

COVID-19 Pandemic and Ramadan Fasting among Patients with Type 2 Diabetes Mellitus

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ABSTRACT This year Ramadan occurs during the global coronavirus disease-2019 (COVID-19) pandemic. Data have shown that patients with type 2 diabetes mellitus (T2DM) are prone to severe disease with COVID-19 and with increased mortality. Acute complications such as dehydration, starvation ketosis, ketoacidosis, and the increased risk of coagulopathy and thrombosis should be considered particularly during this pandemic period. Fasting during Ramadan this year and the COVID-19 pandemic is more challenging, not only for patients with T2DM but also for healthcare providers. We present healthcare providers with important aspects to consider during the COVID-19 pandemic for patients with T2DM who intend to fast during Ramadan and other fasting days.

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Ramadan is the the ninth month of the Islamic calendar and represents one of the five pillars in Islam. Fasting during the month of Ramadan requires abstinence from eating, drinking, and smoking each day from sunrise to sunset. During Ramadan, Muslims consume two main meals, a predawn meal (Suhoor) and a fast-breaking meal after sunset (Iftar). While fasting is considered obligatory for all healthy Muslims, there are exemptions for pregnant or lactating women or those with severe chronic disease or acute illness in which fasting may aggravate their condition [1].

Fasting is not mandatory for patients with type 2 diabetes mellitus (T2DM), in particular among those with uncontrolled disease who are at increased risk for acute complications such as hypoglycemic events, dehydration, thrombosis, hyperglycemic hyperosmolar state, and diabetic ketoacidosis [2]. Similar to other acute infections, the presence of coronavirus disease-2019 (COVID-19) infection may exacerbate these complications. This year Ramadan occurred during the global COVID-19 pandemic. Since

COVID-19 infection can present with different scenarios from asymptomatic to life-threatening, fasting during Ramadan becomes even more challenging for diabetic patients who want to fast, as well as for healthcare providers who treat these patients [3]. The World Health Organization (WHO) published general guidelines for fasting in Ramadan during the COVID-19 pandemic [4].

We highlight important points regarding Ramadan and other fasting days during the COVID-19 pandemic and provide recommendations for healthcare providers who treat those with T2DM who intend to fast during Ramadan.

PRE-RAMADAN MEDICAL ASSESSMENT

The pre-Ramadan period begins 1 to 2 months before the month of Ramadan. For diabetic patients, it is important to treat every patient individually and provide comprehensive and continuous diabetes education. Healthcare providers should assist diabetic patients who intend to fast during Ramadan so that the patient can withstand the Ramadan period safely. A pre-Ramadan assessment should include risk stratification, risk of hypoglycemia, current co-morbidities, previous Ramadan fasting experience, and current anti-diabetic dose adjustment if needed [5]. During the COVID-19 pandemic, Ramadan-focused educational programs for patients with T2DM represent an important element that should be included.

These programs should include a thorough explanation about the importance of glucose monitoring during fasting and non-fasting hours, whether one should stop fasting, meal content and planning to avoid hypoglycemia, dehydration during prolonged fasting and meal types to avoid postprandial hyperglycemia, and weight gain. Ramadan-focused educational programs should include advice about stopping fasting in the case of suspected or diagnosed COVID-19 acute infection. Healthcare providers should be trained to deliver structured patient educational programs, not only during patient visits, but also via telecommunication [6].

THE ROLE OF TELEMEDICINE FOR THE PRE-RAMADAN PERIOD DURING THE COVID-19 PANDEMIC

As healthcare resources continue to be stretched due to the increasing burden of the COVID-19 pandemic, telemedicine, including tele-education, has been shown to be feasible, accept-

able, and effective worldwide and has been allowed for significant improvements in health care outcomes [7]. This modality of communication offers a new means to locate health information and communicate with patients via interactive chats, videoconferences and e-mail. Worthy to mention that since COVID-19 pandemic this platform has become one of the most important modalities for consultation in multiple disciplines. Many studies have shown that telemedicine can improve also T2DM control [8]. Therefore, it is recommended to use this communication modality during pre-Ramadan period and Ramadan fasting.

IMPORTANT ISSUES TO FOCUS ON DURING RAMADAN AND COVID-19 PANDEMIC

Weight and nutrition

Weight gain during the month of Ramadan is related to multiple factors including increased food intake, decreased physical activity, increased insulin dose without glucose monitoring in the absence of medical instructions, and Ramadan-focused education.

Notably, the Ramadan Education and Awareness in Diabetes (READ) program disclosed a 0.7 kg ($P < 0.001$) weight reduction in the education group during Ramadan, while patients in the control group gained about 0.6 kg [9].

Since the COVID-19 outbreak, physical activity has been decreased dramatically due to nationwide lockdowns and medical quarantines of large sectors of the population. In addition, food preparation and intake has increased significantly. These factors represent a major risk for weight gain and obesity that might become more severe during the month of Ramadan [10]. Therefore, intensive healthcare education and diet recommendations are needed.

Patients with T2DM should be instructed to include foods with low glycemic index, avoiding large meals with highly processed carbohydrates at Suhoor and Iftar. Performing mild physical activity is beneficial for avoiding weight gain. In Ramadan physical activity is recommended after Iftar.

Dehydration and thrombosis

Prolonged fasting and limitation of fluid intake may predispose diabetic patients to volume depletion, dehydration, and orthostatic hypotension. There are some main factors that may exacerbate this condition such as excessive perspiration in a hot climate, strenuous physical activity, increased osmotic diuresis due to uncontrolled hyperglycemia, and vomiting associated with headache [11]. Volume depletion and intravascular contraction may predispose patients to a hypercoagulability state, with increased incidence of thrombosis. Increased incidence of retinal vein thrombosis during Ramadan was previously reported [12]. Patients with T2DM without macrovascular complications are prone to hypercoagulability [13].

It is well-known that mortality is twofold higher in patients with T2DM and severe COVID-19 disease. Inadequately con-

trolled hyperglycemia, starvation ketosis, and dehydration may contribute to this increased risk [14]. Data showed greater incidence of diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar state, and euglycemic diabetic ketoacidosis (EDKA) [15].

Healthcare providers should encourage patients with T2DM who fast during Ramadan to drink at least 2 liters of water or unsweetened beverages during the non-fasting hours to avoid dehydration. Acute infections including COVID-19 can be aggravated by dehydration, volume depletion, and development of acute kidney injury (AKI). Therefore, it is recommended that any patient with symptomatic acute illness including COVID-19 should stop fasting.

COVID-19-ASSOCIATED COAGULOPATHY AND RAMADAN FASTING

COVID-19-associated coagulopathy (CAC) has been shown in patients with severe COVID-19 infection [16]. In the early stages of the infection coagulopathy is associated with elevated fibrinogen, D-dimers with minimal changes in prothrombin time (PT), and activated partial thromboplastin time (PTT) and platelet count. D-dimer elevation at admission is a predictor for increased mortality [17]. The mechanisms behind CAC are not fully known. However, dysregulated immune responses with increased pro-inflammatory cytokines, lymphocyte cell-death, hypoxia, and endothelial injury are among the major causes of coagulation disorder in any severe infection [18]. Therefore, in patients with T2DM, who already present with increased risk for coagulopathy, the coexistence of CAC during Ramadan fasting or other religious fasting days might be harmful.

RISK STRATIFICATION AND QUANTIFICATION OF PATIENTS WITH T2DM INTENDING TO FAST RAMADAN DURING THE COVID-19 PANDEMIC

Risk stratification and quantification categories represent a road map that supplies healthcare providers with medical data regarding the risk of fasting for Ramadan during the COVID-19 pandemic. Guidelines and risk stratification have been published [19]. In the current classification, COVID-19 infection risk was included. During the COVID-19 pandemic patients classified with moderate, high, and very high-risk stratification categories should avoid fasting [Table 1].

COVID-19 PANDEMIC AND ANTI-DIABETIC TREATMENT DURING RAMADAN

Metformin

During Ramadan patients with T2DM treated with metformin do not require any dose modification. However, in the presence of dehydration, symptomatic COVID-19 infection, or hospitalization, patients should break their fast and stop metformin particularly in the presence of AKI.

Table 1. Risk categories of patients with type 2 diabetes mellitus who fast for Ramadan during the COVID-19 pandemic

Classification*	Indication
Very high risk	<ul style="list-style-type: none"> • Type 1 diabetes • Pregnancy • Diabetic ketoacidosis within 3 months of Ramadan • Hyperosmolar hyperglycemic coma within 3 months of Ramadan • Severe recurrent hypoglycemia within 3 months of Ramadan • Hypoglycemia unawareness • Sustained poor glycemic control • Average blood glucose \geq 300 mg/dl or HbA1C \geq 10% • Acute illness one month prior to Ramadan • COVID-19 positive patients with severe symptoms admitted to hospital • Intense physical labor while on insulin and sulfonylurea • Chronic kidney failure stage 4 and 5 with or without albumin excretion* • Diabetic patients with nephrotic syndrome independent of eGFR andHbA1C
High risk	<ul style="list-style-type: none"> • Moderate hyperglycemia • Average blood glucose 300–250 mg/dl or HbA1C 10–9% • CKD stage 3 with moderate eGFR decline of 30–59 ml/min/1.73 m² with micro- or macroalbuminuria • Advanced macrovascular complications • COVID-19-positive patients with mild to moderate symptoms at home care • Living alone and treated with insulin or SUs • Patients with co-morbid conditions that present additional risk factors • Very old age with ill health • Treatment with drugs that may affect awareness • Bedouins living in remote areas with limited water supply and minimal healthcare access • Patients on insulin treatment as basal bolus or mixture insulin > 2 injections/day
Moderate risk	<ul style="list-style-type: none"> • Mild hyperglycemia • Average blood glucose 200 mg/dl or 7.5% < HbA1C < 9% • Diabetic patients with short-acting insulin secretagogues and/orSGLT2i • Patients moderately controlled on basal or basal plus or mixture insulin \leq 2 injections • CKD stage 2 with mild eGFR decline of 60–89 ml/min/1.73 m² with or without microalbuminuria • Patients with positive COVID-19 who remain asymptomatic
Low risk	<ul style="list-style-type: none"> • Average blood glucose 150 mg/dl or HbA1C \leq 7.5% • Patients treated with diet and modified lifestyle • Anti-diabetic agents including: metformin, acarbose, TZDs, incretin-based therapy with normal eGFR and normoalbuminuria

*This classification is based on expert opinion and previously published classifications
HbA1C = hemoglobin A1C, eGFR = estimated glomerular filtration rate, TZDs = thiazolidindiones

Incretin based therapy

Incretin-based therapy includes two important classes: the glucagon-like peptide-1 (GLP-1) receptor agonists and the dipeptidyl peptidase-4 (DPP-4) inhibitors. Studies concerning these two classes have demonstrated their efficacy and safety in T2DM patients fasting during Ramadan. These two classes carry a minimal risk of hypoglycemia. No dose adjustment is required for patients with T2DM who develop mild to moderate symptoms of COVID-19 during Ramadan fasting. However, frequent self-blood glucose monitoring is required [20,21].

Sodium glucose cotransporter 2 inhibitors

Sodium glucose cotransporter 2 inhibitors (SGLT2i) represent an important class in the management of patients with T2DM. The cardiorenal protective effect extends the use of this class for patients with heart failure, particularly with reduced ejection fraction and for patients with renal failure without T2DM [22]. The mechanisms behind these cardiorenal outcomes include reduction in preload and after load related mainly to loss of in-

terstitial volume, hematocrit increase related to erythropoietin production, cardiomyocyte bioenergetics improvement as a result of increased lipolysis leading to increased ketone bodies which act as efficient energy fuel substrate. The inhibition of sodium hydrogen exchanger (NHE) represents a pivotal mode of action of this class [23]. Moreover, decreased blood pressure and weight reduction are also considered beneficial effects. In patients with severe COVID-19 associated with impaired tissue oxygenation and lactate accumulation as a result of anaerobic glycolysis and the failure to convert lactate to pyruvate, the use of SGLT2i might be considered favorable in this condition by preventing lactate generation through improving tissue oxygenation via increased hematocrit and reduced oxygen demand as well as improve cell survival induced by NHE inhibition. Despite the benefits of the use of SGLT2i in COVID-19, there are certain risks that should be considered when using this class in the presence of cytokine storm with increased cell damage and increased peripheral lipolysis leading to ketosis [24]. This complication coupled with dehydration and AKI related to any febrile state, could lead to diabetic

ketoacidosis (DKA) and might aggravate CAC. DKA and euglycemic diabetic ketoacidosis (EDKA) are rare, life-threatening complications in patients using SGLT2i [25].

This scenario might be even more pronounced among patients fasting during Ramadan. Thus, extra care should be taken while using SGLT2i in patient fasting during Ramadan during the COVID-19 pandemic.

Therefore, it is recommended to continue SGLT2i in selected patients with low risk for acute event. However, SGLT2i should be discontinued once diabetic patients develop symptoms of COVID-19 infection, fasting should be stopped, adequate hydration should be ensured, blood glucose levels should be frequently monitored, and sick day rules must be followed. Serum and urine ketones measurements and ABG tests are of major importance for hospitalized patients with COVID-19 infection in the presence of hyperglycemia in order to rule out DKA or EDKA particularly in patients using SGLT2i

The initiation of SGLT2i a few weeks before Ramadan fasting is not recommended. Table 2 shows other anti-diabetic recommendations.

ENDING AND RAMADAN FASTING

It is mandatory to end fasting for any patient who presents with any acute illness, including diabetic patients with symptomatic COVID-19 infection. Patients in quarantine without COVID-19 symptoms can cautiously continue their fasting. However, close monitoring, including tele-communication with healthcare providers, is mandatory. General recommendations have been previously [20].

CONCLUSIONS

Patients with type 2 diabetes mellitus who fast during Ramadan or other religious fasting days should be evaluated by healthcare providers during the pre-Ramadan period for safer fasting.

Table 2. Summary of recommendations for anti-diabetic therapies for Ramadan during the COVID-19 pandemic

Anti-diabetic class of treatment	Recommendations during Ramadan	Additional recommendations during the COVID-19 pandemic
Metformin therapy (biguanide)	No dose modification required	In severe COVID-19 infection stop medication
DPP-4 inhibitors, alpha-glucosidase inhibitors, TZDs	No dose adjustment is required	- Ensure adequate fluid intake - Regular glucose monitoring
GLP-1Rc agonists	No dose changes required	In severe cases of COVID-19 discontinue medication particularly in patients with upper gastrointestinal symptoms
SGLT2 inhibitors	No dose adjustment required	- In the presence of dehydration signs, medication should be stopped - For patients with symptomatic COVID-19 with hyperglycemia, discontinue SGLT2i and perform ketones analysis to rule out EDKA or DKA
Sulphonylureas	- Avoid glibenclamide due to increased risk of hypoglycaemia - Use second generation SUs (glimepiride, glicazide) with fewer hypoglycemic events - For once daily dose, switch the same dose to evening before/ during Iftar - For twice daily regimen, reduce the predawn (Suhour) dose to half and keep the same dose at Iftar - Consider changing the dose according to daytime and post-meal glucose levels	- Ensure adequate fluid intake - Monitor of glucose levels - Switch treatment to insulin for hospitalized patients with severe COVID-19 - Continue regular glucose monitoring
Meglitinides	- Reduce the predawn (Suhour) dose to half and keep the same dose at Iftar - Consider changing the dose according to today time and post-meal glucose levels	- Ensure adequate fluid intake - Continue regular glucose monitoring
Insulin treatment Basal regimen	Consider adding a short-acting insulin analog (lispro, aspart, glulisine) of 6–10 units before Iftar (dose adjustment according to post-meal glucose level) Consider decreasing long-acting insulin by 20%	In hospitalized patients with severe COVID-19 under dexamethasone treatment consider adding short acting insulin boluses according to glucose monitoring levels After discharge, adjust insulin dose according to steroid tapering dose and glucose levels
Basal bolus regimen	Decrease the short-acting insulin during the pre-dawn meal (Suhour) by 30–50% and increase the insulin dose by 30–50% at Iftar (dose adjustment according to post-meal glucose)	In patients with symptomatic COVID-19 dose: - Adjust according to glucose levels - Ensure adequate hydration - Continue regular glucose monitoring
Mixture insulin regimen: less recommended during Ramadan	Consider decreasing the dose of insulin at the predawn (Suhour) meal by 30–50% and increasing the dose at the Iftar meal by 30–50% Consider switching to an insulin mixture at Iftar with one that provides high short-acting insulin (lispro mix 50 or insulin as part mix) for controlling post-prandial hyperglycemia	In patients with symptomatic COVID-19 switch to basal bolus regimen

COVID-19 infection should be considered during patient risk stratification before fasting. Incretin-based therapy represents a favorable modality of treatment for patients who intend to fast Ramadan in particular during COVID-19 pandemic. Despite the cardiorenal beneficial effects of SGLT2i, treatment discontinuation is recommended in patients with severe COVID-19 due to increased tendency for DKA and EDKA.

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Capsule

UK variant transmission

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has the capacity to generate variants with major genomic changes. The UK variant B.1.1.7 (also known as VOC 202012/01) has many mutations that alter virus attachment and entry into human cells. Using a variety of statistical and dynamic modeling approaches, **Davies** and co-authors characterized the spread of the B.1.1.7 variant in the United Kingdom. The authors found that the variant is 43% to 90% more

transmissible than the predecessor lineage but saw no clear evidence for a change in disease severity, although enhanced transmission will lead to higher incidence and more hospital admissions. Large resurgences of the virus are likely to occur after the easing of control measures, and it may be necessary to greatly accelerate vaccine roll-out to control the epidemic.

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