Ramadan Fasting and Diabetes (2021): The Year in Review

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Abstract

Introduction The literature on the impact of Ramadan fasting (RF) on diabetes is widely spread in many journals. This makes it not readily accessible to those interested in the subject. We aimed to provide a narrative overview of the global literature production in 1 year (2021) on diabetes and RF.

Materials and Methods This was a narrative, nonsystematic review of the international literature from a single major medical online database (i.e., PubMed) during the year 2021. The search term “Ramadan fasting AND Diabetes” was used, and the relevant literature was narrated in a concise thematic account.

Results The publications spanned a vast array of topics related to diabetes and RF, including epidemiology, assessments of safety and efficacy profiles of older and newer diabetes therapies, hypoglycemia, diabetes education, use of advanced technology for the treatment, and monitoring and impact on pregnancy. Some reports covered the interaction of Ramadan and the novel coronavirus disease 2019 (COVID-19) in relationship to diabetes. Professional concerns, patients’ perspectives, and telemedicine’s role in RF were also addressed.

Conclusion The current narration presents this year’s literature on the safety of fasting practices, care models, and patients’ experiences and perspectives. Work should continue on comprehensive assessments for the interplay of diabetes and RF under different settings. Particular attention should focus on the roles of newer antidiabetic medicines and advanced technology for safer fasting practices.

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Introduction

Ramadan fasting (RF) is observed by adult Muslims worldwide. It entails abstinence from food, water, all oral substances, intravenous fluid therapy, and smoking between dawn and sunset during the ninth month of the Muslims’ lunar calendar. Ramadan’s impact on health and disease stems from the physiological effects of prolonged fasting during the daytime and possible overfeeding in the evening and its various social changes such as reduced working hours and reversal of circadian rhythm. The last three decades witnessed a rising interest in the research in health and disease. Diabetes has been the most extensively studied single medical condition connected to RF. Despite the increased literature volume, concern has been voiced regarding the quality of publications on the subject.

The literature on health aspects of RF is widely spread in many journals, making it not readily accessible to those interested in the subject. We, therefore, aimed to provide a thematic overview of the global research work conducted in the realm of RF during 2021 and on the impact of RF in people with diabetes. We aimed to provide a concise bird’s eye view of the literature published in a year and to identify the evidence base that may guide clinical practices for years to come.

Materials and Methods

This is a narrative, nonsystematic review of the literature retrieved from one online database over a full calendar year (2021). The PubMed search engine of the National Center for Biotechnology Information at the U.S. National Library of Medicine was used. The search term “Diabetes AND Ramadan” was used. Time filter from January 1, 2021, to December 31, 2021, was used to identify the relevant records. Retrieved articles were examined for relevance, reviewed, and narrated thematically.

The aim is to provide reasonably concise but adequately representative themes surrounding RF. One author drafted the initial manuscript. All other authors contributed to the intellectual content using a single version loaded online using Google Docs. Full-text research articles in English were included. No statistical analysis was conducted on the data included in the original articles, and detailed numerical presentations were avoided. All types of articles were included. The final product was refined through several multilateral rounds of discussion.

Highlights of the Literature

The emerging themes from the literature review are summarized in Table 1. They covered epidemiology, basic sciences, pharmacology, glycemic control, hypoglycemia, diabetic emergencies, maternal health, education, professional perspectives, and patients. The various publications are discussed below under these themes.

Epidemiology

Although religious guidance exempts some Muslims with type-2 diabetes mellitus (T2DM) from fasting during Ramadan, many choose to fast. The associated risks for fasting adults with diabetes include hypoglycemia, hyperglycemia, ketoacidosis, dehydration, and thrombosis. Thus, health care professionals must support individuals who choose to fast to minimize risks. Hassanin et al reviewed three epidemiologic studies to understand how fasting patterns during Ramadan and associated clinical outcomes in adults with T2DM have evolved over two decades (2000–2020). Over a while, people with diabetes choosing to fast during Ramadan display increasingly complex profiles in terms of their diabetes, with increased disease duration, greater body mass index (BMI), and elevated pre-Ramadan mean glycated hemoglobin (HbA1c) levels. Despite this, in the most recent study, >85% of adults with T2DM still chose to fast. Increased risk of hypoglycemia remains a major concern despite some improvements over time which could be attributable to enhanced education programs, changes in treatment type and/or dose prior to and/or during Ramadan. Over two decades, the authors highlighted the evolution in fasting patterns, an update for health care professionals to provide appropriate guidance to ensure that RF is safe and rewarding.

Pathophysiology

RF creates lifestyle changes, causing biochemical alterations that affect glucose metabolism and insulin sensitivity. Two studies examined some pathophysiological changes during Ramadan in people with diabetes. First, in an observational study, Hassanin et al examined the immediate effect of fasting on biometric and biochemical parameters in persons with diabetes before and after the fasting month. In addition, they examined the differences between these measures according to type and treatment of diabetes in those who observed the fast and those who did not fast during Ramadan. A total of 342 patients were recruited into the study. All were patients with diabetes considered to have a mild-to-

Table 1 Emerging themes from the review of the literature

| 1. Changing epidemiological pattern of fasting |
| 2. Pathophysiology of fasting during Ramadan in people with diabetes |
| 3. Nutritional aspects of fasting in people with diabetes |
| 4. Pharmacological management of diabetes during Ramadan: old and new |
| 5. Hypoglycemia: risk and ways of mitigation |
| 6. Diabetic and medical emergencies during Ramadan |
| 7. Use of technology for diabetes control: monitoring and insulin delivery |
| 8. Role of telemedicine during Ramadan |
| 9. Maternal and fetal outcomes in women with diabetes or gestational diabetes exposed to Ramadan fasting |
| 10. Professional aspects and patient advocacy |
| 11. Miscellaneous impacts on mental health |
| 12. Challenging aspects of Ramadan fasting and diabetic kidney disease |
moderate risk of complications if they fasted. Males represented 52.3%. Most results showed a U-shape pattern between pre-, during, and post-Ramadan periods. The significant but modest reduction in weight during Ramadan was regained after Ramadan. The authors suggested that for many people with diabetes, fasting is not associated with an increased risk to their glycemic control, weight, and/or blood pressure. Instead, a marginal benefit or no change in all parameters was seen. Second, Harbwono et al. assessed the impact of RF on glycemic control and fetuin-A, a glycoprotein that affects insulin resistance, in patients with T2DM in a prospective study among 37 patients. Anthropometric data and HbA1c, fasting blood glucose (FBG), and fetuin-A levels were measured in three-time points: before, during, and after RF. A bivariate analysis was done to see the effect of RF on those parameters. RF reduced fetuin-A levels 4 weeks and after RF. A bivariate analysis was done to see the effect of RF on those parameters. RF reduced fetuin-A levels 4 weeks after the end of Ramadan compared with pre-Ramadan. After 2 weeks of RF, the authors found a significant reduction in body weight, BMI, FBG, and HbA1c levels which rebounded to baseline level after Ramadan. RF was associated with a significant decrease in fetuin-A level post-Ramadan.

**Nutrition**

The impact of dietary modifications during Ramadan and its potential influence on glycemic control in diabetes were the subjects of two original articles and one review. First, Mohd Yusof et al. assessed dietary intake following structured Ramadan nutrition therapy and determined the association between changes in dietary intake and glycemic control parameters in patients with T2DM. This was done in an 8-week, parallel group, nonrandomized study of 60 T2DM patients who had structured Ramadan nutrition therapy (sRNT; \( n = 38 \)) or standard care (SC; \( n = 22 \)) group. The sRNT group received a diabetes-specific formula, and SC received standard nutrition care throughout the study. The 3-day food records assessed dietary intake at three time points. At baseline, dietary characteristics were comparable; both groups had macronutrient intakes within the recommended range but inadequate intakes of fiber and 11 essential micronutrients. After 8 weeks, the sRNT group significantly reduced intake of carbohydrates, dietary glycemic index (GI), glycomic load, and increased percentage of total energy intake from protein, fiber, pyridoxine, vitamin C, vitamin D, calcium, and chromium compared with the SC group. In the sRNT group, compliance to diabetes-specific formula predicted changes in HbA1c (\( p = 0.024 \)) while fiber intake predicted fasting plasma glucose (\( p = 0.035 \)) after adjusting for age, sex, weight changes, and other dietary variables. Intake of certain nutrients improved significantly in the sRNT group after Ramadan compared with the standard care. The structured Ramadan nutrition plan incorporated diabetes-specific formula that significantly improved glycemic control and dietary adequacy during RF. Second, the high consumption of dates during Ramadan raised questions about its GI and its effect on diabetes control. Therefore, Assaad Khalil et al. evaluated the GI of meals containing dates in 20 healthy patients and 20 age-, sex-, and weight-matched patients with T2DM and the effect of dates on the postprandial glucose excursions. Testing was applied on separate days (on three occasions) with 50 g of glucose and 50 g equivalent of available carbohydrates from nine date meals.

The GI was calculated as ratios of the incremental areas under the response curves for dates compared with glucose using continuous glucose monitoring. No significant difference between the mean GI of dates between the groups was found. However, there was a significant difference in the time of peak blood glucose among varieties of meals containing dates in T2DM. Finally, Mohd Yusof et al. examined the effects of Ramadan-focused nutrition therapy for people with diabetes. They reviewed articles that included nutrition components for adult patients with T2DM between 2010 and 2020. Fourteen studies met their criteria. Eight of 14 studies had an intervention with a control arm.

In comparison to the control group, all studies (\( n = 8 \)) showed a reduction in hypoglycemic events (HEs). However, only half of these studies (\( n = 4 \)) had shown at least one positive clinical outcome. Features of nutrition therapy that appeared to have favorable clinical outcomes include individualized caloric prescription, distributing carbohydrates equally between Suhoor, Iftar, and snacks; providing meal plans; adjusting food intake to suit Ramadan; and incorporating diabetes-specific formula as part of Suhoor or snack.

The review provided evidence for the effectiveness of Ramadan-focused nutrition therapy among people with T2DM and identified key features of nutrition therapy that may provide favorable clinical outcomes. Additional data on dietary quality and adequacy during RF warrants further studies.

**Pharmacological Treatment**

Four reports in 2021 addressed the antidiabetic pharmacological therapies during Ramadan. Two were related to the DIA-Ramadan study, and the other two were systematic reviews and metanalysis.

Raza et al. assessed the safety and effectiveness of gliclazide modified release (MR) of 60 mg in people with controlled or suboptimal-controlled T2DM. These data were extracted from the DIA-Ramadan, an international, observational study conducted in nine Asian and Middle Eastern countries. A total of 220 patients with T2DM were recruited from Pakistan. The primary endpoint was the proportion of patients reporting at least one symptomatic HE during RF. In contrast, secondary endpoints were changes in HbA1c percentage, fasting plasma glucose (FPG; mg/dL), body weight (kg), and proportion of patients reporting any HE (confirmed or severe) comparing pre- and post-Ramadan periods. During Ramadan, 3.6% of patients had experienced at least one symptomatic HE. A significant reduction was observed in the mean HbA1c (\( -0.4\% \)) and body weight (\( -0.7 \text{ kg} \)). Thirteen adverse events unrelated to gliclazide MR were reported during the study period. Also, Hassanine et al. reported another subgroup analysis from the same study (DIA-RAMADAN) by considering three geographically and culturally different regions. Data were captured at inclusion 6 to 8 weeks prior to Ramadan, during Ramadan (4.5 weeks), and 4 to 6 weeks after Ramadan. There were 564 from the...
Indian subcontinent), 354 from the Middle East, and 296 from South-East Asia. Patient baseline characteristics, demographics, fasting habits, and antidiabetic treatments varied between regions. There were similar proportions of symptomatic HE between regions. Significant weight reductions were observed in all regions following Ramadan, with HbA1c and fasting plasma glucose reductions. These subgroup analyses emphasized the safety and effectiveness profile of gliclazide MR 60 mg, the low risk of HEs, effective glycemic control, and body weight reduction in T2DM patients, intending to fast during Ramadan in a single country and all three regions.

Gad et al17,18 conducted two systematic reviews and meta-analyses. The first systematic review and meta-analysis evaluated the safety and efficacy of the newer glucose-lowering therapies on diabetic control, weight, blood pressure, and hypoglycemia in patients with T2DM during Ramadan.19 A total of 20 studies were included. Dipeptidyl peptidase-4 inhibitors (DPP-4i) resulted in a significant reduction in HbA1c and a nonsignificant decrease in weight during Ramadan. Glucagon-like peptide (GLP-1) agonists were associated with a significant decrease in HbA1c and a nonsignificant decrease in weight and systolic blood pressure after Ramadan. Sodium-glucose cotransporter 2 inhibitors (SGLT-2i) were associated with a significant decrease in HbA1c and a nonsignificant decrease in weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP) after Ramadan. The second meta-analysis of five studies focused on the effects of RF on patients with T2DM treated with SGLT-2i.20 During Ramadan, there was a significant reduction in HbA1c and DBP, with a nonsignificant trend for weight reduction and SBP. The number and severity of hypoglycemic episodes were lower in patients treated with SGLT-2i than sulfonylureas. There were no significant changes in the glomerular filtration rate, β-hydroxybutyrate, serum bicarbonate, or anion gap. However, they identified a considerable heterogeneity among studies and a lack of head-to-head studies with structured outcome reporting on the risks and benefits of SGLT-2i during Ramadan. These two systematic reviews and meta-analyses showed (1) clinical benefits with the newer glucose-lowering medications in patients with T2DM who fast during Ramadan and (2) an improvement in HbA1c, less hypoglycemia, and no major adverse effects in patients with T2DM treated with SGLT-2i during Ramadan.

**Hypoglycemia in Ramadan**

HEs are serious complications associated with diabetes management and increased cardiovascular disease risk. Conflicting results have been reported concerning hypoglycemia among people with T2DM observing RF. Three studies addressed different aspects of HEs. First, Tourkmani et al21 evaluated the impact of a Ramadan-focused diabetes education program on hypoglycemia risk and other clinical and metabolic parameters. Seventeen studies were included in this systematic review; five of them met the criteria to compile for a meta-analysis. The included studies had various designs, including randomized controlled trials and quasiexperimental and nonrandomized studies. Overall, the results revealed a significant reduction of hypoglycemia risk (81% reduction) for fasting patients in intervention groups who received Ramadan-focused education compared with patients receiving conventional care (odds ratio [OR] = 0.19). Moreover, HbA1c significantly improved among patients who received a Ramadan-focused diabetes education intervention compared with conventional care. No significant changes were documented in body weight, blood lipids, or blood pressure. Second, Zaghlol et al22 investigated the effect of dosage reduction of four hypoglycemic multidrug regimens on the incidence of acute glyemic complications in people with T2DM during Ramadan. They conducted an open-label, parallel-group, randomized controlled trial at a tertiary care center in Jordan and recruited adults with T2DM who expressed an intention to fast Ramadan and were adherent to one of four regimens, namely, (1) metformin and glimepiride; (2) metformin and vildagliptin; (3) metformin and insulin glargine U-100; or (4) metformin, insulin glargine U-100, and human regular insulin. They randomly assigned participants to low- or regular-dosage therapy. The primary outcome was the incidence of hypoglycemia and hyperglycemia during Ramadan. In contrast, the secondary outcome was the incidence of diabetic ketoacidosis and hyperosmolar hyperglycemic state during the same period. They randomly assigned 687 participants to low-dosage therapy (n = 458) or regular-dosage therapy (n = 229) and included 678 (452 and 226, respectively) in the final analysis. The incidence of hypoglycemia was lower in the low-dosage group than the regular-dosage group, with 23.0%, respectively (OR = 0.15). The incidence of hyperglycemia did not differ between the low- and regular-dosage groups, 70.6 versus 68.1%, respectively (OR = 1.12). No participants experienced diabetic ketoacidosis or hyperosmolar hyperglycemic state. Each 1% decrease in the baseline HbA1c concentration was associated with a 19.9-fold increase in the odds of hypoglycemia. Each 1% increase in the baseline HbA1c concentration was associated with a 15.7-fold increase in the odds of hyperglycemia. Third, Abdelrahim et al23 summarized available scientific evidence on the occurrence of HE and the effects of different moderators on the incidence of HE among patients with T2DM during Ramadan. They conducted a systematic review of available observational studies and randomized controlled trials (RCTs) for patients with T2DM who fasted Ramadan, with HE as the primary outcome. Ten databases were searched, and 68 studies were found (35 RCTs and 33 observational studies). Non-sulfonylurea hypoglycemic medications showed superior effects in lowering the incidence of HE over sulfonylureas. Variable moderators were associated with experiencing HE during Ramadan in observational studies and RCTs, including sex, geographical location, body anthropometric indicators, season, dietary behaviors, fasting duration, time since diagnosis, and prefasting education. The studies concluded that, first, Ramadan-focused diabetes education program mitigates the effects of Ramadan on hypoglycemia risk. Second, the authors concluded that dosage reduction decreases the
incidence of hypoglycemia without a concomitant increase in the incidence of hyperglycemia, diabetic ketoacidosis, and hyperosmolar hyperglycemic state in people with T2DM who fast during Ramadan. This comprehensive systematic review covered the largest number of observational and clinical studies investigating the impact of Ramadan on HE among patients with T2DM. Third the significance of different moderators that influence the effect of RF on hypoglycemia and underpin the superiority of non-sulfonylureas medications over sulfonylureas in lowering the risk for hypoglycemia in people with T2DM during RF.

Diabetic Emergencies
The potential impact of RF on the risk of diabetic emergencies was the subject of two different original studies of different designs and contrasting findings.24,25 First, AlZahrani et al26 examined the variation in visits at the emergency room (ER) during Ramadan compared with other lunar months at a tertiary care hospital in Jeddah city concerning diabetes emergencies. A retrospective study was conducted by electronic medical record review of patients aged 18 years and older with diabetes emergencies who visited the ER of a military hospital from the 9th to 11th lunar months during 2017 to 2018 for diabetes-related emergencies. Persons with diabetes who visited the ER and were 18 years old were included. The frequency of ER visits, sociodemographic characteristics, and clinical features were determined. Within the selected study period, a total of 24,498 episodes were recorded in ER. The prevalence of diabetes emergencies visits was only 0.84%. The study included 133 patients (54.1% men and 45.9% women). The majority (73.7%) were on insulin therapy, more than half of whom (51.9%) had T2DM. There was a significant difference by age group (p = 0.001) in the prevalence of diabetes emergency visits between the three lunar months Shaban, Ramadan, and Shawal of 7.5, 4%, respectively. However, the highest prevalence was not in Ramadan. Despite some correlations being identified, the study found no significant differences between the frequency of ER visits and various demographic, clinical factors, and diabetes profiles between Ramadan and other preceding and succeeding lunar months.

In contrast with previous studies, a downward prevalence trend was found, from Shaban to Ramadan to Shawal. This indicated that fasting during Ramadan does not negatively impact diabetic emergencies compared with other months. Hyperglycemia among T2DM and insulin-treated patients has recorded the highest feature of diabetes emergencies visits during the 3 months studied with no significant differences between the months. Also, Tong CV et al19 determined admissions for diabetes emergencies among patients who fasted or planned to fast 1 month before, during, and 1 month after Ramadan 2019 in public hospitals in Malaysia. They conducted a prospective cross-sectional study in 18 public hospitals in Malaysia from April 7, 2019, to July 2, 2019. All adult Muslim patients with a previous diagnosis of diabetes who were admitted for hypoglycemia, DKA, or Hyperglycemic Hyperosmolar State (HHS) were included if they had fasted and had intentions to fast, including a total of 295 admissions. The pre-Ramadan period recorded the highest number of admissions (119), followed by during (106) and post-Ramadan (70). Hyperglycemic emergencies accounted for two-thirds of total admissions. Thirty-seven admissions for hypoglycemia occurred during the pre-Ramadan period compared with 32.1% during Ramadan. Contributing factors included the use of sulphonylurea (59.6%), the presence of nephropathy (54.5%), and a history of hypoglycemia (45.5%). Admissions for DKA were more common than HHS (119 vs. 77) and highest during the Ramadan period (36.1%). Most of the admissions for hyperglycemic emergencies were T2DM (75.9% for DKA and 97.4% for HHS). Only 31.5% of patients admitted for diabetes emergencies recalled having received Ramadan advice in the past. The first study’s findings highlighted the need for T2DM and insulin-treated patients to be thoroughly assessed by the physicians. Appropriate in-depth health education and guidance should be given to them. However, the second study reassuringly concluded that admissions for diabetes emergencies were highest during the pre-Ramadan period followed by Ramadan and the post-Ramadan period suggesting that fasting during Ramadan does not increase admissions for diabetes emergencies.

Maternal Health
Three studies considered various aspects of the impact of RF and maternal health and pregnancy outcomes. First, Hassanein et al20 explored the safety of fasting in gestational diabetes mellitus (GDM) in Ramadan while understating the glycemic variability. Twenty-five patients with GDM who chose to fast were enrolled and provided optimum care that included Ramadan-focused education and Free-Style Libre Flash Continuous Glucose Monitoring (FSL-CGM). CGM was utilized for 2 to 4 weeks prior to Ramadan and compared with 2 to 3 weeks during Ramadan. The average glucose improved significantly, while time in target and percent above target numerically improved during Ramadan compared with pre-Ramadan. There was a significant increment in the number of HEs in Ramadan. The average lowest blood glucose reading reduced significantly by 14 mg/dL, with an average duration of HEs increasing significantly by 38.5 minutes. The study reinforces the importance of structured education before Ramadan to deliver optimal care for the management of diabetes. Strikingly FSL-CGM demonstrated that hypoglycemia is significantly increased during RF. There was an effective reflection of hyperglycemic spikes immediately post-Iftar. Second, in a prospective, case-controlled study, Hossain et al27 studied the perception and knowledge about the maternal effects of RF in 215 pregnant women with spontaneous conception and singleton pregnancies. Pregnant women who fasted for 7 or more days were considered cases (n = 123), and those who did not fast were considered controls (n = 92). Primary maternal outcomes included preterm delivery, pregnancy-induced hypertension, and GDM. Only 2.8% of women knew about exemption from fasting is during pregnancy. Sixty-five percent of women reported weakness as the main reason for not fasting. The rate of gestational diabetes, pregnancy-induced hypertension, and preterm delivery were numerically but not...
The most recent International Society of Pediatric and Adolescent Diabetes practice guidelines recommended its use in young people with diabetes; observing Ramadan ensures safe fasting. At a meeting, together with several regional diabetes experts, patient representatives, and international expert advisors to review the evidence for isCGM and propose guidelines for its use in the MENA region (Deeb et al). The authors strongly recommended using isCGM for patients in MENA and present general recommendations and compressive specific guidance for physicians and patients which they believe will also have wider resonance.

Role of Technology in Diabetes Management

Diabetes mellitus imposes a significant burden worldwide and in the Middle East and North Africa (MENA). Glucose monitoring is a cornerstone of diabetes management. Hba1c has always been the primary metric for assessing glycemic control, but its use is linked with multiple pitfalls. As an alternative, continuous glucose monitoring is becoming a standard of care in many countries. Intermittent scanning glucose monitoring (isCGM) has acquired worldwide popularity and has been proven to improve glycemic control, hypoglycemia detection and prevention, and quality of life. The most recent International Society of Pediatric and Adolescent Diabetes practice guidelines recommended its use in young people with diabetes; observing Ramadan ensures safe fasting. At a meeting, together with several regional diabetes experts, patient representatives, and international expert advisors to review the evidence for isCGM and propose guidelines for its use in the MENA region (Deeb et al). The authors strongly recommended using isCGM for patients in MENA and present general recommendations and compressive specific guidance for physicians and patients which they believe will also have wider resonance.

Patients with T2DM on multiple glucose-lowering therapies who fast during Ramadan are at increased risk of hypoglycemia. Elhadd et al assessed the utility of the flash glucose monitoring (FGM) system after adjusting the dose of insulin and sulphonylureas (sulfonylureas were used before; we need to decide which one to use) to mitigate the risk of hypoglycemia in patients with T2DM who fast during Ramadan. Patients with T2DM on either basal insulin or a sulphonylurea and at least two other glucose-lowering agents received structured education and adjustment of insulin or sulphonylurea dose according to the PROFAST Ramadan protocol. Glucose variability and episodes of hypoglycemia were assessed using the FGM system using (FreeStyle Libre) before and during Ramadan. A total of 33 patients with T2DM (on sulphonylurea [SU+]; n = 21), on basal insulin (BI+; n = 12) aged 50.8 years with a diabetes duration of 13.1 years were studied. The average sensor glucose was 154 mg/dL (8.5 mmol/L), with 65.2% in the target range before Ramadan, and the average sensor glucose was 156 ± 36 mg/dL (8.6 mmol/L) with 67.1% in the target range during Ramadan. The incidence of hypoglycemia in the whole group and the SU+ and BI+ groups and eHba1c, average glucose and time within range did not change in the SU+ and BI+ groups, respectively, before and during Ramadan. The authors concluded that structured education with adjusting the dose of glucose-lowering medications alongside the use of the FGM could effectively mitigate the increased risk of hypoglycemia in patients with T2DM on multiple glucose-lowering therapies who fast during Ramadan.

Saadane et al assessed the effect of RF on several glucose metrics using FGM. Complete FGM data for 29 to 30 days before, during, and after Ramadan were available for 40 patients, including 13 type-1 diabetes mellitus (T1DM) and 27 T2DM patients (on insulin with or without oral hypoglycemic agents). Indicators of mean glucose, glucose variability (GV), and time in different glycemic ranges were analyzed. RF was associated with an increase in time in hyperglycemia and a decrease in both the time in hypoglycemia and time in the target range. However, predictably, RF was associated with a significant reduction in GV during the daytime but not nighttime with an increase in the ensuing nonfasting period. In insulin-treated patients, RF is associated with an increase in time in hyperglycemia, a reduced time in the target range, and a nocturnal increase in GV, indicating a need for more refined management algorithms.

Fasting among people with T1DM imposes the risk of metabolic decompensation. Automated insulin dosing systems can allow better glycemic control without safety concerns. The utility of prolonged and repetitive fasting has not been studied. In an observational study, Aldibbiat et al reviewed and analyzed validated glycemic data from people with T1DM who observed fasting during Ramadan in 2019 and 2020 using automated insulin dosing systems. Six profiles met the inclusion criteria. The average age was 33.7 years, diabetes duration was 23.5 years, BMI was 23.6 kg/m², and HbA1c was 6.3%. During Ramadan, the average glucose was 7.0 mmol/L, coefficient of variation was 28.5%, percentage of time in the range of 3.9 to 10 mmol/L was 88.8%, and

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percentage time at <3.9 mmol/L was 2.5 ± 1.3%. The number of fasting days was 27.3, and the number of days where fasting was broken due to diabetes was one ± 1.5/participant. No significant differences in glycemic outcomes were noted between Ramadan and non-Ramadan periods. In this first clinically validated study, automated insulin dosing systems showed a safe and effective management strategy to support prolonged and consecutive fasting in people with T1DM.

Various studies have evaluated the safety and efficacy of insulin pumps during Ramadan. Some studies reported favorable outcomes in reducing hypoglycemia and hyperglycemia. However, there is no consensus on basal insulin adjustments and the utility of advanced technical features of insulin pumps. AlGhatam et al. investigated the effects of different insulin pump settings on time in range in patients with T1DM during Ramadan. Thirty patients deemed to have low-to-moderate risk from fasting were divided into either a control group (basal insulin adjustments only) or an intervention group (temporary basal rate and extended bolus features in addition to the basal insulin modifications). The percentage of time spent at different glucose ranges as measured by continuous glucose monitoring. The percentage of time spent within target increased significantly in the intervention group from 63 to 76%. The intervention group spent less time than controls in hyperglycemia (levels 1 and 2). There was no significant difference in the percentage of time in hypoglycemia. The authors concluded that incorporating technological approaches of pump therapy with clinical practice guidelines could improve glycemic control during Ramadan. Finally, Valenzano et al. reported a single patient’s experience suggesting that in well-instructed and strongly motivated patients observing RF, technology may significantly limit the risk of hypoglycemia while helping to achieve adequate glucose control, reduce insulin doses, and provide empowerment and satisfaction. It is conceivable that progress in diabetes treatment technologies will soon allow even more flexible and personalized therapeutic approaches, thus making RF more easily feasible for people with diabetes.

**Experiences with Telemedicine during Ramadan**

The lockdown period affected access to health care during the COVID-19 pandemic. To overcome this situation, telemedicine became available as an alternative to conventional follow-up for patients with diabetes during the fasting month of Ramadan. Three reports addressed this issue in different settings. First, Motaib et al. compared the effectiveness of telemedicine consultation of patients with diabetes during Ramadan with conventional follow-up. This comparative cross-sectional study in Morocco included 61 patients with diabetes followed-up by conventional consultation in 2019 Ramadan and by telemedicine in 2020 Ramadan. For each patient and in both Ramadan periods (2019 and 2020), they conducted a pre-Ramadan assessment, screening for acute diabetic complications during RF, and an evaluation of weight and HbA1c of patients after Ramadan. There was no significant difference in terms of hypoglycemia (18.0 vs. 32.8%), minor hyperglycemia (13.1 vs. 11.47%), and major hyperglycemia or ketoacidosis (3.3 vs. 6.6%) in Ramadan 2020 than in Ramadan 2019. Fasting was interrupted less often in 2020 than in 2019 (8.2 vs. 11.5%; p = 0.012) and there were no significant variations of weight (+0.62 vs. –0.77; p = 0.09). There was a significant difference in HbA1c levels between Ramadan 2020 and Ramadan 2019 (—0.36 vs. –0.61 in 2019, respectively, p < 0.05). Second, Zabeen et al. reported their telemedicine experience with T1DM patients using insulin pumps who fasted for Ramadan 2020 during the COVID-19 pandemic in Bangladesh. The routine diabetes outpatient care changed to telemedicine care. Nine patients who wished to fast for Ramadan contacted their diabetes team over the phone. The mean age was 19.3 years, and five were females. Most of the patients fasted >20 days. Hyperglycemia and mild hypoglycemia were common complications during fasting. There was no episode of severe hypoglycemia or diabetic ketoacidosis, and none of the patients required admission. Third, Al-Soﬁani et al. described a protocol of a diabetes telemedicine clinic that utilized a patient management flow algorithm and virtual educational sessions on diabetes and Ramadan in Saudi Arabia. (this study was as two studies in one; they had a management protocol and virtual educational sessions on Ramadan; we should only report the part of Ramadan). High satisfaction was reported by the 210 patients who attended the “Diabetes and Ramadan” virtual educational session, whereby 88% of them recommended continuing this activity as a virtual session every year. The three studies were discordant in their conclusions. In contrast, the first study from Morocco showed that telemedicine follow-up in patients with diabetes during Ramadan did not provide an effective glycemic control as conventional monitoring despite relative weight change and hypoglycemia results. On the contrary, the study from Bangladesh proposed that during the COVID-19 crisis, patients with T1DM using an insulin pump could fast safely during Ramadan with the support of the telemedicine service by the diabetes team. Also, the simplicity of the diabetes telemedicine clinic protocol from Saudi Arabia yet the high satisfaction reported by patients and healthcare provider (HCP)S made the authors suggest that it is a suitable model to be adopted by clinics, especially during pandemics or disasters in resource-limited settings. They emphasized that the clinic model could be quickly implemented since it does not require technological tools other than those widely available to most persons living with diabetes currently. They were able to reduce the number of patients, HCPs successfully, and staff physically present in the clinics during the COVID-19 pandemic without negatively impacting the patients’ nor the HCPs’ satisfaction with the visits which can be translated into other settings of staff and resource shortage.

**COVID-19 and Ramadan**

Data have shown that patients with T2DM are prone to severe disease with COVID-19 and 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. Zaina et al. stressed that health care providers must consider the impact that COVID-19 infection can have on patients with T2DM who intend to fast during Ramadan and other fasting days. Several studies in 2021 continued to address the interplay between diabetes and COVID-19. Elmajnoun et al. summarized the impacts of the COVID-19 pandemic on children and young adults with T2DM and identified the knowledge gaps in the literature. They also explored the potential of intermittent fasting in reversing the pathogenesis of diabetes and highlighted how this approach could prevent these patients from developing chronic complications. Having reviewed the currently limited evidence, it has been found that the incidence of COVID-19 among children with T2DM seems to be not much different from children without diabetes. However, these patients are still vulnerable to any infection. Several studies have reported that prevention programs, such as intermittent fasting, are adequate to protect these patients from developing complications.

Moreover, observing RF as a type of intermittent fasting could benefit some children with established diabetes, pre-diabetes, and people at risk with appropriate support. Children and young adults with T2DM are not at risk of severe COVID-19 infection compared to adults with diabetes. More work is needed to identify the impact of COVID-19 and assess the efficacy and safety of intermittent fasting, including RF, among these groups. Implementing cost-effective programs may have a significant impact in minimizing the incidence of diabetes. Moreover, this could be effective, particularly at the prediabetes stage, by preventing the development of T2DM and subsequent complications linked to disease and infection.

The DAR Global survey of RF during the COVID-19 pandemic aimed to describe the characteristics and care in participants with T2DM with a specific comparison between those <65 and ≥65 years according to Hassanein et al. Participants were consented to answer a physician-administered questionnaire following Ramadan 2020. The impact of COVID-19 on the decision of fasting, intentions to fast, and duration of Ramadan and Shawal fasting, hypoglycemic and hyperglycemic events were assessed. Specific analysis comparing <65 and ≥65 years were performed. Among the 5,865 participants, 22.5% were ≥65 years old. Concern for COVID-19 affected fasting decision for 7.6% (≥65 years group) versus 5.4% (<65 years group). More participants ≥65 years of age did not fast (28.8 vs. 12.7%, <65 years). Of the 83.6% participants fulfilling RF, 94.8% fasted ≥15 days, and 12.6% had to break the fast due to diabetes-related illness. The average number of days fasting within and post-Ramadan were 27 and 6 days, respectively, regardless of age. Hypoglycemia and hyperglycemia occurred in 15.7 and 16.3% of participants, respectively, with 6.5 and 7.4% requiring hospital care, respectively. Self monitoring of Blood Glucose (SMBG) was performed in 73.8% of participants and 43.5% received Ramadan-focused education. During the COVID-19 pandemic, universally high rates of RF were observed regardless of the fasting risk level. Glycemic complications frequently occurred with older adults requiring higher rates of acute hospital care. Risk stratification is essential, followed by pre-Ramadan interventions, Ramadan-focused diabetes education, and self-monitoring to reduce and prevent complications, emphasizing older adults. The DAR Global survey also determined the impact of the COVID-19 pandemic on the intentions to fast and the outcomes of fasting in <18 versus ≥18 years age groups with T1DM. Muslim people with T1DM were surveyed in 13 countries between June and August 2020, shortly after the end of Ramadan (April 23–May 23, 2020), using a simple questionnaire. Hassanein et al. 71.1% of Muslims with T1DM fasted during Ramadan. Concerns about COVID-19 were higher in individuals ≥18 years (p = 0.002). The number of participants who decided not to fast plus those who received Ramadan-focused education were significantly higher in the ≥18-year group (p < 0.05). Hypoglycemia (60.7%) and hyperglycemia (44.8%) were major complications of fasting during Ramadan in both groups, irrespective of age. They concluded that the COVID-19 pandemic had a minor impact on the decision to fast Ramadan in the T1DM cohort. This was higher in the age group of ≥18 years compared with those <18 years group. Only regional differences were noted for fasting attitude and behavior among T1DM groups. This survey highlights the need for Ramadan focused diabetes education to improve glucose control and prevent complications during fasting.

Based on historical information on other vaccines, growing concerns around the uptake of the COVID-19 vaccine during Ramadan are focused on whether the injection invalidates the fast, any possible side-effects, and whether people have to break the fast. The public and health care professionals needed to be made aware of the announcements by Muslim scholars advising that the COVID-19 vaccine is permissible during Ramadan without invalidating the fast (Ali et al.). A statement made in March 2021 from the president of Two Holy Mosques in Saudi Arabia should allay any religious concerns. Previous vaccination programs highlight the critical role that religious leaders play in promoting acceptability and education of their communities toward vaccination during Ramadan. The authors called for Imams to use Friday prayer sermons to promote the acceptance of vaccines, dispelling myths with worshippers. However, they highlighted that some people still do not wish to be vaccinated during fasting hours despite these efforts. They also proposed to extend vaccination times outside of fasts, such as during special Ramadan nightly prayers, Taraweeh. They used mosques as vaccination sites to allow vaccinations during Ramadan, including in nonfasting hours. Concerns about vaccine-related side-effects and required to break the fast should be addressed and weighed against the severe morbidity related to COVID-19.

**Miscellaneous Medical Problems**

Despite the positive effects of fasting on health, there are no guidelines or clear recommendations regarding fasting after metabolic/bariatric surgery (MBS). The current study reports the result of the modified Delphi consensus among expert MBS with experience in managing patients who fast after
MBS. A committee of 61 well-known MBS from 24 countries was created to participate in the Delphi consensus (Kermani-saravi et al.). The decision regarding fasting must be coordinated among the surgeon, the nutritionist, and the patient. At any time after MBS, 96.7% advised stopping fasting in the presence of persistent symptoms of intolerance. Seventy percent of the experts recommended delaying fasting after MBS for 6 to 12 months after combined and malabsorptive procedures according to the patient’s situation and surgeon’s experience, and 90.1% felt that proton pump inhibitors should be continued in patients who start fasting less than 6 months after MBS. There was a consensus that fasting may help weight loss, improvement/remission of nonalcoholic fatty liver disease, dyslipidemia, hypertension, and T2DM among 88.5, 90.2, 88.5, 85.2, and 85.2% of experts, respectively.

Anjum et al studied the effect of RF on renal function of people with diabetes in a prospective, observational, longitudinal study conducted at Baqai Institute of Diabetology and Endocrinology between April and July 2019. People with T2DM were recruited using convenient sampling. Demographic data along with renal function were recorded before Ramadan. Kidney functions were assessed in those who came for follow-up at 6 weeks, 3 months, and a year after Ramadan. A total of 70 people with diabetes participated in this study with a mean age of 53.11 years. A significant decline in estimated Glomerular filtration rate (eGFR) was noted around 6 weeks post-Ramadan, with a significant improvement of eGFR at 3-month follow-up. The normalization of kidney functions among the study participants was observed even after 1 year of Ramadan. In this study, post-Ramadan assessment of creatinine clearance showed a significant fall among fasting people with diabetes, though it remained within normal limits. Significant improvement and reversal of kidney functions were noted in those who followed within 3 months. Yousuf et al explored the association of RF with depression, anxiety, and stress symptoms in people with diabetes. An observational study was conducted at Baqai Institute of Diabetology and Endocrinology between May to July 2017 by using the DASS-21 scale to assess depression, anxiety, and stress pre and post-Ramadan. A total of 150 people with diabetes participated in this study. One hundred people were in the fasting group, and 50 were in the nonfasting group. In the fasting group, pre-Ramadan depression, anxiety, and stress symptoms were present in 45, 45, and 49% of people which significantly improved to 23, 26, 35 post-Ramadan ($p < 0.0001, < 0.0001$, and 0.001), respectively. In the nonfasting group, pre-Ramadan depression and anxiety symptoms were present in 34 and 50% of people which improved to 30 and 40% post-Ramadan ($p = 0.625$ and 0.227), respectively; however, this was not statistically significant improvement while no improvement was observed in stress symptoms. In conclusion, there was a significant improvement in depression, anxiety, and stress symptoms in diabetes post-RF.

**Professional Perspectives and Patients’ Advocacy**

Current knowledge and research on diabetes and Ramadan form the basis for evidence-based clinical practice. Therefore, gaps need to be identified and bridged. To this end, two studies addressed this issue using different approaches.44,45 Beshyah et al explored this issue using different approaches. The survey addressed three main domains, such as perceived current knowledge gaps and unmet needs in research on RF and diabetes, barriers to research, and future directions for furthering the evidence in this field. The majority of respondents (65.7%) were senior physicians in adult endocrinology/diabetes (45.9%) working at tertiary centers (65.2%). The majority (67.3%) reported seeing an average of 20+ patients with diabetes weekly and felt “very or fairly confident” in managing diabetes during RF (67.7%). The knowledge gaps identified were the management of high-risk patients with diabetes (54.1%) such as renal impairment (59.8%) and pregnancy (61.5%). The main barriers to research were lack of adequate funding to academic centers (75.7%) and lack of interest in institutions in the subject (64.6%). Future efforts should be directed at conducting extensive epidemiological studies (49.5%) or double-blinded, placebo-controlled clinical trials (48.6%) to address the former gaps. Research findings should be widely disseminated via hands-on workshops (recommended by 70.3% of respondents) or international conferences (61.2%). The second study, Bandarian et al analyzed RF research output during the past 5 years to identify research gaps in this field. After screening, 393 documents were identified and classified. Of these documents, 53 were review articles and 338 original articles. More than 96% of studies were clinical, while basic science studies were too limited. Among the study topics, DM was the most common topic (at 31%), followed by metabolic disorders and nutrition, respectively. These two studies concluded that (1) RF is an essentially religious issue that needs more attention, (2) there is a comprehensive agreement regarding the knowledge gaps in the management of diabetes during RF, (3) research should be directed toward clinical and basic studies in other health and disease conditions other than nutrition and metabolic disorders, and (4) future efforts should address these critical deficiencies.

Yilmaz et al examined the approaches of family physicians in Turkey toward the fasting of patients with diabetes and whether they used international treatment guidelines when making recommendations. In addition, the study also aimed to increase the awareness of family physicians about this issue before Ramadan. Before Ramadan 2018, a structured electronic questionnaire unique to the study was prepared based on the guidelines of the International Diabetes Federation (IDF) and the American Diabetes Association (ADA). The questionnaire was circulated through platforms where family physicians gathered via social media and mail groups and sent a secure link to family physicians in Turkey. Moreover, the total knowledge level, attitude, and approach scores were calculated from the questions prepared from the relevant guidelines. Participating in the survey were 262 family physicians. Only 22% of the family physicians stated that they were aware of the international guidelines for
Ramadan and diabetes management, and only 10% said that they had read them. The mean knowledge level, attitude, and approach scores were lower than expected, and a significant difference was found between the scores and academic titles. The lack of international guidelines on the subject and knowledge and experience about DM patient management during the month of fasting stood out as the most significant problem. This study revealed that the awareness and competence of family physicians in disease management should be increased and that of fasting before, during, and after Ramadan in patients with DM which has an increasing prevalence in Turkey.

Little research has been conducted on training students of different health professions to deliver culturally appropriate care to patients observing religious fasting. Amin et al.47 aimed to formulate an online educational module on caring for patients with diabetes, observing religious fasting, and evaluating the module’s impact. Third-year doctor of pharmacy students participated in an online module at the end of their core pharmacist-patient communication class. The module involved discussions and case scenarios addressing Muslim, Jewish, and Hindu patients with diabetes considering fasting. Students were provided with Ramadan Communication (AMCOM), a tool designed to facilitate the counseling of patients on religious fasting. They were encouraged to use principles of motivational interviewing in addressing cases. A 13-item questionnaire was administered before and after the module. Answers on an open-ended item addressing students’ experiences with the module were analyzed qualitatively using conventional content analysis. Of 140 students taking the class, all completed the module, and 135 completed both questionnaires. The module elicited a statistically significant improvement in confidence across all 13-survey items. The computed aggregate score increased from 2.65 (0.56) to 3.66 (0.50; p < 0.001), with 71% of students finding the module to be helpful or extremely useful. The qualitative analysis provided insight into students’ experiences, including how the module improved student confidence and opportunities for module improvement. A brief online module significantly improved pharmacy students’ confidence in working with patients from different cultures and religions considering religious fasting.

Inadequate preparation for RF can result in increased complications. Zainudin and Yeoh46 reviewed the current practice of Muslims with DM in Singapore who intend to fast during Ramadan, with particular attention on locally available evidence. Adequate preparation for RF, including pre-Ramadan assessment, optimization of glycemic control, structured Ramadan-focused diabetes education, medication adjustment, glucose monitoring, and test fasting, can lead to benefits in terms of improvements in metabolic control and reduced risk of fasting-related complications in people with DM. While there are ongoing efforts to reduce risk during this period, larger scale national programs are needed to avert complications and assess the long-term effects of RF in the local population.

An observational study in Bangladesh concluded that high HbA1c alone is not a reason not to fast during Ramadan in children, adolescents, and young adults with T1DM. Zabeen et al.49 investigated the ability, frequency of acute complications, and impact on glycemic control in uncontrolled T1DM who fasted during Ramadan. Also, 74 patients with T1DM who insisted on fasting were enrolled one month prior to Ramadan and given intensive education by the diabetes team on insulin dose, glucose monitoring, and dietary adjustments. Patients were divided into two groups: group A, HbA1c < 9% (<75 mmol/mol) and group B, HbA1c ≥ 9% (≥75 mmol/mol) and different variables were compared. Most patients fasted 58 (78.4%) for more than 15 days. There was no significant difference while comparing the breaking of the fast in the two groups. Although hypoglycemia was a common acute complication among them, there was no significant difference in the frequency of hypoglycemia between the two groups—a significantly increased insulin requirement in both groups during Ramadan, increasing basal insulin in those well controlled. There was also a significant reduction of post-Ramadan mean HbA1c in both groups. The study concluded that children, adolescents, and young adults with T1D with poor glycemic control could fast safely during Ramadan with proper education and intensive monitoring.

The IDF-DAR guidance was most recently updated in early 2021. The most notable change is the shift to a scoring system from a tabulated risk categorization to determine and classify the risk of harm from fasting derived from an online survey. This change may be appealing and is welcomed. However, such a system and the methodology underpinning it is not without limitations. A commentary by Ghouri et al.50 highlighted some of these limitations and the associated limited safe options available to individuals with diabetes desiring to fast during Ramadan. Overlooked clinical considerations that deserve formal recognition include the role of technology (aspects relating to glucose monitoring and/or insulin delivery) and previous experience of safe RF. Furthermore, the duration of fasting (which can almost double in temperate regions from winter to summer) needs greater emphasis. They also advocate separate scoring systems for people with T1DM and complex T2DM. The guidance acknowledges that fasting is an individual’s decision. However, the general message needs to be more person-centered and currently only presents a binary approach to fasting—all-or-nothing choices. They propose and discuss additional options, including trial fasting of voluntary fasts, starting the fast and terminating due to health and/or safety, intermittent fasting, and winter fasting.

Understanding the perceptions and how Muslims with chronic diseases manage their health issues during Ramadan, especially as a minority population, is very important. Alshehri et al.37 examined Muslims’ (1) perceptions of fasting exemptions, (2) medication usage behavior, (3) perceptions of relationships with health care providers, and (4) factors impacting health management during Ramadan. This qualitative study employed four focus groups (two women and two men). Adult Muslims (18 years or more) with chronic diseases were invited to participate. Participants were asked open-ended questions about their fasting ability, medication
usage behaviors, health care access, and collaboration with providers during Ramadan. Trained researchers conducted the focus groups interviews in both English and Arabic. Each focus group was recorded, and three investigators independently transcribed the data and extracted themes and categories. Coding terminology issues were resolved through discussion.

Twenty-five Muslims with chronic diseases (e.g., diabetes, hypertension, renal failure, and anemia) participated. The most prominent themes/subthemes were as follows: (1) fasting exemption (e.g., uncontrolled medical conditions), (2) no fasting exemption (e.g., controlled medical conditions), (3) nonoral medication use during Ramadan, (4) health care provider involvement during Ramadan, and (5) factors impacting health management during Ramadan. Muslim patients perceive fasting as an essential religious practice, so they self-modify their medication-taking behaviors. Educating health care providers about Muslim culture, especially their strong desire to fast, may lead to Muslims better managing their medications and viewing healthcare providers as knowledgeable health care providers. Nassar et al.12 evaluated the effects of structured education on safe fasting among patients with diabetes. They included patients with diabetes eligible for the Ramadan fast. The control group included 494 patients who received standard diabetes education, while the intervention group included 407 patients who attained structured diabetes education. The patients were required to register their responses in a written, structured questionnaire before and after Ramadan. In addition, patients were advised to keep a log of their hypoglycemic episodes. The study showed that structured diabetes education improved patients’ blood glucose levels/glycemic control and outcomes during their RF. The structured diabetes education helped reduce the incidence of HEs and hyperglycemic crises. It also increased the acceptance and frequency of blood sugar level measurements among patients during Ramadan. The authors proposed that the standard diabetes management plan include structured diabetes education measures to improve outcomes effectively. The providers should screen the patients with diabetes before Ramadan and educate them to improve their safe fasting practices.

Conclusion
RF continues to draw significant attention among health care providers globally. The volume of the literature on the interplay between RF and diabetes in 2021 was relatively lower than in the preceding couple of years.6–8 The themes were, however, essentially similar to the previous years. The gaps in research and limitations in knowledge were recognized. Despite cultural and geographical differences in fasting patterns, the overarching desire for all patients and the physicians looking after them is safety. This year’s work has focused on technology, the safety of antidiabetic medications, emergencies, COVID-19, and the role of technology in optimizing management and monitoring. Of course, religion is an aspect of life, and so is fasting for a person living with diabetes. While the arena of research and knowledge on fasting during Ramadan has grown significantly, possibly the data on the impact of education and advice from religious leaders of RF outcomes is an area that warrants further exploration.

Compliance with Ethical Principles
No ethical approval is required.

Data Availability
This review is based on fully published original work cited in the references list.

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