was broken down by the type of SU, the highest incidence was among those treated with glibenclamide (25.6%) followed by glimepiride (16.8%) and gliclazide (14.0%) [32]. A similar outcome was observed in a large observational study comparing vildagliptin with SU treatment during Ramadan. Symptomatic hypoglycaemic events occurred in 31.8% of individuals on glibenclamide but in fewer individuals treated with gliclazide (19.2%) or glimepiride (17.9%) [25]. In addition, glibenclamide demonstrated significantly more hypoglycaemic events with midday blood glucose <4.5 mmol/L when compared to repaglinide (7.9% and 2.8%, respectively, p=0.001) [11]. Lowering the dose of glibenclamide did not affect the incidence of hypoglycaemic events [33]. More modern SUs such as glimepiride, gliclazide and gliclazide modified release (MR) are therefore much more preferred over conventional SUs such as glibenclamide as the newer drugs have a more favourable safety profile in terms of hypoglycaemia.

No significant differences were observed in the proportions of individuals reporting hypoglycaemic events treated with vildagliptin or gliclazide in the STEADFAST trial (6.0% and 8.7%, respectively, $p=0.173$) [23]. The incidence of hypoglycaemia is also low during the Ramadan fasting period for glimepiride as shown in an open-label observational study where the incidence was just 3% in newly-diagnosed individuals and 3.7% in those previously-treated, and was also comparable to that observed before and after fasting [34]. Similarly, no statically significant differences in hypoglycaemic events were observed when glimepiride treatment was compared with either repaglinide or insulin glargine therapy [9, 10]. Recently, a new trial looking into the modified-release formulation of gliclazide during Ramadan was published. In this large real-world study of 1214 people with T2DM treated with gliclazide MR +/- other OADs, the rates of confirmed hypoglycaemia during Ramadan were 1.6% with no severe hypoglycaemia. Moreover, HbA1c, FPG and weight all improved compared to the baseline measurement [35].

These studies demonstrate that people with T2DM can continue to use modern SUs such as gliclazide MR, gliclazide and glimepiride and fast safely during Ramadan. The use of older drugs within this class, such as, glibenclamide should be avoided during Ramadan. The use of these drugs should be individualised following clinician guidance and medication adjustments are outlined in **Figure 3**.



BG, blood glucose; SU, sulphonylurea

FIGURE 3

Dose adjustments for sulphonylureas in people with T2DM fasting during Ramadan



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

SGLT2 inhibitors including dapagliflozin, canagliflozin, empagliflozin and ertugliflozin are the newest class of OADs. SGLT2 inhibitors have a unique mode of action whereby they increase the excretion of glucose by the kidneys by reducing reabsorption in the proximal tubule, consequently decreasing blood glucose [36]. 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 can be a safe treatment option for people with T2DM that fast during Ramadan. However, some safety concerns were raised, such as an increased risk of dehydration in vulnerable patients, which may be a particularly pertinent issue during Ramadan. The previous 2016 IDF-DAR guidelines were in favour of using SGLT2I, but there remains a need for caution during among those on loop diuretics, the elderly and those with renal impairment [37].

Over the last 5 years, a greater number of studies assessing the use of SGLT2I have been published. Cardiovascular outcome trials (CVOTs) including CANVAS, EMPA-REG OUTCOME, and DECLARE-TIMI 58 provided evidence of cardiovascular benefits in people with diabetes that took SGLT2I [38-42]. These information were used to important diabetes related guidance such as that of the ADAs, where SGLT2I and GLP1-RA showed cardiovascular benefit and were placed ahead of other classes of drugs in people with cardiovascular disease (CVD) or chronic kidney disease (CKD) or people at risk of these issues [40].

Meanwhile, the use of SGLT2I in people with T2DM that fast during Ramadan have also been studied recently and the outcomes of these are summarised in **Table 6**.

The results of these studies, alongside the importance of SGLT2I as a class for people with or at risk of CVD/CKD, prompted the authors of the Canadian diabetes and Ramadan guidelines to advise on withholding SGLT2I only in circumstances of significant volume depletion such as frequent vomiting or diarrhoea and in situations where medications such as ACE-I and diuretics are used [43].

TABLE 6: STUDIES OF SODIUM-GLUCOSE CO-TRANSPORTER-2 (SGLT2) INHIBITORS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia during Ramadan	Dehydration/Fluid homeostasis
Dapagliflozin	W. S. Wan et al., (2016) [41]	N=110 patients Study type: Randomised, open-label, two-arm parallel group study Country: Malaysia Additional medication(s): Metformin Comparators: SU	Individuals with any reported event of hypoglycaemia: 6.9% in SGLT2i against 28.8% in control; p=0.002	Postural hypotension was reported in 13.8% of those in the SGLT2I group and 3.8% in those control group, this difference was not statically significant; p=0.210 3.5% of individuals on Dapagliflozin reported feelings of thirst

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TABLE 6: STUDIES OF SODIUM-GLUCOSE CO-TRANSPORTER-2 (SGLT2) INHIBITORS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia during Ramadan	Dehydration/Fluid homeostasis
Canagliflozin	Mohamed Hassanein et al., (2017) [44]	N=379 Study type: Prospective, comparative, observational study Country: Lebanon, Kuwait, UAE Additional medication(s): Metformin with or without DPP-4 inhibitors Comparators: SU	Individuals with symptomatic events of hypoglycaemia: 3.7% had an event in the and SGLT2i group compared to 13.2% in the SU group, adjusted odds ratio 0.27 (95% CI 0.10 – 0.72) p=0.009	Hypovolemia was seen in 16.1% of SGLT2i group and 5% of the SU group The adjusted odds ratio for SGLT2i against SU was 3.5 (95% CI 1.3 – 9.2) p=0.011
Canagliflozin, Dapagliflozin	Alaaeldin Bashier et al., (2018) [45]	N=417 Study type: Retrospective, observational study Country: UAE Additional medication(s): other oral hypoglycaemic agents (OHA) not including SU, insulin Comparators: SGLT2i with insulin; SGLT2i with SU; SGLT2i with OHA	Symptomatic events of hypoglycaemia: 27% of all individuals experienced symptomatic hypoglycaemia Confirmed events of hypoglycaemia: 18.7% 37.8% of those treated with SGLT2i and insulin saw a confirmed case of hypoglycaemia compared to 18.0% among those treated with SGLT2i and OHAs; p<0.005	Feelings of thirst were seen among 13.1% of those treated with SGLT2i and insulin compared to 6.1% among those treated with SGLT2i and OHA; p 0.03
Canagliflozin, Dapagliflozin	Y. Shao et al., (2018) [46]	N=68 Study type: Prospective, observational controlled cohort study Country: Singapore Additional medication(s): SUs, other oral antidiabetic drugs (OAD), insulin Comparators: Individuals not using SGLT2Is	Individuals experiencing events: There were no statistically significant differences seen among both groups No cases of severe hypoglycaemia were reported	There was a decrease seen in systolic blood pressure in both groups but no significant differences were seen between both groups
Dapagliflozin, Canagliflozin	Abdelgadir et al., (2019) [47]	N=95 Study type: Prospective, controlled study Country: UAE Additional medication(s): SUs, other oral hypoglycaemic agents (OHA) not including SU, insulin Comparators: Individuals not using SGLT2Is	Hypoglycaemic events measured through flash glucose monitoring systems: 3.9% of those on SGLT2i had events compared to 3.3% of those not on SGLT2i, this difference was non-significant; p=0.97	No reported cases of any adverse events No statistically significant changes to systolic blood pressure reported in either group

N, number of patients included in study; UAE, United Arab Emirates; SU, sulphonylurea



The results of the studies in Table 6 have prompted several diabetes and Ramadan experts to reconsider the current recommendations for the use of SGLT2-I during Ramadan fasting [48]. However, these studies indicate the following recommendations:

- For stabilisation, SGLT2Is should be initiated at least two weeks to one month prior to Ramadan. SGLT2Is are recommended to be administered at the time of evening meal (*Iftar*). However, if the indication for SGLT2I initiation is cardiovascular or renal protection, then the pre-Ramadan initiation should be conducted with a lower dose.
- Increasing fluid intake during the non-fasting hours of Ramadan is recommended.
- Raising awareness among physicians about recent guideline changes and the benefits of new antihyperglycaemic agents is important.
- When choosing an antihyperglycaemic therapy, the impact on heart failure and renal function must be considered.
- SGLT2I do not require treatment modifications during Ramadan, however if an individual is on multiple medications a review of the doses should be made to avoid the risk of hypoglycaemia.
- SGLT2I use when fasting during Ramadan should be in accordance with the usual safety and prescribing measures as recommended by each drug SMP.

**SGLT2 inhibitors have a low risk of hypoglycaemia.
NO DOSE ADJUSTMENTS are required during Ramadan.**

3.9 Individuals on multiple antidiabetic therapy

The availability of several new glucose lowering therapies has made it increasingly common for individuals to be prescribed multiple drug regimens while fasting during Ramadan. The risk of hypoglycaemia may be amplified, especially since individuals on multiple glucose lowering therapies are likely to be older and with multiple comorbidities. Indeed, in the large multi-country, retrospective observational CREED study the group on multiple therapies was found to be at a higher risk of developing hypoglycaemia [49].

In a prospective study investigating dose adjustments of multiple antidiabetic agents for individuals with T2DM that fasted during the month of Ramadan (PROFAST Ramadan Study), Elhadd *et al.* assessed the incidence of hypoglycaemia. The methodology included the implementation of the DAR-IDF guidelines with pre-Ramadan education and adjustments of oral (50% reduction in sulphonylurea, a maximum of 1 g metformin, no changes in DPP4I or SGLT2I) and injectable (50% reduction in insulin, no change in GLP-1) glucose-lowering therapies. The overall incidence of hypoglycaemia (symptomatic and confirmed with blood glucose reading) during Ramadan was 16.3%, with the highest incidence in the group on insulin, SU and other agents (31.3%). The risk of hypoglycaemia was greatest among individuals on a combination of basal insulin, DPP4I and metformin and those on four or more glucose lowering therapies [50].

Furthermore, in a subgroup of individuals who underwent flash continuous glucose monitoring (FGM), it was found that individuals that were more physically active were shown to be more prone to asymptomatic hypoglycaemia [51]. The mitigation of hypoglycaemia in individuals that fasted during Ramadan was achieved by reducing the dose of basal insulin or SU according to the PROFAST-Ramadan protocol, confirming earlier findings from Elhadd *et al.* [52].

Recently, data from a Fitbit-2 pedometer and Freestyle Libre flash continuous glucose monitoring system and applied artificial intelligence (AI) and machine learning models have been developed to predict hyperglycaemic and hypoglycaemic excursions in individuals who fast during Ramadan [53]. These prognostic models can be very useful in the future in risk stratifications and medication recommendations. Further studies are needed in this area where individuals that fast during Ramadan can have their glycaemic profile data collected, this may be best conducted using continuous glucose or flash glucose monitoring systems.

Several other studies comparing individuals on multiple glucose lowering therapies have been published recently. The canagliflozin in Ramadan Tolerance Observational Study (CRATOS) study, assessed individuals with T2DM who fasted during Ramadan. This study showed that those on canagliflozin and metformin with or without a DPP4I had a lower risk of hypoglycaemia when compared to those on an SU with metformin, with or without a DPP4I. However, only 57% of the canagliflozin group and 50% of the SU group were on 3 agents [44].

In another study of individuals with T2DM who did not undergo adjustments to their oral agents, it was found that a lower rate of overall hypoglycaemia (rate ratio of 0.26, 95% CI 0.16-0.44; $p < 0.001$) and nocturnal hypoglycaemia (rate ratio of 0.17, 95% CI 0.08-0.38; $p < 0.001$) was associated with the use of insulin degludec/insulin aspart compared to biphasic insulin aspart 30 [44].

More recently in the ORION study, individuals with T2DM who fasted during Ramadan and did not undergo any adjustments to their oral agents (where 74% were on metformin, 47% on DPP4I, 45% on SU and 24% on SGLT2I) or basal insulin reported a very low incidence of overall hypoglycaemia [54].

One can conclude that the risk of hypoglycaemia among individuals on multiple antidiabetic agents is determined by multiple factors, of which include their medication, duration of their diabetes, renal function, pre-Ramadan glycaemic control and presence of other comorbidities. Risk stratification and dose adjustment of therapies using AI based algorithms utilising continuous glucose and activity monitoring may allow optimal outcomes tailored to the individual patient.



3.9.1 CONSIDERATIONS AND RECOMMENDATIONS:

1. Many individuals on multiple antidiabetic agents have a long duration of diabetes, multiple comorbidities and renal impairment. Hence, they are at higher risk of hypoglycaemia when fasting during Ramadan.
2. Individuals with T2DM on 3 or more antidiabetic agents who fast during Ramadan, should receive counselling and comprehensive advice on diet, lifestyle and drug dose modifications prior to Ramadan.
3. Individuals on 3 or more drug combinations, especially those on both insulin and SU should be considered at an increased risk of hypoglycaemia. An approximate 25-50% reduction in the dose of insulin is advised, depending on the subsequent risk score after risk stratification. A reduction in the dose of SUs is also advocated in these individuals.
4. Newer technologies including continuous glucose monitoring and activity monitoring need to be harnessed through AI to reduce the risk of hypoglycaemia in people with diabetes that are on multiple antidiabetic agents and fast during Ramadan.

3.10 Insulin treatment for T2DM

Many individuals with T2DM are on insulin therapy to control their diabetes and a variety of insulin regimens are used. These include long/intermediate basal insulins (insulin glargine, insulin detemir, insulin degludec or neutral protamine Hagedorn insulin) that are often combined with oral agents; basal insulin with bolus prandial rapid or short-acting insulins (lispro, glulisine, aspart or regular human insulin); and premixed insulins (fixed ratio combinations of short and intermediate acting insulins) [55].

Insulin use during fasting carries a risk of hypoglycaemia, especially when more complex insulin regimens are used. Although a small number of randomised trials and observational studies (**Table 7**) have been conducted to assess some insulin regimens during Ramadan, however information from large RCTs in this area are lacking.

TABLE 7: STUDIES EVALUATING INSULIN TREATMENTS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
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

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TABLE 7: STUDIES EVALUATING INSULIN TREATMENTS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
Basal insulin: glargine	Cesur et al., (2007) [9]	N=65 Study type: Observational Country: Turkey Additional medication(s): NR Comparators: SU (glimepiride), insulin secretagogue (repaglinide)	Individuals experiencing event: No significant difference between treatment groups of glimepiride, repaglinide or insulin glargine (14.3%, 11.1%, 10.0%, respectively) No severe episodes were noted	No significant difference between groups in terms of glycaemic control	No change in BMI in any group was identified
	Salti et al., (2009) [56]	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 individuals) Comparator: None	Events before, during and after Ramadan: (156, 346, 153, respectively) the increase from pre-Ramadan to during Ramadan was statistically significant, $p<0.001$ The subsequent decrease from during Ramadan to post-Ramadan was also statistically significant, $p<0.001$	No major changes observed during Ramadan	NR
Glargine 300	Hassanein et al., (2020) [35]	N=1214 Study type: Real-world observational trial Countries: Bangladesh, Egypt, Indonesia, India, Kuwait, Malaysia, Saudi Arabia, UAE Additional medication(s): any other OAD or GLP1RA	The proportion of individuals with confirmed hypoglycaemia during Ramadan was 1.6% (total cases in all assessment periods before, during and after Ramadan 1.7%) There were no severe cases of hypoglycaemia during or after Ramadan	HbA1c levels were 7.5% (9.4 mmol/L) pre-Ramadan and 7.2% (8.9 mmol/L) post Ramadan; change of -0.3% $p<0.001$ Fasting Plasma Glucose reduced by 9.7 mg/dL at post-Ramadan compared to pre-Ramadan; $p<0.001$	Body weight was seen to decrease by 0.5 kg; $p<0.001$

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TABLE 7: STUDIES EVALUATING INSULIN TREATMENTS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
Prandial insulin: lispro	Akram et al., (1999) [57]	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)	Individuals experiencing event: The proportions of individuals experiencing the number of events were similar for both treatment groups Events per individual per 14 days: Individuals on Insulin lispro had fewer events (1.3%) than people on soluble insulin (2.6%); p<0.002 No severe episodes	Increases in postprandial BG (mmol/L): Insulin lispro was associated with smaller increases when compared to soluble insulin (1 hour after meal: 3.0 and 4.3, respectively; p<0.01 2 hours after meal: 2.6 and 4.0, respectively; p=0.008)	NR
Premixed insulin regimens					
Insulin lispro Mix 50 (evening) and human insulin Mix 30 (morning)	Hui et al., (2009) [58]	N=52 Study type: Observational Countries: UK Additional medication(s): NR Comparator: Human insulin Mix 30 (twice daily)	Hypoglycaemic events during compared to before Ramadan: Group 1 - insulin lispro Mix 50 and human insulin Mix 30 led to a non-significant decrease of 0.04; p=0.81 Group 2 - Human insulin Mix 30 led to a non-significant increase of 0.15; p=0.43 The between group difference was not significant; p=0.36	HbA1c change: both groups were associated with decreases in HbA1c levels during Ramadan Group 1 - insulin lispro Mix 50 and human insulin Mix 30 led to a decrease of 0.48% (p = 0.0001) Group 2 - Human insulin Mix 30 led to a decrease of 0.28% (p = 0.007) Between-group difference, p<0.001	No significant differences in weight changes were observed between groups However, the reduction in weight pre-Ramadan and after Ramadan in group 1 (individuals on insulin lispro Mix 50 and human insulin Mix 30) was statistically significant; p<0.001

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TABLE 7: STUDIES EVALUATING INSULIN TREATMENTS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
Premixed insulin regimens					
Insulin lispro Mix 25	Mattoo et al., (2003) [59]	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 individuals per 14 days: Proportions of events were similar for both treatment groups	Daily glycaemia (mmol/L) Overall glycaemia: Glycaemia among those on Insulin lispro (9.5 mmol/L) was significantly lower than soluble insulin (10.1 mmol/L); p=0.004 Pre-evening meal glycaemia: Glycaemia among those on Insulin lispro (7.1 mmol/L) was significantly lower than soluble insulin (7.5 mmol/L); p=0.034 2 hours post-evening meal glycaemia: Glycaemia among those on Insulin lispro (10.5 mmol/L) was significantly lower than soluble insulin (11.6 mmol/L); p<0.001	No significant changes in body weight were observed
	Hajjaji et al., (2019) [60]	N=40 Study type: Prospective observational study Countries: Libya Additional medication(s): Oral antidiabetic medications Comparator: Human insulin Mix30 twice daily	Hypoglycaemia: Minor episodes were experienced in 6 individuals in total (3 in each treatment group)	Blood glucose levels: During Ramadan, individuals on insulin 50% insulin lispro, 50% insulin lispro protamine suspension mix (experimental group) saw a decrease in the blood glucose levels by 21.1 mg% (1.2 mmol/L) more than the decrease in the Mixtard 30 group (control). This difference was statically significant (p<0.001)	NR

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TABLE 7: STUDIES EVALUATING INSULIN TREATMENTS IN PEOPLE WITH T2DM THAT FASTED DURING RAMADAN

Study drug	Authors (Date)	Study details	Hypoglycaemia	Glycaemic control	Body weight changes
Premixed insulin regimens					
Insulin detemir and biphasic insulin aspart	Shehadeh et al., (2015) [61]	N=245 Study type: Open-label, prospective, randomised controlled trial Countries: Israel Additional medication(s): Metformin, SU (not all patients) Comparator: Standard care – ADA recommended insulin regimen	Individuals experiencing an event: This in the intervention group (aspart and detemir) had lower risk of hypoglycaemia (4.8%) when compared to standard care (ADA recommended regimen) (21.4%), p<0.001	Intervention was non-inferior to standard care in terms of blood glucose levels	NR
IDegAsp-70% insulin degludec and 30% insulin aspart	Hassanein et al., (2018) [62]	N= 263 Study type: Phase III open label randomised trial, Countries: Algeria, India, Lebanon, Malaysia and South Africa Additional medication(s): Oral antidiabetic drugs Comparator: Biphasic insulin Aspart 30, twice daily	The rate of overall hypoglycaemia throughout the treatment period was statistically significantly lower in the IDegAsp arm compared with in the BIAsp 30 arm, estimated rate ratio (ERR) 0.26, 95%CI: 0.16-0.44; p < .0001 This corresponded to a 74% reduction in the rate of overall hypoglycaemia.	Glycaemic control: Glycaemic control was maintained in both treatment arms throughout the study period. No statistically significant differences between the arms were reported	NR
Biphasic insulin aspart	Soewondo et al., (2009) [63]	N=152 Study type: Observational Countries: Indonesia Additional medication(s): Oral hypoglycaemic agents (not all patients) Comparator: None	Hypoglycaemic events: At the end of the study there were no clear differences found in the number of events compared to baseline	Biphasic aspart reduced all glycaemic indices - fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (2-hr PPG), and glycosylated hemoglobin (HbA1c)	No significant changes in body weight or BMI were observed

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

Many individuals on insulin therapy elect to fast irrespective of their risk level and the advice of their physicians. It is, therefore, important that the physician gathers information about the individual's intention to fast and then assist the individual to fast safely. While the primary focus of concern is often placed on the risk of hypoglycaemic, care should also be given to glycaemic control during the Ramadan period.

As with all diabetic therapies, the insulin regimen must be individualised according to the individual's needs by taking into account their education, preferences, diet and lifestyle. Some authors recommend switching twice daily premixed or intermediate-acting insulin to long-acting or intermediate-acting insulin in the evening and rapid-acting insulin with meals [64]. Asking people with diabetes to change their regimen only for the Ramadan period may lead to errors, non-adherence and require additional education that is not readily available due to time and resource constraints. The physician/HCP should therefore assess whether a new treatment regimen is needed or whether modification of the dosing regimen of the insulins used prior to Ramadan is required. The individual's pre-Ramadan glycaemic control will determine whether insulin dose reductions are required. People who have controlled their diabetes well prior to Ramadan will usually require a dose reduction to minimise the risk of hypoglycaemia. This dose reduction is often not applicable in individuals with a history of poor control as insulin doses would likely be insufficient.

There is some evidence that insulin analogues, when used in place of human insulin, can reduce the risk of hypoglycaemia in people with diabetes [65] and also people with T2DM that fast during Ramadan [57]. Additionally, Akram *et al.* showed that insulin analogues could be associated with a lower risk of post-prandial hyperglycaemia when compared to human insulin [57]. There are also practical advantages associated with insulin analogues. Insulin analogues are injected just before a meal or even after a meal, meaning individuals that are fasting can administer the injection at the time of breaking the fast or at the time of *Suhoor* instead of 30 minutes prior to the meal.

It is therefore recommended that individuals wishing to fast be switched to insulin analogues for the month of Ramadan if hypoglycaemia, convenience and postprandial hyperglycaemia are areas of concern. The starting dose of insulin analogues should be 20-30% lower than the dose of regular insulin [66].

It must be emphasised that the administration of insulin via the subcutaneous, intramuscular or intravenous routes do not cause a breaking of the Ramadan fast. Individuals are still able to take their morning insulin or correction insulin doses after the fast has commenced.

In addition, modifications of insulin regimens, monitoring of blood glucose levels and self-titration of insulin doses while fasting all need implementation to enable safe fasting during Ramadan for individuals with diabetes.



3.10.1 Evidence for insulin use in Ramadan

3.10.1.1 Basal insulin

There is an increasing body of evidence supporting the safety of basal insulin for use in individuals with T2DM fasting during Ramadan.

In many studies, basal insulin was used in combination to oral hypoglycaemic agents. An observational study conducted on people with T2DM that fasted during Ramadan and were treated with insulin glargine and glimepiride saw a significant increase in mild hypoglycaemic events compared with the pre-Ramadan period; it was also found that a lower weight and smaller waist circumference was associated with this increased risk [56]. Two smaller observational studies found insulin glargine as safe for use during Ramadan, finding no evidence of increases to the risk of hypoglycaemia when compared with non-fasting individuals or when compared with individuals taking other OADs [7, 9]. A larger prospective observational study across 11 countries (the ORION trial) demonstrated that the second-generation basal insulin analogue, glargine 300u/ml, could be used safely in combination with oral agents in a real-world clinical setting. In this study, the majority of participants fasted for the full month of Ramadan and there was a low incidence of symptomatic hypoglycaemia and no episodes of severe hypoglycaemia. This study also demonstrated that glycaemic control can be successfully intensified in the Ramadan period without an added risk of hypoglycaemia [54].

3.10.1.2 Prandial insulin

Pre-meal administration of rapid or short-acting insulins may be required, in addition to long-acting basal insulin, to help control postprandial blood glucose. Akram *et al.* demonstrated this by compared the effects of two such insulins taken before *Iftar* during Ramadan — rapid-acting analogue insulin lispro and short-acting soluble human insulin. The postprandial rise in blood glucose levels after *Iftar* and the rate of hypoglycaemia were both significantly lower in the lispro group [57].

3.10.1.3 Premix insulin

Premixed insulins that combine short- and intermediate-acting insulins can be more convenient for individuals with diabetes, as they require fewer injections than basal-bolus regimens. However, they may be associated with a higher risk of hypoglycaemia in non-fasting individuals [67, 68].

Moreover, an open-label randomised trial compared the effects of two premixed insulin formulations on glycaemic control during Ramadan (analogue insulin lispro Mix25 – 25% short-acting lispro or 75% intermediate-acting lispro protamine; and human insulin 30/70 – 30% short-acting soluble human insulin or 70% intermediate-acting natural protamine hagedorn). Overall glycaemia was significantly lower among individuals on insulin lispro Mix25 compared with those on human insulin 30/70. Treatment effects were greatest when glycaemia levels were compared before and after *Iftar*. There was no difference observed in the number of hypoglycaemic episodes between treatments [59].

A prospective observational study in Indonesia found that biphasic insulin aspart reduced all glycaemic indices following Ramadan when compared to the period before Ramadan, without an increase in body weight or an additional risk of hypoglycaemia [63]. A multinational, randomised treat-to-target trial, comparing IDegAsp (co-formulated with 70% ultralong-acting analogue insulin degludec and 30% rapid-acting analogue insulin aspart) twice daily (BID) to twice daily BAsp 30 (70% intermediate-acting aspart and 30% rapid-acting aspart) demonstrated that IDegAsp achieved similar levels of control to blood glucose levels but with the added benefit of a lower risk of overall and nocturnal hypoglycaemia [62].

The commonest premix insulin formulations are low-ratio premix insulins with 25-30% short/rapid-acting insulin and 70-75% intermediate-acting insulin. This poses a challenge during Ramadan as the lower ratio of short/rapid acting insulin may provide inadequate prandial cover in the evening for the resultant post-prandial hyperglycaemia. Since the dose of prandial insulin cannot be independently adjusted there is also a risk of both post-prandial hyperglycaemia and hypoglycaemia after the morning meal.

A regimen of premixed insulin lispro Mix50 (50% lispro and 50% lispro protamine) in the evening and regular human insulin with natural protamine hagedorn (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 [58]. A similar study from Libya also demonstrated improved post-prandial glucose control without an increase in hypoglycaemia [60]. 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 randomised study. The new regimen was found to be non-inferior to standard care with a significantly lower hypoglycaemic event rate [61]. These studies demonstrate that in appropriately selected individuals, pre-mix insulin can be safely used when fasting during Ramadan.

3.10.1.4 Insulin dose adjustments and monitoring

Specific recommendations on the optimal dosing and regimen strategies are difficult to make as there is limited evidence in the area of fasting during Ramadan. The results from the studies described in **Table 7** indicate that 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.

It must be emphasised that individuals need to be educated on SMBG and self-titration of insulin doses to ensure safe fasting. The times for monitoring are dependent on the insulin regimen used. Those individuals that are high risk or very high risk should check their blood glucose levels several times throughout the day when fasting. Similarly, those that are at the highest risk of hypoglycaemia (i.e. individuals on treatment regimens that are not glucose dependent such as insulin or SUs) should increase their levels of SMBG so that there are



several checks throughout the fasting period each day — those on premixed insulins should aim for at least 2-3 daily readings and whenever hypoglycaemic symptoms appear, individuals on other insulin regimens should aim to use the 7-point blood glucose monitoring method (a check of blood glucose levels when fasting; post-breakfast; pre-lunch; post-lunch; pre-dinner; post dinner; and midnight).

CHANGES TO LONG AND SHORT-ACTING INSULIN DOSING DURING RAMADAN

Long/intermediate-acting (basal) insulin	Short-acting insulin
<p>NPH/detemir/glargine/glargine 300/degludec ONCE-DAILY Reduce dose by 15-30% Take at <i>Iftar</i></p>	<p>Normal dose at <i>Iftar</i> Omit lunch-time dose Reduce <i>Suhoor</i> dose by 25-50%</p>
<p>NPH/detemir/glargine TWICE-DAILY Take usual morning dose at <i>Iftar</i> Reduce evening dose by 50% and take at <i>Suhoor</i></p>	

Fasting/pre- <i>Iftar</i> /pre- <i>Suhoor</i> blood glucose	pre- <i>Iftar</i>	pre- <i>Iftar</i> */post- <i>Suhoor</i> **
	Basal insulin	Short-acting insulin
<70 mg/dL (3.9 mmol/L) or symptoms	Reduce by 4 units	Reduce by 4 units
<90 mg/dL (5.0 mmol/L)	Reduce by 2 units	Reduce by 2 units
90-126 mg/dL (5.0-7.0 mmol/L)	No change required	No change required
>126 mg/dL (7.0 mmol/L)	Increase by 2 units	Increase by 2 units
>200 mg/dL (16.7 mmol/L)	Increase by 4 units	Increase by 4 units

*Reduce the insulin dose taken before *Suhoor*; **Reduce the insulin dose taken before *Iftar*

FIGURE 4
Dose adjustments for long or short-acting insulins

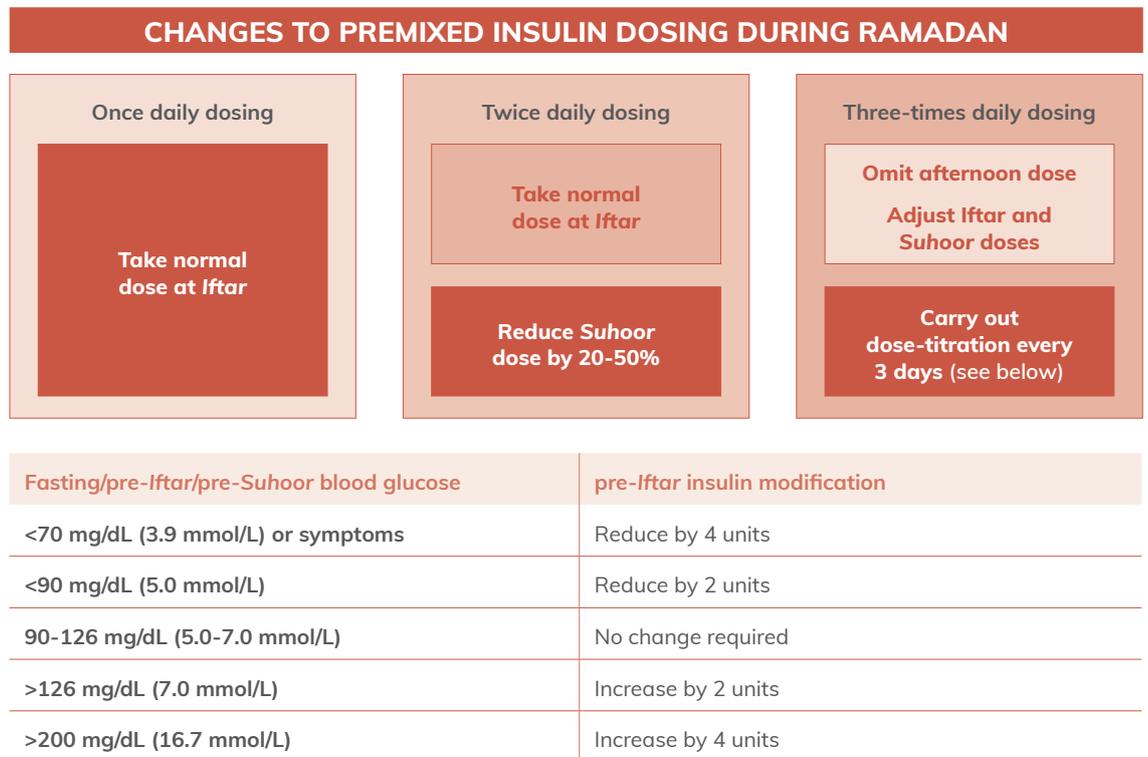


Table adapted from Hassanein et al. (2014) [66].

FIGURE 5

Dose adjustments for premixed insulin

3.10.1.5 Insulin pump users

Recommendations for dose adjustments in people with T2DM that are on insulin pump therapy are presented in **Figure 6**. Other information that may be useful for insulin pump users are presented in the **chapter 9: Management of Type 1 diabetes when fasting during Ramadan**.

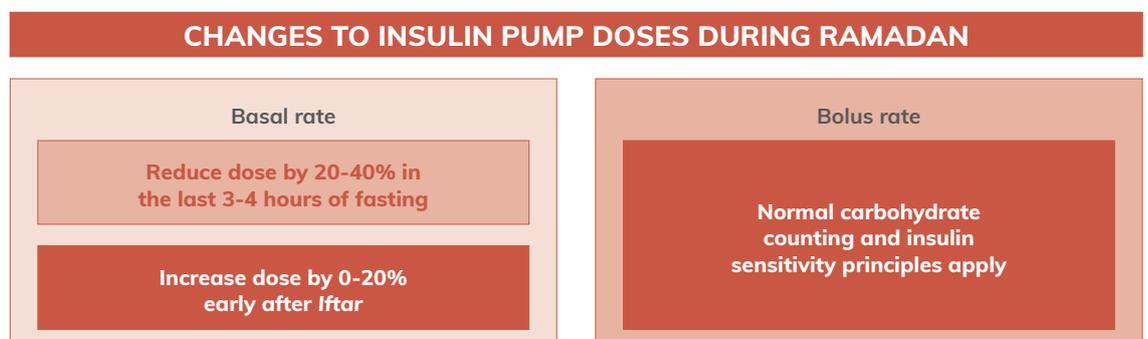


FIGURE 6

Dose adjustments for insulin pump therapy



4. POST-RAMADAN FOLLOW-UP

Eid ul-Fitr, a 3-day festival, marks the end of Ramadan and individuals with T2DM 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 fasting during Ramadan. It should be stressed to the patient that fasting safely one year does not guarantee that they can fast safely the next nor make them a low risk for the Ramadan due to the progressive nature of diabetes.

SUMMARY

- A pre-Ramadan assessment is vital for any Individual with T2DM that 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.
- There are advantages and disadvantages associated with the different treatment options for people with T2DM that seek to fast during Ramadan.
 - Individuals taking metformin, SUs, insulin secretagogues or insulin will need to make dose adjustments to reduce the risk of hypoglycaemia.
- Individuals on multiple antidiabetic therapies will find themselves at a greater risk of hypoglycaemia
 - Counselling is recommended to individuals on 3 or more antidiabetic agents
 - Dose reductions need to be made to accommodate for the increased risk of hypoglycaemia.
- Artificial intelligence in the form of machine learning prognostic modelling can be a useful tool for future use in risk stratification and planning strategies for dose modifications.
- A post-Ramadan follow-up consultation is recommended to reassess treatment regimens and discuss fasting experiences during Ramadan.
- With the correct advice and support from HCPs most people with T2DM can fast safely during Ramadan.

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