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Fasting during Ramadan: A Comprehensive Review for Primary Care Providers

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Abstract: Diabetes mellitus has become a non-infectious pandemic. The incidence of T2D has risen dramatically and recent rates have increased in many countries including Muslim countries. As the number of people who participate in Ramadan increases, health care professionals will need to become familiar with the traditions and help people stay healthy during the holy month of Ramadan. A key part of Ramadan is the practice of one month of fasting from sunrise to sunset. While this is a religious practice, it has significant impacts on the management of people with diabetes. This article will discuss the traditions associated with Ramadan and how to help people safely manage their diabetes while participating in Ramadan.

Keywords: Ramadan; fasting; diabetes; management; guidelines

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1. Introduction

The holy month of Ramadan (one of the five pillars of Islam) falls on the ninth month of the lunar calendar. Fasting from dawn to sunset is a key component of Ramadan. While this is practiced by millions of people globally, some health conditions such as diabetes can make this practice more challenging. Comprehensive guidelines have been recently published by the International Diabetes Federation [1]. A survey of 262 family physicians in Turkey indicated only 22% stated they were aware of international guidelines for Ramadan and diabetes management, and only 10% acknowledged having referred to the guidelines [2].

There was a recent comprehensive review evaluating publications regarding diabetes management during Ramadan [3]. This review is intended to provide practical advice for busy health care professionals who are helping their patients with diabetes safely participate in Ramadan.

2. What Is Ramadan?

Every year, millions of Muslims fast around the world during the holy month of Ramadan, partaking in a tradition that has roots in all monotheistic Abrahamic faiths and has existed as a pillar of ritual obligation of Islamic faith. Muslims fast from dawn till dusk, consuming a pre-dawn meal known as Suhoor and abstaining from food, water, and sexual activity until the sun sets when they break their fast with a meal known as Iftar. The holy month of Ramadan is determined by the sighting of the moon and thus does not align with the Gregorian calendar. Muslims fast throughout the 29 or 30 days of Ramadan, concluding the month with the Islamic holiday, Eid-al-Fitr [4]. Fasts vary from 10 to 18 or more hours depending on location and seasonal variations [4]. In addition to fasting, many Muslims continue to work during the day and may alter their sleep schedule to participate in extra night prayers known as Taraweeh, which can involve hours of standing in congregational prayer.

Fasting during Ramadan is one of five essential pillars or foundational ritual beliefs of Islamic faith. Consequently, many Muslims desire to fast during the holy month. According

to a 2013 Pew research poll of 38,000 Muslims across the globe, 93% say they fast during Ramadan [5]. In a 2007 survey, 77% of Muslim Americans consider fasting to be important to them [5]. Muslims from diverse cultural and health backgrounds partake in Ramadan fasting due to an emotional and spiritual connection to the month. This includes Muslims with type 1 and type 2 diabetes, who may be at greater risk for adverse health outcomes when fasting.

According to the Epidemiology of Diabetes and Ramadan(EPIDIAR) study conducted during 2001, of 12,243 subjects with type 1 and type 2 diabetes in 13 countries, "42.8% of patients with type 1 diabetes and 78.7% of patients with type 2 diabetes reported fasting at least 15 days during Ramadan" [6]. This includes individuals with diabetes who may have been advised to abstain from fasting due to the threat of adverse health outcomes. Given that many Muslims with diabetes choose to fast, health practitioners must be prepared to tailor therapeutic and lifestyle management to the rigors of a 10–18 h fast. Since the last publications related to this topic, this review article covers updated current guidelines in addition to discussing the metabolic effects of Ramadan fasting and diabetes management.

3. Do All Muslims Have to Fast during Ramadan?

While many Muslims feel an obligation to fast in honor of the tradition and for spiritual attainment, Muslim religious scholars have derived exceptions for various populations based on holy texts. Holy Quran Sura 2 verses 183–185 clearly exempts certain categories from fasting including individuals with chronic illnesses in who fasting may be detrimental to health [7]. In 2005, and updated in 2010, the American Diabetes Association (ADA) published guidelines for the management of diabetes during Ramadan fasting, stratifying patients into four risk categories: very high, high, moderate, and low, based on diabetes type, glycemic control, and comorbidities [8,9]. In 2009, a collection of Muslim scholars including the 19th session of the Council of International Fiqh upheld this stratification and the avoidance of fasting in the very high- or high-risk categories [1,8,10]. The International Diabetes Federation (IDF) and Diabetes and Ramadan Alliance (DAR) have formulated comprehensive guidelines for health professionals caring for diabetes patients who observe Ramadan fast [1]. Additionally, the Mufti of Egypt, a scholar from the Al-Azhar University, which is an internationally upheld institution of Islamic creed, supported IDF-DAR stratification guidelines and clarified the Islamic exemption of fasting among the following populations [1]:

- Emergent and chronic illness that can be exacerbated by the act of fasting [10]
- Pregnant women [10]
- Elderly with chronic medical conditions [10]
- People with mental illnesses [10]
- Children before they reach puberty [4]
- Travelers [4]

Furthermore, the Mufti clarified that Muslims with diabetes should break their fast if there are concerns for an adverse event and/or if they are instructed to do so by their physician. For patients who are in the moderate and low risk categories, the decision to fast should be practiced after discussion with a physician [10].

4. What Do Muslims Eat during Ramadan?

While Ramadan is a month of fasting, the consumption of high-calorie, high-fat, and carbohydrate-rich foods is common during the non-fasting hours in most cultures [11]. Muslims around the globe cook and serve traditional Suhoor and Iftar meals, in addition to snacks that may be consumed between the two meals at night. Often, these meals may contain an excess of simple carbohydrates, syrups, and oils. In a study of 30 Tunisian male participants, it was found that caloric intake increased with a decreased frequency of meals. This included increased mono-unsaturated fatty acids, poly-unsaturated fatty acids, and cholesterol intake [12]. Furthermore, individuals may alter their daily activities to include less exercise to stave off dehydration, especially if they are fasting in hotter climates. The

existing model of consuming simple carbohydrates in excess at dusk and dawn may lead to inadequate glycemic control due to inability to fine-tune insulin and glucose release in response to perturbations in blood glucose.

In addition to various cultural foods, one staple food consumed during Ramadan includes dates. People often break their fasts with dates. Dates contain almost 100% of the suggested daily intake of insoluble fiber [13]. Dates also contain a high fructose and protein concentration. One study including citizens of the United Arab Emirates with type 2 diabetes evaluated the glycemic indices and post-prandial excursions of study participants consuming 50 g of carbohydrates from dates versus 50 g of carbohydrates from glucose. The study found that dates ranked low in glycemic index and caused minimal spikes in postprandial glucose [13]. Low glycemic index diets have been shown to improve HbA1C levels in persons with type 2 diabetes [13].

5. Physiology of the Fast

The normal human physiology in the fed state functions with an increase in secretion of insulin by the beta cells of the pancreas after consumption of a meal with simultaneous inhibition of glucagon secretion due to paracrine effect on the alpha cells. Insulin stimulates hepatic and muscle glucose uptake and glycogen synthesis. During fasting in healthy individuals, as glucose levels fall in the first few hours of fasting, insulin secretion is suppressed. As glucose levels fall below the physiological range (65–70 mg/dL or 3.6–3.9 mmol/L), glucagon and epinephrine are secreted [14]. These counterregulatory hormones stimulate hepatic glycogenolysis and gluconeogenesis to maintain glucose within the physiological range. As duration of fasting progresses to 12–36 h, the hepatic glycogen stores are depleted, and lipolysis of adipose tissues ensues with release of fatty acids [14]. This metabolic switch in glucose metabolism occurs whereby the liver converts the fatty acids to ketones, beta-hydroxybutyrate (β-OHB) and acetoacetate which are used as an alternate source of fuel for the brain, muscle, erythrocytes, and other tissues [14].

In individuals with type 2 diabetes where insulin resistance is a primary defect, the metabolic switch may be delayed, resulting in a longer duration to generate fatty acid for energy [14]. This can potentiate hypoglycemia with Ramadan fasting that lasts 12–18 h when compared to fasting that may last for 10 h. Hyperglucagonemia as seen in type 2 diabetes, when accompanied by consumption of high glycemic index foods at sunset meal (Iftar) can contribute to hyperglycemia [14]. In type 1 diabetes with absolute insulin deficiency and late stages of type 2 diabetes with progressive beta-cell failure, augmented gluconeogenesis and ketogenesis resulting in significant hyperglycemia can occur in the absence of exogenous insulin [1,4,14,15] As these patients also demonstrate impaired counterregulatory hormone responses to hypoglycemia and/or experience hypoglycemia unawareness, they are at risk for severe hypoglycemia [16]. Thus, people with diabetes are at higher risk of complications such as hypoglycemia, hyperglycemia, diabetic ketoacidosis, dehydration, and thrombosis [15].

It is well known that there are daytime variations in glucose tolerance in healthy individuals with decreased glucose tolerance and reduced insulin sensitivity in the later part of the day [17]. The dawn phenomenon, an increase in blood glucose levels and/or insulin requirements in the early morning hours, occurs at a greater magnitude in individuals with diabetes [17]. In patients with diabetes who on more than two medications, especially those with hypoglycemic potential (e.g., sulfonylureas and secretagogues), have been observed to have an increase in the mean amplitude of glycemic excursion(MAGE) in the early stages of Ramadan compared to before (p-0.006) but not in the late- and post-Ramadan periods [18].

6. Metabolic Effects of Ramadan Fasting

In patients with type 2 diabetes who fasted for 15–21 days, a statistically and clinically significant reduction in A1c of approximately 0.5% was found [19].

A 2012 meta-analysis of 35 studies showed a 1.24 kg weight reduction (95% confidence interval (CI), −1.60 to −0.88 kg) during the month of Ramadan fasting and the regaining of a

mean weight of 0.72 kg (95% CI, 0.32 to 1.13 kg) during the 2 weeks following Ramadan [19]. Although there has been a significant reduction in fat percentage in overweight and obese people, leading to weight loss [14], it is not a universal outcome, and weight change with Ramadan fasting shows significant inter-individual variability [15].

A 2013 meta-analysis of 30 cohort studies found a decrease in LDL and fasting blood glucose levels after Ramadan fasting in healthy males and females compared with levels prior to Ramadan [1,19]. A statistically significant increase in HDL cholesterol in females and a decrease in total cholesterol and triglycerides in males was noted [1,19]. A study in Saudi Arabia of healthy men between age 18 and 39 years indicated that fasting glucose levels were elevated slightly at end of third week (RW3) and after Ramadan (AR) compared to before Ramadan (BR) (BR = 74.60 mmol/L vs RW3 = 81.52 mmol/L and AR-86.51 mmol/L). The fasting glucose indicated a slight but statistically significant elevation during the end of Ramadan (p = 0.011), but elevated values were within normal levels (BR = 74.60 mml/L vs. RW3 = 81.52 mmol/L and AR = 86.51 mmol/L) [20]. In a study on 65 healthy Thai subjects that investigated the effect of Ramadan fasting on biochemical parameters, there were no changes in anthropometry, blood pressure, lipid profiles and body composition in both males and females before Ramadan, at the end of Ramadan, and after one month of Ramadan [21]. Fasting blood glucose levels were significantly increased a month after Ramadan when compared to baseline (5.09 $\pm$ 0.50 versus 4.83 $\pm$ 0.38 mmol/L, p = 0.016) in women [21]. There have been inconsistent results in several other studies across the world in which fasting blood glucose and lipid profile were either significantly increased or significantly decreased or remained unchanged [21]. These variations could be attributed to varied dietary intake, physical activity, age, gender, cortisol secretion, and varied duration of fasting depending on the geographical locations [21]. While most metabolic studies have been conducted in healthy subjects, more research is required to explore the effect of Ramadan fasting on people with diabetes.

Studies have indicated that in the final week of Ramadan, there is a reduced rate of oxygen consumption and slower heart rate, indicating the slowing of metabolism [14]. Hassanein et al. observed that there does not appear to be a significant change in the resting metabolic rate and total (24 h) daily energy expenditure [15]. Some studies have reported lower concentrations of inflammatory markers, CRP, IL-6, and TNF-α [14,19,22]. Adiponectin and leptin are adipokines secreted by adipocytes. Adiponectin appears to increase insulin sensitivity, and leptin is associated with insulin resistance. Adiponectin levels were lower and leptin levels were elevated in a Saudi study that was conducted in healthy practitioners during Ramadan [14]. The data are conflicting in another study showing an increase in adiponectin levels during Ramadan [23], but no studies have been performed on individuals with diabetes [14,15]. Ghrelin, an appetite-stimulating hormone, was reported to have a marked reduction in the last week of Ramadan in overweight and obese individuals [1,14].

In individuals who attend late-night Taraweeh prayers and wake up for pre-dawn, Suhoor meals may have a sleep duration of 2 to 6 h, depending on the geographical location and time of year. Changes in the sleep time impact the circadian rhythm, with epigenetic studies showing alterations in the circadian rhythm controlling genes during Ramadan [15]. With an altered circadian cycle, there may be a reduction in total sleep duration and decrease in the proportion of rapid eye movement (REM) sleep, which can affect insulin resistance [14]. Cortisol secretion was noted to be reversed during Ramadan with a shift towards lower morning cortisol and higher evening cortisol levels at the end of first week of Ramadan with eventual reversal back to near baseline by the end of week 3 of Ramadan [14]. The typical high morning-to-evening cortisol ratio reduced from 2.55 to 1.22 during Ramadan fasting [15]. It is well known that cortisol affects insulin sensitivity and is associated with a rise in blood glucose levels [15]. This coupled with the consumption of large quantities at and after Iftar can cause blood glucose to rise higher and more glycemic variability in people with diabetes [15].

The gut microbiota has emerged as an integral role player in the progression of chronic diseases of obesity and diabetes. Although the specific effect of Ramadan fasting on the gut microbiome has not been extensively studied, a small pilot study from Turkey revealed that gut microbiomes were significantly enriched after the end of Ramadan fasting [1,14]

7. Pre-Ramadan Visit

A pre-Ramadan visit six to eight weeks before Ramadan is recommended to complete risk stratification and review hypoglycemia and treatment including hypoglycemia unawareness and clarify common misconceptions [1].

8. Risk Stratification

Fasting during Ramadan does carry an increased risk of adverse events among Muslims with diabetes. The EPIDIAR study discovered a trend of increased risk of severe hypoglycemic events during Ramadan requiring hospitalization [6]. The ADA classifies hypoglycemia as level 1 to 3. Level 1 is defined as glucose <70 mg/dL and ≥54 mg/dL. Level 2 is glucose < 54 mg/dL, and level 3 is a severe event characterized by altered mental status and/or physical status requiring assistance for treatment of hypoglycemia [16]. Individuals may exhibit adrenergic and neuroglycopenic symptoms that include but are not limited to shakiness, profuse sweating, irritability, intense hunger, nervousness, tachycardia, and confusion [16]. If left untreated, this can progress to a loss of consciousness, seizure, coma, and death [16]. Some patients may not exhibit typical symptoms of hypoglycemia due to altered counterregulatory responses and exhibit hypoglycemia unawareness [16]. Hence, it is critical that fingerstick glucose be monitored frequently and providers discuss this with patients who are fasting.

As per the latest IDF-DAR 2021 guidelines, a risk calculator or scoring system has been recommended for risk stratification. It takes into consideration various factors and individuals are placed into the risk category based on the score as in Table 1 [1].

Table 1. IDF-DAR 2021 risk factors and scores for risk stratification [1].

Risk Factors	Score
Diabetes type and duration	
Type 1 diabetes	1
Type 2 diabetes	0
Duration of diabetes	
Duration ≥ 10 years	1
Duration < 10 years	0
History of hypoglycemia and hypoglycemia unawareness	
Hypoglycemia unawareness	6.5
Recent severe hypoglycemia	5.5
Recurrent hypoglycemia	3.5
Hypoglycemia < once a week	1
No hypoglycemia	0
Glycemic control	
A1c > 9%	2
A1c 7.5–9%	1
A1c < 7.5%	0
Type of Treatment	
Multiple daily premixed insulin regimen	3
Basal bolus regimen/Insulin pump	2.5
Once daily premixed insulin	2
Basal insulin only	1.5

Table 1. *Cont.*

Risk Factors	Score
Older generation sulfonylureas (Glibenclamide)	1
Second generation sulfonylureas(SU) or Repaglinide	0.5
Non-insulin and non-SU agents	0
Self-monitoring of blood glucose(SMBG)	
No adequate SMBG checks	2
Suboptimal SMBG checks	1
Adequate SMBG checks	0
Occurrence of Diabetic ketoacidosis/ Hyperglycemic hyperosmolar state	
In last 3 months	3
In the last 6 month	2
In the last 12 months	1
None	0
Cardiovascular complications/co-morbidities	
Unstable	6.5
Stable	2
None	0
Renal complications/co-morbidities	
GFR < 30 mL/min/Stage 4 CKD	6.5
GFR 30–44 mL/min/Stage 3b CKD	4
GFR 45–59 mL/min/Stage 3a CKD	2
GFR $\geq$ 60 mL/min	0
Pregnancy	
Blood glucose not within target range	6.5
Blood glucose within target range	3.5
Not pregnant	0
Frailty and cognitive function	
Impaired cognition or Frail	6.5
>70 year without home support	3.5
None	0
Physical labor	
High intense	4
Moderate intense	2
None	0
Prior Ramadan experience	
Negative experience	1
No particular experience	0
Fasting hours based on location	
$\geq$16 h	1
<16 h	0
Score 0–3 Low risk	Should be able to fast
Score 3.5–6 Moderate risk	Advised not to fast
Score > 6 High risk	Should not fast

As was mentioned previously, Muslims with diabetes will continue to fast during Ramadan regardless of their risk category. Those who continue to fast should have a scheduled pre-Ramadan assessment visit with their health care providers (HCPs) at least one month before Ramadan and develop a plan for managing their diabetes throughout the month. The plan should include engaging in regular blood glucose monitoring, continuing baseline intermittent light to moderate intensity exercise, and taking medications with

any directed modifications by the physician. Furthermore, decisions should be based on appropriate testing including baseline HbA1C, vitals, and lipid panel. The physician should utilize the pre-Ramadan visit as an opportunity to conduct screening for microvascular complications including diabetic foot exam and eye examinations. Ramadan is an ideal time to promote smoking cessation as well, given that smoking is prohibited during the fast and that Muslims often indicate Ramadan as a salient reason to quit (Figure 1).

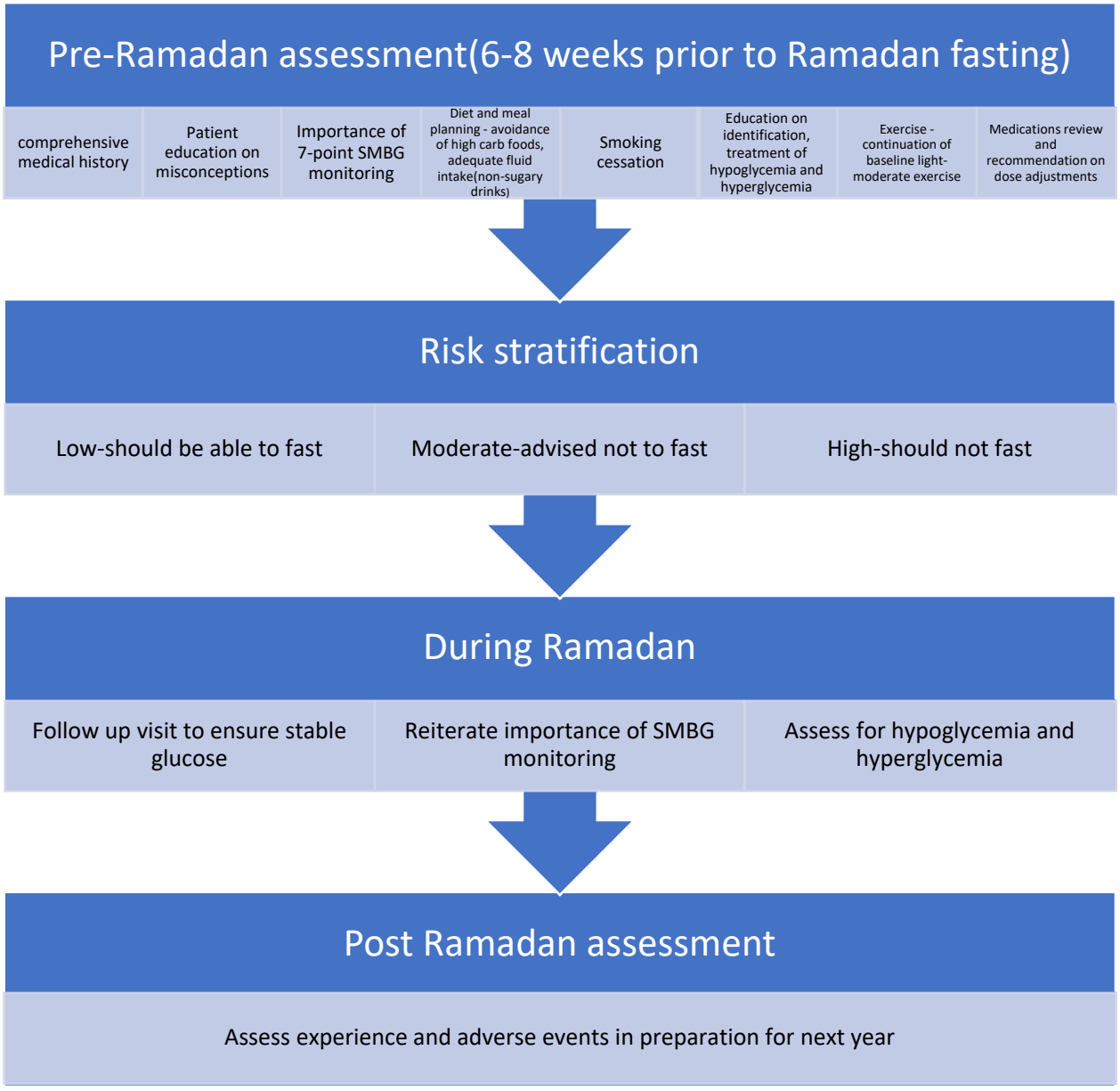


Figure 1. Pre-Ramadan assessment and risk stratification for patients with diabetes during Ramadan fasting [1,14].

9. Clearing Patient/Family Misconceptions about Diabetes during Ramadan

Misconceptions about the permissibility of aspects of diabetes care during the fast can hinder compliance and increase the frequency of complications. In one study, 77% of participants did not check their blood glucose due to the misconception that pricking fingers to provide blood for monitors voided their fasts [24]. These misconceptions should be dispelled by the physician during the pre-Ramadan visit. Assurances should be given from sources that Muslims are familiar with including Quranic proofs and scholarly opinions

supported by evidence, known as fatwah [25]. See Table 2 for a summarized list of some misconceptions.

Table 2. Common patient/family misconceptions regarding diabetes treatment during Ramadan.

Misconception	Reality Supported by Evidence
Pricking my fingers and drawing blood to check blood glucose breaks my fast	Taking small amounts of blood for medical testing does not break the fast [24,25]
Injecting insulin breaks my fast (This includes insulin pumps)	Injected medications that provide no caloric contribution do not break the fast [24,25]
I cannot abstain from fasting or break my fast due to complications from my diabetes	Muslims facing acute or chronic illness that places their wellbeing at jeopardy can avoid fasting or break a fast [24,25]

10. Knowing When Patients Should Break the Fast

At the initial pre-Ramadan visit, patients and their families should be instructed about symptoms of hypoglycemia and how to manage them using the 15–15 rule. Centers for Disease Control and Prevention(CDC) in the United States and American Association of Diabetes Educators(AADE) recommend 15–15 rule or Rule of 15 as consuming 15 g of carbs (e.g., 15 g of carb = $\frac{1}{2}$ cup or 4 ounces of fruit juice/regular soda or 4 glucose tablets or 1 tube glucose gel or 6 jellybeans or 1 tablespoon of sugar or honey) and recheck blood glucose in 15 min [26,27]. If blood glucose is still below 70 mg/dL, repeat 15 g of carbs until hypoglycemia is corrected [26,27]. Once the glucose returns to normal, the individual should eat a meal or snack to prevent recurrent hypoglycemia. Individuals with severe hypoglycemia who are unable to take by mouth safely require the administration of glucagon [16]. Providers should ensure that a glucagon emergency kit is prescribed for all individuals and educating caregivers and family members on how to administer it if needed, seek emergency medical attention if hypoglycemia is persistent, and notify health care providers for any medication adjustments as needed.

In a study of 477 Muslims with type 1 and type 2 diabetes fasting in Saudi Arabia during Ramadan, only 2.8% of patients with type 1 and 17.8% with type 2 broke their fast in response to a hypoglycemic event [28]. Patients should be reassured that breaking the fast at the threat of bodily harm is permissible per unanimous Islamic scholarly consensus.

11. Monitoring Blood Glucose

Patients with diabetes fasting during Ramadan should regularly monitor their glucose, and if possible, document their findings in a log. The EPIDIAR study found that physicians educated participants about blood glucose monitoring in 89% of type 1 patients and 80% of type 2 patients, but only 67% of type 1 patients and only 37% of type 2 patients reported actually monitoring glucose levels [6]. While this discrepancy may be a result of forgetfulness or even misconceptions about pricking fingers during the fast, a lack of insurance coverage for extra testing strips can prevent checking blood glucose [29]. Extra monitoring may be required during Ramadan fasting if they are on medications (including sulfonylureas or insulin) and if they are participating in long nightly Taraweeh prayers which may increase glucose utilization, increasing the risk of hypoglycemia. Recommended timings for fingerstick glucose monitoring are before the pre-dawn meal (Suhoor), morning, midday, mid-afternoon, pre-sunset meal (Iftar), 2 h after Iftar, and at any time if symptoms of hypoglycemia or hyperglycemia occur [1].

In the United States, people with diabetes now have the option to subscribe to diabetes programs at monthly costs often covered by insurance, which provide unlimited testing strips and coaching programs [30]. Physicians can also take on an advocacy role for their patients during Ramadan, documenting the need for additional testing strips for approval by insurances.

IDF-DAR guidelines recommend the use of CGM as the method of choice if available for patients with diabetes who observe Ramadan fasting [1]. Studies have indicated that continuous (CGM) and flash or intermittently scanned glucose monitoring (FGM or iCGM) provide the benefit of predicting hypoglycemia and assessing glycemic excursions during Ramadan fasting [11].

12. Diabetes Medications

According to the EPIDIAR study, the majority of participants with type 1 (78.7%) and type 2 (74.8%) diabetes maintained the same pre-Ramadan dosage of their oral anti-diabetic medications and insulin doses were not modified in 64% of both type 1 and type 2 diabetes patients [6]. Continuing unmodified pre-Ramadan dosages can pose a risk of hypoglycemia in patients on insulin and sulfonylureas, especially if the glucose intake decreases in tandem with decreased fluid intake during fasting time. Consequently, the ADA and IDF-DAR have produced guidelines for physicians to follow based on experienced practices throughout the Muslim world [1,9]. It is notable that only a few randomized controlled trials of oral medications including the VIRTUE, STEADFAST, and VECTOR trials have been performed comparing the efficacy and risks of DPP-4 inhibitors (vildagliptin) against sulfonylureas agents [31–33] The Treat 4 Ramadan trial compared GLP-1 receptor agonist, liraglutide against sulfonylureas [34]. The results of these studies are summarized in Table 3.

Table 3. Selected pharmacologic studies in patients with type 2 diabetes participating in Ramadan.

Study	Study Design	Conclusions
VIRTUE	RCT of 1300 participants in Asia and the Middle East who fasted during Ramadan—684 treated with Vildagliptin and 631 treated with Sulfonylurea therapy in addition to Metformin and/or lifestyle change.	Fewer participants experienced hypoglycemic events in the Vildagliptin study arm compared to the Sulfonylurea study arm (5.4% vs. 19.8% $p < 0.001$). An increased proportion of participants in the Sulfonylurea arm experienced adverse events consisting mostly of hypoglycemic events compared to the Vildagliptin arm (22.8% vs. 10.2%). Vildagliptin may thus be a safer option than Sulfonylurea in managing type 2 diabetes during Ramadan fasting [31]
STEADFAST	Double Blind RCT of 557 participants with type 2 diabetes who fasted during Ramadan randomized to receive either Vildagliptin or Gliclazide plus Metformin.	Vildagliptin is safe for use by type 2 diabetes during Ramadan and is associated with lower risk of hypoglycemic events compared to Gliclazide (3.0% vs. 7.0%, respectively $p = 0.039$) [32]
VECTOR	RCT of 72 participants with type 2 diabetes who fasted during Ramadan—30 participants took Vildagliptin and 41 took Gliclazide in addition to Metformin therapy	No participants in the Vildagliptin arm experienced a hypoglycemic event compared to 35 hypoglycemic events in the Gliclazide arm [34]. Vildagliptin lowered the mean HbA1c from 7.6% to 7.2% compared to no effect at baseline HbA1c 7.2% in the Gliclazide arm [33]
Treat Ramadan 4 Trial	RCT of 99 participants with type 2 diabetes who fasted in Ramadan—randomly assigned to Liraglutide or Sulfonylurea.	Significant weight loss and diastolic blood pressure were observed in the Liraglutide arm compared to Sulfonylurea arm. No episodes of severe hypoglycemia occurred in either group, but the Sulfonylurea arm reported instances of blood glucose falling below threshold of 3.9 mmol/L more than Liraglutide group [34].

13. Insulin

People with type 1 diabetes and type 2 diabetes with beta cell loss should be on a modified insulin regimen during Ramadan. Basal insulins consist of long-acting insulin analogues such as glargine U-100, glargine U-300, insulin Detemir, Degludec or NPH. Glargine has been shown to be superior in preventing hypoglycemic events compared to

NPH and regular insulin during Ramadan [4]. Glargine U-300 and Degludec have been shown to have less risk of hypoglycemia in individuals observing Ramadan fasting [1]. As there is limited evidence on insulin regimen strategies during Ramadan fasting, insulin dosing adjustments must be individualized. IDF-DAR guidelines, in general, recommend a reduction in the basal insulin dose and modification of bolus insulin as in Table 4 [1].

Table 4. Guidance on insulin use in patients with diabetes mellitus participating in Ramadan [1].

Type of Insulin	Dosing Frequency	Recommended Change
Basal insulin (insulin glargine/NPH/Degludec/Detemir)	Once daily	Reduce dose by 15–30% and Take at Iftar (sunset meal)
Basal insulin (insulin glargine/NPH/Degludec/Detemir)	Twice daily	Take usual morning dose at Iftar (sunset meal), Reduce evening dose by 50% and Take at Suhoor (pre-dawn meal)
Short-acting insulin/Bolus insulin		Take normal dose at Iftar (sunset meal), Skip lunch time dose and Reduce Suhoor (pre-dawn meal) dose by 25–50%

In Individuals on basal-bolus regimen whether type 1 or type 2 diabetes, authors suggest titrating bolus insulin doses daily based on pre-sunset and pre-dawn blood glucose as in Table 5 [1]. Regular insulin can be switched to rapid acting insulin analogs (e.g., lispro, glulisine or aspart), which has been shown to decrease postprandial glucose excursions and limit hypoglycemic episodes [1].

Table 5. Suggestions regarding adjusting bolus insulin doses during Ramadan-Insulin dose titrations based on blood glucose.

Pre-Sunset, Pre-Dawn Blood Glucose	Rapid- or Short-Acting Insulin Dose Adjustment
>250 mg/dL	Increase dose by 20%
>180 mg/dL	Increase dose by 10%
100–180 mg/dL	No change
<100 mg/dL or symptoms of hypoglycemia	Reduce dose by 10%
<70 mg/dL	Reduce dose by 20% and preferably avoid fast

Modifications to premixed insulin can include switching from 70/30 NPH/Regular to 50/50 premix insulins injected before Suhoor and Iftar meals, a practice which has shown improvement in HbA1C and a decrease in hypoglycemic events [1,4,8]. Refer to Figure 2.

An insulin pump and CGM provide a valuable asset for diabetes patients fasting during Ramadan. Several studies including a systematic review and meta-analysis of individuals with type 1 diabetes have shown insulin pump use while fasting was associated with lower rates of severe hypoglycemia, severe hyperglycemia, and better glycemic variability [1,35,36] Sensor-augmented pumps with low-glucose and predictive low-glucose suspend features allow insulin delivery to be automatically suspended for up to 2 h when the glucose level falls below a pre-set threshold. Elbarbary investigated this technology in adolescents with type 1 diabetes during Ramadan and observed a significant reduction in hypoglycemia [37]. Advanced insulin technology thus allows individuals to safely fast during this month without fear of complications [1]. For diabetes patients who are on an insulin pump, IDF-DAR guidelines recommend reduction in basal insulin rate by 20–40% in the last 3–5 h of fasting and increase in dose by 10–30% after Iftar up to midnight. Prandial insulin bolus can be calculated based on usual insulin carb ratio and insulin sensitivity factor, which can remain unchanged [1]. As foods higher in fat may be consumed at Iftar meals, extended or dual-wave bolus can be considered [1].

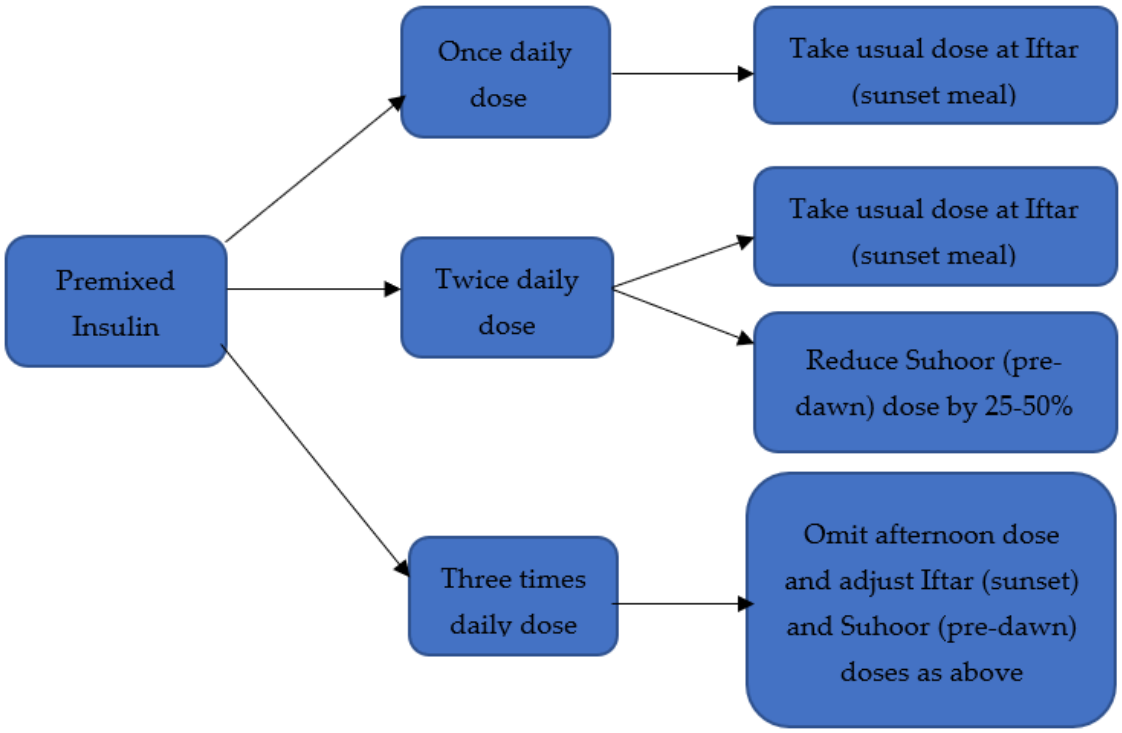


Figure 2. Guidance regarding the use of premixed insulin in patients with diabetes during Ramadan [1].

14. Sulfonylureas

In a multinational observational study involving 1378 individuals with type 2 diabetes treated with Sulfonylurea and who fasted during Ramadan, nearly 20% experienced one or more symptomatic hypoglycemic episodes, with the highest among those on older-generation sulfonylureas (glibenclamide (25.6%) followed by glimepiride (16.8%) and gliclazide (14.0%)) [38]. Generally, sulfonylureas should be avoided in individuals who are fasting, due to the risk of hypoglycemia. The reality is that sulfonylureas are widely prescribed as a second line to metformin and continue to be taken during Ramadan. The older drug glibenclamide is associated with more hypoglycemic events compared to second-generation sulfonylureas including gliclazide, glipizide, and glimepiride. Consequently, these are the preferred sulfonylurea, although dose adjustments may be required [1,8]. If on once-daily dosing, the does is to be taken at Iftar (sunset meal), and the dose may be reduced in cases of well-controlled diabetes. If on twice-daily dosing, the Iftar (sunset meal) dose remains the same, but the Suhoor (predawn meal) dose should be reduced, especially in cases of well-controlled diabetes at baseline [1,14]. The authors do not suggest using Glyburide nor extended-release formulations in people who are fasting. Furthermore, the authors recommend that people take the immediate-release formulations with meals to minimize the risk of hypoglycemia during fasting.

15. Metformin

Metformin is a safe oral antidiabetic drug for Muslims who wish to fast during Ramadan. No dose adjustments are required for once-daily, twice-daily, and extended-release formulations. It can be taken at Iftar (sunset meal) with once-daily dosing and added to Suhoor (predawn meal) with twice-daily dosing [1,14]. The dosage should be modified, however, if taken three times per day: one dose should be taken at Suhoor, and two doses should be taken at Iftar by combining the afternoon and evening doses [1,4,14].

16. Incretin-Based Therapies

Incretin-based therapies including DPP-4 inhibitors and GLP1 receptor agonists (GLP-1 RAs) have generally proven safe and effective in randomized control studies com-

pared to sulfonylureas while fasting during Ramadan. These studies are summarized in Table 3. Vildagliptin, a DPP-4 inhibitor, and liraglutide, a GLP-1 receptor agonist, have both shown, based on these trials, to have a lower risk of causing hypoglycemic events compared to sulfonylureas [31–34]. IDF-DAR guidelines indicate that dosages do not have to be modified, although few concrete studies exist to support this [1,8,9]. GLP-1 RAs may increase the risk of hypoglycemic events when combined with sulfonylureas, so caution must be taken when continuing multiple medications in patients who intend to fast during Ramadan. As some patients may experience gastrointestinal side effects of nausea, vomiting or diarrhea while initiating GLP-1 RA, the authors recommend starting at least eight weeks before Ramadan to ensure adequate time to monitor for side effects.

17. SGLT2 Inhibitors

IDF-DAR guidelines recommend that SGLT2i may be cautiously used during Ramadan fasting [1,14]. SGLT2i should be initiated at least two-to-four weeks prior to Ramadan to ensure stabilization of the medication effects [1,14,39] No dose adjustments are required, but it is preferably to take the medication at Iftar (sunset meal) [1,14]. People with diabetes on SGLT2 inhibitors who fast during Ramadan must be advised to increase their fluid consumption during the non-fasting hours to minimize the risk of dehydration [39]. Studies on safety concerns during Ramadan fasting indicated an increased risk of volume depletion with canagliflozin when compared to sulfonylurea but no increased risk with dapagliflozin in another study [39]. The continued use of SGLT2 inhibitor during Ramadan did not increase the risk of hypoglycemia or risk of diabetic ketoacidosis [39]. However, SGLT2 inhibitors should be avoided during the month of Ramadan fasting in specific groups of patients such as the elderly, those with renal impairment, those on diuretics, and those at risk of hypotension [1,39].

18. Alpha-Glucosidase Inhibitors

This class includes the drug Acarbose, which has a low risk of hypoglycemia; hence, dose adjustments may not be needed [1,14]. No randomized controlled studies have examined the efficacy and risks of acarbose in type 2 diabetes who fast. Acarbose may cause osmotic diarrhea, which can lead to dehydration that can be exacerbated by fasting [40].

19. Thiazolidinedione

While few studies exist that test the efficacy and risk of thiazolidinedione use during Ramadan fasting, they are generally considered safe to use because of their low risk of hypoglycemia. Dosages do not have to be modified during Ramadan and taken with Iftar [1,4,9].

20. Meglitinides

Repaglinide is an insulin secretagogue. Doses may be reduced and taken during pre-dawn and sunset meals [1,14].

Refer to Figure 3 for suggested dose adjustments on oral and non-insulin injectables for diabetes patients during Ramadan fasting.

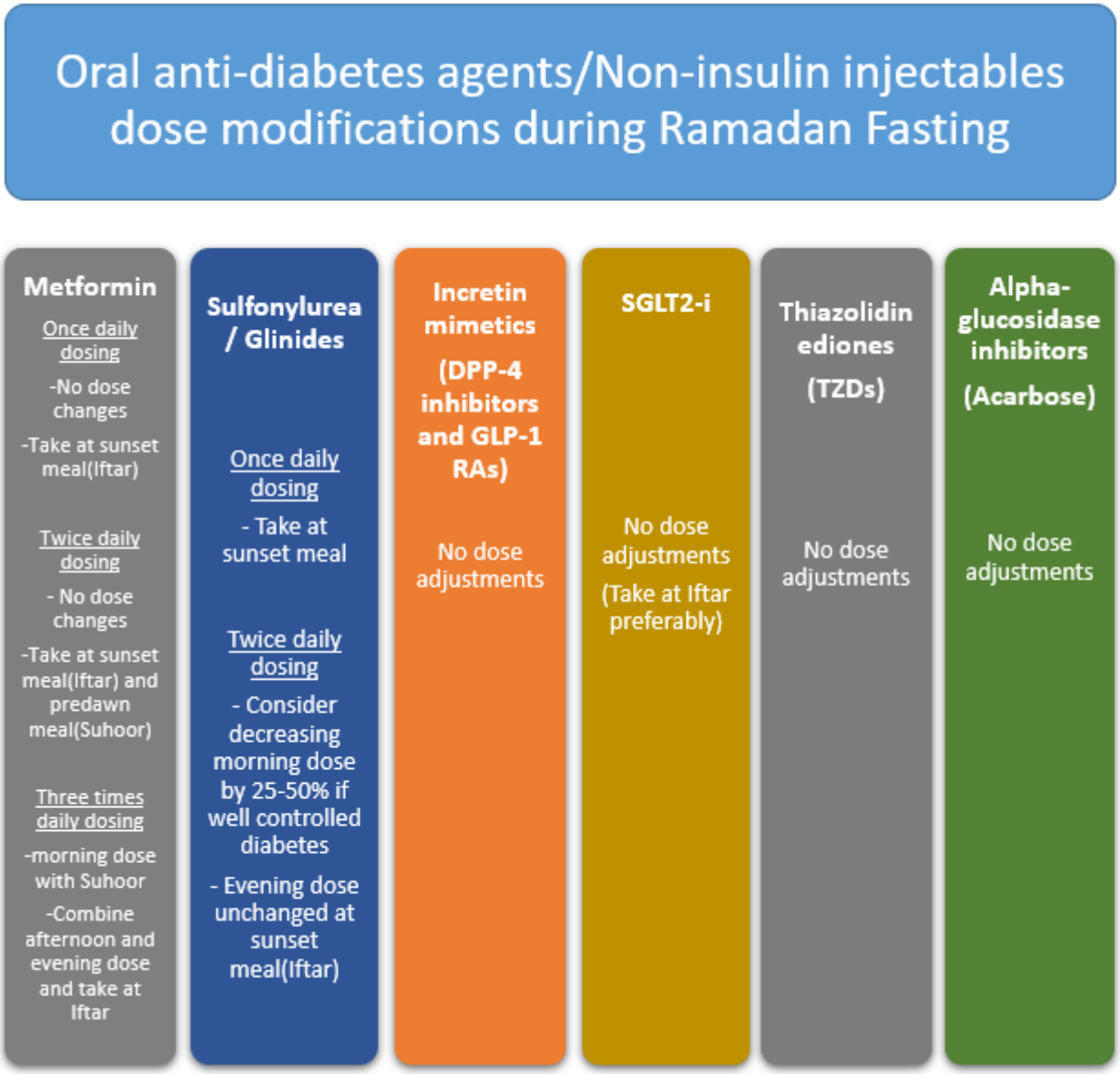


Figure 3. Oral anti-diabetes agents and non-insulin injectables dose modifications during Ramadan fasting.

21. Emergency Room Visits and Hospitalizations

It is valuable for inpatient and emergency-room providers to be aware of things that are permissible and those that invalidate the fast. Although injections via any route for medical treatment such as antibiotics, insulin, vaccinations, and blood draw for diagnostic purposes do not invalidate the fast, conditions that invalidate the fast include saline or dextrose-containing intravenous fluids, blood transfusion, and dialysis [41]. Hence, when individuals who are fasting for Ramadan require hospitalization or emergency-room visits, it is permissible to break the fast if conditions that invalidate the fast are necessary for medical treatment and if withholding may be life-threatening.

22. Conclusion and Future Applications

Ramadan is a spiritually enriching time for Muslims across the globe. There is a growing population of Muslims with diabetes, and there are often misconceptions regarding Ramadan practice and diabetes management. It is important for healthcare providers (HCPs) to understand cultural–religious practices during Ramadan in order to provide

individualized patient tailored care. This starts with a pre-Ramadan assessment to plan to safely participate in fasting.

While multiple guidelines have been published on this topic (ADA and the IDF-DAR), further research is needed to provide evidence of optimal management. The use of continuous glucose monitoring devices during Ramadan itself provides a valuable opportunity. HCP's benefit from learning about cultural and religious norms of their patients with diabetes. This knowledge would allow providers to be a better source of information and support for patients and be able to provide the best possible care.

23. Take Home Points

As the significant number of people who have diabetes and participate in Ramadan is increasing, it is important for HCP to be knowledgeable about Ramadan practices to best advise patients while fasting.

Many patients have misconceptions about diabetes management and Ramadan. HCP can consider the length of the fast, current health conditions, and treatments when advising patients.

The informed HCP can help people with diabetes to safely participate in the holy month of Ramadan.

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