



# Ramadan fasting and diabetes, latest evidence and technological advancements: 2021 update

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## Abstract

Development of updated guidelines for management of diabetes in Ramadan Fasting is of paramount importance. Nonetheless, evidence-based guidelines in the field of Ramadan Fasting and Diabetes are scarce. Moreover, findings of some recent research such as effects of Ramadan fasting on microbiota, genetics and epigenetics, hormonal changes (such as adiponectin, leptin, testosterone...), and alternations in circadian rhythm should also be reviewed and included on a yearly basis. It is documented that self-monitoring of blood glucose (SMBG) is of vital importance for patients with type 1 diabetes who fast, and advantages of continuous glucose monitoring (CGM) or flash glucose monitoring (FGM) techniques should be highlighted. Moreover, the recent findings about applications of advanced insulin delivery technology in patients with diabetes who fast in Ramadan should also considered in the annual updates of the guidelines.

**Keywords** Ramadan Fasting · Fasting · Diabetes

## Introduction

In 2019, globally, approximately, 460 million people were living with diabetes, and this number is forecast to increase to 700 million in 2045, a rise of no less than 51%. [1] On the other hand, by 2045, the number of patients living with diabetes is predicted to increase at least twofold in the Islamic World where a great proportion of the population fast. [2] Therefore, it is imperative that related literature and guidelines on the subject of Ramadan Fasting and diabetes should be updated on a regular basis.

As diabetes is a metabolic disease which involves multiple organs, diabetic patient are at a high risk for development of a wide range of potential fasting-related complications such as dehydration, hypoglycemia, hyperglycemia, and diabetic ketoacidosis (DKA). It should not be overlooked, however, that fasting can be quite beneficial for certain diabetic

patients provided that they strictly adhere to the evidence-based guideline and pious physicians' advice [3].

People with diabetes are generally confronted with serious risks such as hypoglycemia and hyperglycemia. Notwithstanding all such risks, many still choose to fast, even those for whom fasting is religiously prohibited. For instance, It is documented that adults with T1DM have a pronouncedly higher incidence of severe hypoglycemia and diabetic ketoacidosis (DKA) if they fast during Ramadan. [4] Nonetheless, many patients with the disease choose to fast every year. Therefore, it is imperative that safe Ramadan Fasting instruction for patients with different types of diabetes should be developed so that the risks involved can be minimized, and this group of diabetic patients can fast in a reasonably safer manner. The major aim of this commentary is to review and update the existing knowledge in the field of Ramadan Fasting for clinicians whose guidance is sought by Muslim patients with diabetes all across the world.

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## Diabetes education and ramadan fasting

In all patients with diabetes, Ramadan-focused education is of paramount importance for heightening their awareness of the possible associated risks, and formulation of effective strategies to minimize them. High-risk individuals

who choose to fast should have access to ample education and support so that the potential risks, particularly those of hyper- and hypoglycemia can be minimized. It should be emphasized that in all educational programs, optimal blood glucose monitoring should be considered as the principal consideration for minimization of the risk of complications [5].

Lifestyle modification can be considered as another key component of Ramadan Fasting education in individuals with diabetes. The fasting-feeding nature of the ritual can predispose diabetic patients to hypoglycemia during the day and hyperglycemia after iftar at night. [6] In most Islamic cultures, consumption of high-calory, high-fat, and carbohydrate-rich meals, confectionaries, and beverages is commonplace in Ramadan, which can adversely affect blood glucose levels and increase the risk of development of hyperglycemia and related complications. [7] This should be strongly discouraged in all educational programs. Moreover, due to the high risk of hypoglycemia and dehydration, patients with diabetes should be prohibited from strenuous exercise, particularly late in the evening and before iftar. [6] Patients should also be informed that consumption of large amounts of high glycemic index (GI) carbohydrates [8] and alternations in physical activity and sleeping patterns can lead to weight gain during Ramadan. [9] Symptoms of hypoglycemia and hyperglycemia should be clearly explained to diabetic patients, and they need to be thought to measure their blood sugar and immediately discontinue fasting if they develop. [10] They also need to be advised that, in case of hypoglycemia, a small amount of a fast-acting carbohydrate (a glass of fruit juice) should be consumed, and they need to retest their blood glucose levels again after 20 min. [11] When there is little opportunity for face-to-face, such as the current Covid-19 pandemic, communication technology and mobile phones should be utilized, which are demonstrated to be effective tools for diabetes education.

## Management of patients with type 1 diabetes

During Ramadan Fasting, proper use of specific insulin types and regimens, and vigilant blood sugar monitoring can be of life-saving importance in minimization of the risk of hypoglycemia. In a recent global survey of individuals with T1DM who chose to fast, it was observed that the majority of the patients experienced episodes of hypoglycemia with different durations and severities. [12] In this regard, the substantial benefits latest diabetes-control technology can confer should not be underestimated. It is demonstrated that in patients with type 1 diabetes who fast, continuous subcutaneous insulin infusion (CSII) devices can be markedly more effective in reducing the risk for hypoglycemia in

comparison with the traditional insulin injection regimens. [13] Moreover, during the recent years, the advent of the low-glucose suspend (LGS) feature for insulin pumps has proved to be of great benefit in reducing the episodes of hypoglycemia, and helped fasting patients with type 1 diabetes to perform the ritual in a safer manner [14].

People with T1DM who choose to fast should regularly check their blood glucose levels, ideally using a continuous glucose monitoring (CGM) device. Findings of a recent study has provided credible evidence indicating that real-time CGM is significantly advantageous over the conventional blood sugar monitoring methods in terms of improvement of several adverse diabetes outcomes including reducing HbA1c, minimizing blood glucose fluctuations, decreasing the risk of hypoglycemia, and increasing the Time in Range (TIR) (which is defined as the time spent in the target range of plasma glucose between 70 and 180 mg/dL). [15] However, it should be mentioned that in children and adolescents with T1DM, the effectiveness of CGM depends on the compliance of the patients and duration of the sensor use during fasting hours. [16] Besides improvement of glycemic control, in Ramadan Fasting, the use of technologically-advanced diabetes control technologies is demonstrated to be of great benefit in prediction of hypoglycemia and glycemic excursions. [17–19] Several studies have highlighted the advantages of other advanced technologies such as flash glucose monitoring (FGM) systems in fasting patients with T1DM [20].

In some Islamic cultures, food and beverage consumed during Ramadan is traditionally high in fat and carbohydrates, and patients with T1DM should be warned against the grave consequences. [21] Besides, drinking large amounts of water and liquids before dawn should be discouraged, and instead, moderate and continuous consumption of water and beverages during non-fasting hours should be promoted [22].

In terms of insulin therapy for management of patients with type 1 diabetes who fast in Ramadan, several guidelines recommend that pre-prandial bolus insulin is advantageous over the insulin administered during or after Sahar and Iftar. They also recommend that frequent self-monitoring of blood sugar (SMBG), or ideally continuous glucose monitoring (CGM), should provide the basis for proper adjustment of insulin doses. [23] In this regard, several studies recommend that administration of a long-acting insulin analogue in conjunction with a premeal dose of rapid-acting insulin analogue should be advocated as this approach is demonstrated to be associated with a lower risk of hypoglycemia, particularly in children and adolescents [24].

In most observational studies, the safety and efficacy of first-generation basal insulin analogues (such as glargine) in fasting individuals with controlled T1DM have been documented. [25] Nonetheless, in a few studies, it has been observed that this regimen may lead to significant decline in

plasma glucose concentrations with a tendency towards hypoglycemia, which often occurs close to the end of the fasting hours. [26] To minimize this risk, some authors have suggested that the basal insulin dose should be reduced in Ramadan. [27] Most authors have recommended that the pre-Ramadan basal dose should be reduced by 20% and given earlier in the evening, although some have proposed a reduction of up to 40% [28].

Basal insulin should, ideally, be administered earlier in the day. This is of great importance for reducing the exposure of the body organs and tissues to active insulin in circulation during the last hours of fasting. This approach is confirmed by several studies which have used continuous glucose monitoring devices, and most of them have demonstrated that approximately 70% of the hypoglycemic events occurs in the last 6 h of fasting. [29] Nonetheless, there is no consensus about the precise necessary adjustments to insulin doses during Ramadan for favorable glycemic control without the risk of hyperglycemia. In this regard, Alalwan et al. have proposed administration of a pre-Iftar dose equal to that of a pre-Ramadan lunch dose and a pre-dawn dose equal to a usual pre-Ramadan evening dose of rapid acting insulin. [30] Similarly, the precise timing of the doses remains controversial. One study has demonstrated that administration of a bolus dose of rapid-acting insulin 20 min before a meal results in a significantly better postprandial glucose control than when the insulin bolus is given just before meals or immediately after them. This timing is particularly very important when high-fat and high-protein meals are ingested, which usually occurs in Iftar [31].

As regards the type of insulin, particularly in children and adolescents, it has been shown that the use of long acting insulin analogues are preferable over intermediate acting insulins as the latter leads to a steady fall in blood glucose levels in the last hours of fasting prior to the iftar meal. [32] It should be mentioned here, that insulin pumps have proved to be impressively effective in management of patients with type 1 diabetes who fast during Ramadan. Adjustments of an insulin pump can greatly facilitate reducing the risks of both hypoglycemia caused by prolonged daytime starvation and hyperglycemia due to excessive iftar meal, as compared with the conventional regimen of several insulin injections. The ability to lower the basal insulin infusion rate or even suspending it by insulin pumps can enable persons with diabetes to fast safer and minimize the risk of hypoglycemic bouts during fasting hours [27].

## Management of patients with type 2 diabetes

There is universal consensus that most patients with type 2 diabetes mellitus (T2DM) may fast during Ramadan without any major concern. Nonetheless, similar to patients with

type 1 diabetes, patients with type 2 diabetes may be confronted with several challenges associated with the fasting-feasting nature of the ritual and the metabolic consequences. More specifically, wide fluctuations in blood glucose levels can lead to severe hyperglycemia and hypoglycemia, and their associated risks.

Prior to Ramadan, clinicians should perform a comprehensive evaluation and assessment for all patients with type 2 diabetes who intend to fast during Ramadan, and consider individualized approaches for their patients. In these pre-Ramadan visits, all patients need to be provided with detailed guidance on all related aspects such as nutrition, proper hydration, physical activity and exercise, and self-monitoring of blood sugar. Most importantly, they should receive clear guidance about the symptoms of potential critical situations, and be advised about how to break the fast in such situations. They should also be required to measure their blood glucose levels more frequently and vigilantly during Ramadan, and the advantages of the use of continuous glucose monitoring (CGM) or flash glucose monitoring (FGM) systems need to be mentioned to them, so that they procure and use them if affordable.

The type, dose, and timing of the anti-diabetic medications each patient takes is immensely influential in the management potential risks involved in their use, but most antidiabetic agents used for treatment of type 2 diabetes are generally considered safe. It should be mentioned, however, that in patients who take several glucose lowering medications, the risk of hypoglycemia may be amplified. [33] Particularly, in patients who take a basal insulin in combination with a DPP4I, metformin, or other glucose lowering agents, the risk of hypoglycemia can greatly increase [34].

Severe complications in fasting individuals who take metformin are quite uncommon, and generally, fasting people with T2DM may continue its consumption without any concern. Similar to Metformin, Acarbose can be safely prescribed to fasting patients with type 2 diabetes. Likewise, despite scarcity of research on using Thiazolidinediones in Ramadan, hitherto, no concern has been raised regarding their prescription to type 2 diabetes patients who fast. Nonetheless, one study on 86 fasting type 2 diabetic patients demonstrated that their consumption may lead to weight gain. [35] Moreover, it should be noted to patients with diabetes that they should not start taking Thiazolidinediones in Ramadan, and this class of glucose-lowering agents should be taken with iftar and not Sahar.

Short-acting insulin secretagogues (such as repaglinide and nateglinide) act through stimulation of pancreatic  $\beta$  cells which leads to increased insulin secretion. Results of several studies have provided convincing evidence that this class of antidiabetic medications does not lead to hypoglycemia bouts, and its use in Ramadan Fasting is quite safe. [36–38]. Similarly, use of Glucagon-like peptide-1 receptor agonists

(GLP-1 RAs) is associated with minimal risk of hypoglycemic attacks in Ramadan Fasting when used alone, but there are some risks involved in their use if they are prescribed in combination with other antidiabetic medications (such as insulin or sulfonylureas). [39] As regards Dipeptidyl peptidase-4 (DPP-4) inhibitors, similar to the previous classes of antidiabetics mentioned, several studies have demonstrated that the risks involved in taking this class of medications during Ramadan Fasting is considerably low [40].

As Sulphonylureas (SUs) SUs stimulate pancreatic  $\beta$  cells to produce more insulin, traditionally, many clinicians are concerned that this class of antidiabetics may impose some degree of hypoglycemia risk during Ramadan Fasting. [41] Nonetheless, several studies have demonstrated that people with T2DM who fast in Ramadan may continue using newer SUs such as gliclazide, gliclazide and glimepiride without any concern, [38] but older drugs of this class, (such as, glibenclamide) should definitely be discontinued in Ramadan [40].

Notwithstanding the fact that Sodium-glucose co-transporter-2 (SGLT2) inhibitors (such as dapagliflozin, canagliflozin, empagliflozin and ertugliflozin) are generally believed to be safe in people with T2DM who fast during Ramadan, some studies have concluded that the risk of dehydration may be increased by their use in fasting patients who are particularly vulnerable in this regard. As a result, several guidelines have prohibited their prescription in individuals with frequent vomiting, diarrhea, or intake of ACE-I and diuretics [42].

It is widely believed that type 2 diabetes patients who take insulin during Ramadan are at greater risk for development of hypoglycemia, particularly when insulin is used in complex regimens along with other antidiabetic medications. Nonetheless, findings of several studies have demonstrated that insulin would be tolerated well provided that the conventional twice daily premixed or intermediate-acting dose would be changed to one dose of long-acting or intermediate-acting insulin in the evening, and two doses of rapid-acting insulin with Shar and Iftar. [27] Findings of some studies have suggested that total substitution of insulin by insulin analogues may reduce the risk of hypoglycemia in people with T2DM who fast during Ramadan. [43, 44] It should be mentioned, however, that fasting patients with type 2 diabetes who wish switch to insulin analogues for the month of Ramadan need to begin with a starting dose of 20–30% lower compared to the regular insulin dose [45].

Basal insulin is generally considered safe in Ramadan Fasting. Authors of one study in a group of fasting patients with T2DM who were taking insulin glargine and glimepiride have observed and reported only mild hypoglycemic events. [46] Authors of another study have contended that the second-generation basal insulin analogue, glargine, may be safely used in Ramadan Fasting in combination with other oral antidiabetic medications. [47] It should be

noted, moreover, that in addition to long-acting basal insulin, injection of rapid or short-acting insulins may be necessary for proper management of post-prandial hyperglycemia episodes. [44] As they require fewer injections in comparison with the regimens requiring basal-bolus injection, premixed insulins which contain both short- and intermediate-acting insulins can be advantageous in management of fasting patients with type 2 diabetes. Nonetheless, some authors have raised concerns that their use may be associated with a higher risk of hypoglycemia [48].

## Considerations in pregnant women with diabetes

Regardless of religious fatwas and decrees in different countries and various branches of Islam, every year, many pregnant Muslims choose to fast in Ramadan. [49, 50] Therefore, all clinicians who visit fasting patients need to familiarize themselves with the principles of the management of fasting pregnant women with diabetes so as to minimize the risks associated.

Different studies have published contradictory conclusions on the subject of healthy pregnancy and Ramadan Fasting. Whilst Some studies have concluded that healthy non-diabetic pregnant women may fast without any threat to either the mother or the fetus, [51, 52] some authors have reported decreased placental weight in pregnant women who fast as a potential threat (although without affecting the birth weight). [53] Regardless of such controversies in healthy pregnant women, the current general consensus for fasting women with pre-existing T1DM or T2DM is that they are categorized as the high-risk fasting group and should not be allowed to fast during Ramadan [54].

It should not be overlooked, however, that a considerable number of pregnant women do fast during Ramadan, and clinicians should acquaint themselves with the basic knowledge and skills for management of pregnant patients with diabetes who choose to fast against medical advice. Traditionally, many experienced clinicians believe that pregnant women with diabetes should be managed with insulin, metformin, or glibenclamide. Notwithstanding of the safety and efficacy of this approach, in Ramadan Fasting, clinicians should be advised against prescription of glibenclamide to pregnant women [40, 41].

## Elderly individuals with diabetes

Although the elderly with diabetes are considered as being at a higher risk for development of the related complications, every year, many senior diabetic individuals observe the ritual [28] In this group of fasting patients, it is of utmost

importance that diabetes-related comorbidities and complications should be thoroughly evaluated and monitored. In the elderly with diabetes, diabetic kidney disease, cardiovascular disease (CVD), retinopathy, and other complications of diabetes are notoriously common [55] Moreover, elderly patients are at greater risk for dementia, volume depletion, visual impairment, and consequently, they are vulnerable to falls which may lead to hip fracture [56–58] Therefore, fasting individuals in advanced ages should be prescribed antidiabetic medications with minimal risks for development of hypoglycemia which may lead to falls and fractures. Besides, this group of patients should be informed of the critical importance of regular self-monitoring of blood glucose levels.

## Diabetes complications and ramadan fasting

There is universal concern that people with diabetes microvascular and macrovascular complications who fast during Ramadan may impose an exaggerated risk of exacerbation of them on themselves. [28] It is documented that diabetes per se is a great risk for development of cardiovascular disease (CVD), and the rate of stroke is significantly increased in diabetic patients. [59] Therefore, some unhealthy practices associated with the ritual in some cultures (such as binge intake of high amounts of carbohydrates and fats in Iftar and Sahar meals) can amplify the risk of CVD or stroke in Ramadan. [60] Nevertheless, fasting can be beneficial in this regard if practiced responsibly as favorable and tight glycaemic control during Ramadan can effectively mitigate the risk for cardiovascular incidents and stroke [61].

Patients with diabetes are at a higher risk for development of different kidney-related complications. [62, 63] It is demonstrated that fasting diabetic patients with CKD are more apt to have high levels of urinary NAG (N-acetyl- $\beta$ -D-glucosaminidase which is a marker of renal tubulopathy) in comparison with healthy fasting individuals, and this high level is closely correlated with blood glucose levels. [64] In one study, Mbarki et al. observed that in diabetic patients with CKD who fasted renal function was deteriorated. [65] Similarly, other authors have concluded that more severe adverse renal outcomes are common in fasting patients with higher stages of CKD during Ramadan. [66] Interestingly, it is even contended that the risk for development of CVD is significantly increased in diabetic patients with CKD who fast during Ramadan. [67] Notwithstanding such findings, a meta-analysis carried out on the mean differences of the eGFR before and after Ramadan has concluded that there existed no significant difference (mean difference 0; 95% CI -0.19 – 0.19). [68] But regardless of contradictory findings about Ramadan fasting in diabetic patients with CKD, in most guidelines, it is recommended that those with stable renal function may fast, and temporary changes are believed to fade away after Ramadan [69].

## Conclusion

In management of patients with diabetes in Ramadan, education and risk assessment should be given priority over any clinical decision-making or intervention. Accordingly, different risk groups should receive their personal Ramadan-specific diabetes management plans. It should be taken into consideration by all clinicians and general practitioners that Ramadan Fasting can make great alternations to the levels of different hormones, and this may adversely (or favorably) affect the health of patients living with diabetes. On the other hand, there are several physical and spiritual health benefits to patients with diabetes which are conferred through Ramadan Fasting. Therefore, it is imperative that people with diabetes consult with their clinicians prior to commencement of Ramadan Fasting on an annual basis.

## Declarations

**Conflict of interests** The authors declare none

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