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RESEARCH ARTICLE

Optimizing Ramadan fasting: A randomised controlled trial for people with type 2 diabetes during Ramadan applying the principles of the ADA/EASD consensus

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Abstract

Background: Fasting during the holy month of Ramadan is one of the five pillars of Islam. Fasting is not meant to create excessive hardship on the Muslim individual according to religious tenets. It is important that health professionals are aware of potential risks associated with fasting during the month of Ramadan (mainly hypoglycemia and hyperglycemia).

Aims: To explore the impact of applying the principles of our 2020 recommendations for the management of type 2 diabetes (T2D) during the month of Ramadan.

Methods: A multinational randomized controlled trial (RCT) was conducted in five Muslim majority countries. Six hundred and sixty participants were deemed eligible for the study; however, 23% declined to participate later for various reasons. In total, 506 participants were enroled and were equally randomized to the intervention or the control group. At the end of the study, data from 231 participants in the intervention group and 221 participants from the control group were collected after 12.6% and 8.7% were, respectively, lost to follow-up. Participants were randomized to receive a Ramadan-focussed education with treatment for diabetes adjusted as per our 2020 recommendation update compared with the local usual care (control group). Results are presented using mean, standard deviation, odds ratio (OR), and percentages.

Results: At the end of the study, the number of hypoglycemic episodes in the intervention group was less than in participants who received usual care. The intervention group had significantly lower severe hypoglycemia compared to the control group with an OR of 0.2 [0.1–0.8]. Compared to baseline, both groups had a significant reduction in glycated haemoglobin (HbA1c), but the improvements were significantly greater in the intervention group. Whilst body weight reduced and high-density lipoprotein cholesterol increased with the intervention, these changes were not significantly different from usual care.

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published.

Conclusions: A pre-Ramadan assessment of people with T2D coupled with pre-Ramadan education and an adjustment of glucose-lowering treatment as per our updated 2020 recommendations can prevent acute complications and allow a safer fast for people with T2D. We have shown that such an approach reduces the risk of developing severe hypoglycemia and improves the metabolic outcomes in people with T2D.

KEYWORDS
diabetes mellitus, education, hypoglycemia, insulin, oral hypoglycemic drug, Ramadan fasting

1 | INTRODUCTION

Fasting during the holy month of Ramadan is one of the five pillars of Islam. Fasting is not meant to create excessive hardship on the Muslim individual according to religious tenets; therefore, Muslims who are pregnant or have an illness are exempted from fasting according to the Quran (the Muslim holy book). Nevertheless, many Muslims with diabetes insist on fasting during Ramadan, thereby creating a medical challenge for themselves and their health care providers (HCPs). It is important that health care professionals are aware of potential risks associated with fasting during the month of Ramadan (mainly hypoglycemia and hyperglycemia). These are global health challenges not only in Muslim majority counties where Islamic religion is foremost, but also in other parts of the world including Europe and America where Muslims live as a minority.

In September 2005, Diabetes Care published a working group report suggesting recommended best practice for the management of diabetes during Ramadan.[1] This report is updated every 5 years. Based on the recommendations, all people with diabetes who wish to fast during Ramadan should receive a full clinical assessment and Ramadan-focussed education prior to the start of Ramadan in order to achieve safe fasting. According to these reports, people with type 1 diabetes (T1D) and pregnant women with diabetes should be strongly discouraged from fasting because of the high risk of developing serious and potentially life threatening acute metabolic complications. In the 2020 recommendation update,[2] the working group report aimed at implementing the updated 2018 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus report[3] into the statement for the management of type 2 diabetes (T2D) during the month of Ramadan.

The 2020 recommendations were well received by the medical community and people with T2D worldwide, but there were requests to provide evidence to prove that the recommendations proposed in the 2020 update can be applied in practice to ensure safe and effective fasting. Thus, the present study was conducted to examine the usefulness of these recommendations in achieving a safer fasting for people with T2D during Ramadan. In addition to the implementation of safe therapeutic interventions, an individualised education programme can address issues including meal planning, exercise, medical assessment, blood glucose monitoring, and recognising and managing acute metabolic complications before and during the month of Ramadan. The aim was to apply a physician-recommended T2D treatment regimen that is associated with a low risk of hypoglycemia, effective in reducing hypoglycemia, and weight neutral or facilitating weight loss.

2 | MATERIAL AND METHODS

2.1 | Study design

A multinational randomized controlled trial (RCT) was conducted in five Muslim countries. Participants with T2D were recruited from diabetes clinics in Jordan, Pakistan, India, Morocco, and Algeria. They were randomized to receive Ramadan-focussed education with treatment for diabetes adjusted as per our 2020 recommendations update compared with the local usual care. Education was delivered individually with the option of conducting group patient education classes if desired and if the situation permitted as well as using the tele-medicine technology when it was applicable. The collaborating centres in the participating countries identify at least two clinics per country.

2.2 | Study population

Clinics had to screen charts for patients with T2D aged between 20 and 79 years, not pregnant, and with no history of any chronic illness with contraindications to fasting (i.e., end stage renal disease, liver disease, recent myocardial infarction, etc.). Potential candidates were contacted to confirm their eligibility and to check if they were willing to participate in the study. Participants were included (i) if they were able to consent to participate, (ii) if they were planning to fast during the month of Ramadan 2021, (iii) were willing to attend an education programme if assigned to the intervention group, (iv) willing to attend face-to-face or virtual meetings with the study coordinator according to the country/institute situation and regulation in the 2 months before and after Ramadan to answer questionnaires, undergo physical assessments, and provide blood samples, (v) willing to perform at least 2–4 times daily blood glucose monitoring and to log the values

during the month of Ramadan 2021, and (vi) willing to receive the therapeutic intervention at least 3 weeks before the start of Ramadan. The enroled participants were assessed twice: once within 2 months before the start of Ramadan for the pre-Ramadan assessment, blood draw, and survey interview, and then participants were either randomized to the individualised patient education group or usual care group (control group) and assessed again within 2 months after the end of Ramadan for the post-Ramadan assessment, repeat blood draw, and survey interview.

2.3 | Study intervention

Participants assigned to the intervention group were subjected to an individualised patient education session and a possible treatment adjustment based on our 2020 recommendations prior to Ramadan fasting. Newer drugs with potential cardiometabolic benefits were encouraged to be used as per the ADA/EASD consensus report to optimise management in the intervention group.

The collaborating centres had given the 2020 Ramadan recommendations and were responsible for training the staff of the intervention group on how to deliver the objectives of the patient education programme directly to their participants with T2D. The patient education programme was a 2-h education session that addressed issues involving pre-Ramadan medical assessment, meal planning, physical activity, blood glucose monitoring, and recognising and managing acute metabolic complications before and during Ramadan. It was held before Ramadan between 15 February and 12 April 2021 and delivered by a culturally sensitive dietician, diabetes specialist nurse, or community health worker. During the pre-Ramadan assessment, when needed, physicians adjusted the treatment regimen as per the 2020 recommendations to prevent both hypoglycemia and hyperglycemia episodes.

In the usual care group, physicians received an English, Urdu, or Arabic copy of the 2020 recommendation for the management of diabetes while fasting during Ramadan and patients received usual care. All participants provided signed informed consent. The assessments were conducted according to the local ethical policies of the respective countries/regions and procedures approved by the Institutional Review Boards.

2.4 | Data collection and study outcome

Data were collected at the clinic, cleaned, and submitted to the respective countries collaborating centres. The collaborating centres grouped, anonymised and sent the data to the primary data management and analysis centre. Study participants were identified by a unique study code.

Information on participants was collected from the pre- and post-Ramadan survey interviews, laboratory test results and clinical assessments. Patients were asked to measure and log their blood glucose levels and to indicate any symptoms or signs of hypoglycemia. It was recommended that they monitored their glycaemia at least 2–4 times per day during Ramadan using capillary blood samples. Use of glucose-lowering therapies was documented at baseline and follow-up.

The primary study outcome was the reduction in the frequency of hypoglycemic episodes and elimination of severe hypoglycemia compared to the control group. Hypoglycemia was defined as self-monitored blood glucose <70 mg/dl (3.9 mol/l) with or without self-reporting symptoms of hunger, palpitations, anxiety, tremors, sweating, and headache, or a hypoglycemic episode requiring medical assistance (level 3 hypoglycemia or severe hypoglycemia).

The main secondary outcomes were the percentage achieving the following composite outcome:

The combination of lack of severe hypoglycemia or reduction in hypoglycemic event and sustained or improved HbA1c, weight maintenance or reduction as well as changes in blood pressure and lipid profile.

Weight maintenance is defined as $\pm$0.9 kg changes, weight gain/reduction $\pm\geq$1 kg, HbA1c maintenance $\pm$0.29% (3.2 mmol/mol), and HbA1c improvement/deterioration: $\pm\geq$0.3% (3.3 mmol/mol). The primary and secondary outcomes between the intervention and control groups were compared.

2.5 | Sample size

The sample size was estimated for the primary outcome in a two independent sample study (intervention and control group). Two hundred participants were needed in each group to have a power of 80% and 20% allowed for dropout (p value < 0.05). However, based on the previous study carried out in 2015.[4] Seventeen percent of the recruited patients might fail to comply with the study requirements. Thus, taking into account the possible withdrawal, at least 250 participants were required in each of the two groups.

2.6 | Statistical analysis

Baseline sociodemographic and clinical variables for each group and for the study sample were summarised using median (interquartile range [IQR]) for continuous variables and counts (percentages) for categorical variables. For each type of hypoglycemia, the total number of events, the median number of events per participant, and the number of participants with one or more events were calculated in both groups. Odds ratios (OR) were also calculated to compare the odds of a participant reporting one or more of each type of hypoglycemic event in the intervention group compared to the control group.

The composite outcomes were analysed using logistic regression, with the dependent variable defined as the number of participants achieving all end point targets for the composite outcome in question. Linear regression was used to analyse the clinical outcomes, adjusting for the baseline value of the relevant outcome. Glucose-

lowering drug use was compared at baseline and follow-up. Supplementary models for the composite and clinical outcomes were run adjusting for study site and potential prognostic factors (age, sex, insulin use) in addition to the baseline value of the relevant outcome for the clinical variables. A further supplementary analysis was conducted to investigate the number of hypoglycemic episodes and composite outcomes only including participants who reported their blood glucose at least three times a day. The bootstrap method was used to generate confidence intervals for all models (500 replications).

All analysis was conducted in Stata v17.0, and statistical significance was set at probability (p) < 0.05.

3 | RESULTS

Out of potential participants, 660 patients were deemed eligible for the study; however, 23% later declined to participate for various reasons (Figure 1). In total, 506 patients were enroled and were equally randomized to the intervention or the usual care group. At the end of the study, data from 231 patients in the intervention group and 221 patients in the control group were collected after 12.6% and 8.7% were lost to follow up in the two groups, respectively.

The baseline epidemiological, socioeconomic, and clinical characteristics of participants in both groups were homogeneous (Table 1).

Over half of the participants were recruited from Jordan. Men and women were equally distributed. The median age of the intervention group and the control group was 56 years (range 49–62) and 54 years (48–60), respectively. Patients from both groups had similar socio-economic status. At least 70% finished high school and more than half were unemployed. In the baseline clinical assessment, most patients had a confirmed T2D with a median duration of 7 years (4–12) years. The median value of glycated haemoglobin (HbA1c) was 7.3% (6.5–8.2) [56.3 (47.5–66.1) mmol/mol] and 7.5% (6.7–8.6) [58.5 (49.7–70.5) mmol/mol] in the intervention and control groups, respectively. Baseline characteristics of participants included in the analysis of the primary outcome (severe hypoglycemic events) by the treatment group are shown in (Supplnemetary Table 1).

Almost all patients in this study were on glucose-lowering medication; 83.6% took metformin, 46.8% dipeptidyl peptidase 4 inhibitors (DPP4-I), 40% sulphonylureas, 20.8% were prescribed insulin injections, 17.8% took sodium-glucose cotransporter-2 inhibitors (SGLT2-I), 2.4% glucagon-like peptide-1 receptor agonists (GLP-1RA), and 19.6% had a combined oral and subcutaneous regimen (Figure 2).

Most of the participants were overweight or obese with a median body mass index (BMI) of 29.6 kg/m^2 (26.6–33.2). The median systolic blood pressure (SBP) was 130 mmHg (120–141) and diastolic BP (DBP) was 80 mmHg (71–85). The median total serum cholesterol was 161 mg/dl (134–194) [4.2 (3.5–5.0) mmol/l] and a median of serum triglycerides (TG) was 148 mg/dl (113–200) [1.7 (1.3–2.3) mmol/l].

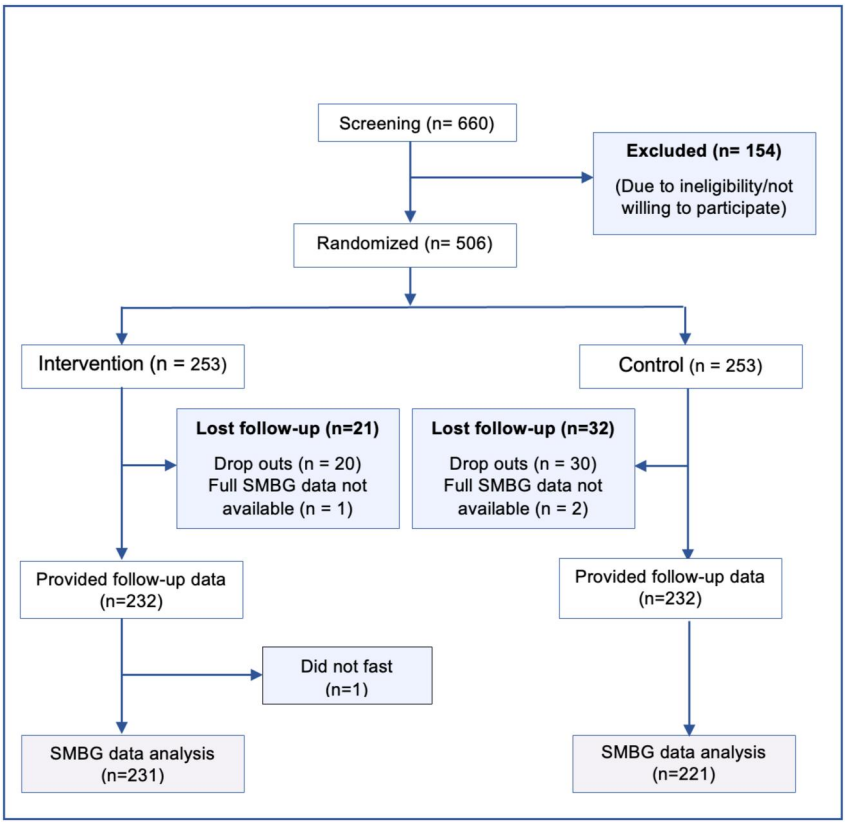

FIGURE 1 CONSORT diagram of participants throughout the study.

TABLE 1 Baseline characteristics of participants by the treatment group

	Intervention (n = 253)	Control (n = 253)	Total (n = 506)
Study site, *n* (%)			
Algeria	10 (4.0)	10 (4.0)	20 (4.0)
India	18 (7.1)	18 (7.1)	36 (7.1)
Jordan	136 (53.8)	122 (48.2)	258 (51.0)
Morocco	19 (7.5)	17 (6.7)	36 (7.1)
Pakistan 1	15 (5.9)	30 (11.9)	45 (8.9)
Pakistan 2	55 (21.7)	56 (22.1)	111 (21.9)
Sociodemographic variables			
Sex, *n* (%)			
Male	131 (51.8)	117 (46.2)	248 (49.0)
Female	119 (47.0)	135 (53.4)	254 (50.2)
Missing	3 (1.2)	1 (0.4)	4 (0.8)
Age, years	56 (49–62)	54 (48–60)	55 (48–61)
Education, *n* (%)			
Illiterate	19 (7.5)	22 (8.7)	41 (8.1)
Less than high school	54 (21.4)	59 (23.3)	113 (22.3)
High school graduate	77 (30.4)	68 (26.9)	145 (28.7)
Associate degree	15 (5.9)	14 (5.5)	29 (5.7)
College degree	56 (22.1)	58 (22.9)	114 (22.5)
Master's degree	24 (9.5)	25 (9.9)	49 (9.7)
Professional degree	7 (2.8)	5 (2.0)	12 (2.4)
Missing	1 (0.4)	2 (0.8)	3 (0.6)
Occupation, *n* (%)			
Office job	73 (28.9)	70 (27.6)	143 (28.3)
Physically active job	39 (15.4)	26 (10.3)	65 (12.8)
Not employed	137 (54.1)	154 (60.9)	291 (57.5)
Missing	4 (1.6)	3 (1.2)	7 (1.4)
Clinical variables			
Diabetes duration, years	7 (3–12)	7 (4–13)	7 (4–12)
Diabetes type, *n* (%)			
Type 2 DM	219 (86.5)	220 (87.0)	439 (86.8)
Not known	5 (2.0)	2 (0.8)	7 (1.4)
Missing	29 (11.5)	31 (12.2)	60 (11.8)
Clinical parameters, median (IQR)			
Weight, kg	80 (70–91)	81 (70.2–90.2)	80 (70–90.7)
BMI, kg/m^2	29.4 (26.5–32.5)	29.7 (26.8–33.7)	29.6 (26.6–33.2)
HbA1c, % [mmol/mol]	7.3 (6.5–8.2) [56.3 (47.5–66.1)]	7.5 (6.7–8.6) [58.5 (49.7–70.5)]	7.4 (6.6–8.4) [57.4 (48.6–68.3)]
Systolic blood pressure, mmHg	130 (120–143)	132 (121–140)	130 (120–141)
Diastolic blood pressure, mmHg	79 (71–85)	80 (71–84)	80 (71–85)
Total cholesterol, mg/dl [mmol/l]	160 (132–194) [4.1 (3.4–5.0)]	163 (134–192) [4.2 (3.5–4.9)]	161 (134–193) [4.2 (3.5–5.0)]

(Continues)

TABLE 1 (Continued)

Clinical variables			
LDL cholesterol, mg/dl [mmol/l]	91 (76–119) [2.4 (2.0–3.1)]	96 (71–119) [2.5 (1.8–3.1)]	92.5 (74–119) [2.4 (1.9–3.1)]
HDL cholesterol, mg/dl [mmol/l]	40 (35–47) [1.0 (0.9–1.2)]	42 (35–48) [1.1 (0.9–1.2)]	41 (35–48) [1.1 (0.9–1.2)]
Triglycerides, mg/dl [mmol/l]	142.5 (108.5–196.5) [1.6 (1.2–2.2)]	151 (119.5–203.5) [1.7 (1.3–2.3)]	148 (114–200) [1.7 (1.3–2.3)]
Use of drugs, *n* (%)			
Any glucose-lowering drug	250 (99.6)	247 (100.0)	497 (99.8)
Any oral glucose-lowering drug	239 (94.8)	240 (97.6)	479 (96.2)
Metformin	210 (83.3)	208 (83.9)	418 (83.6)
Sulphonylurea	99 (39.3)	101 (40.7)	200 (40.0)
DPP-4 inhibitor	120 (47.6)	114 (46.0)	234 (46.8)
SGLT2 inhibitor	33 (15.8)	39 (19.9)	72 (17.8)
TZD/AGI[a]	61 (24.2)	76 (30.7)	137 (27.4)
Insulin	53 (21.0)	51 (20.6)	104 (20.8)
(GLP-1RA) non-insulin injectable	7 (2.8)	5 (2.0)	12 (2.4)

Abbreviations: AGI, alpha glucosidase inhibitors; BMI, kg/m^2, body mass index, kilogramme per square metre; DPP-4, *dipeptidyl peptidase 4*; GLP-1RA, glucagon like peptide-1 receptor; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; kg, kilogramme; LDL, low-density lipoprotein; mg/dl, milligrammes per decilitre; mmHg, millimetre of Mercury; mmol/l, millimole/litre; SGLT2, Sodium-glucose cotransporter-2; type 2 DM, type 2 diabetes; TZD, Thiazolidinedione.

[a]In light of the small number of participants enroled in the alpha glucosidase inhibitor study group (representing only 5 participants, accounting for 1% of the total study population), this study group was combined with the thiazolidinedione group. These two drug classes have been deemed to have an acceptably similar risk of hypoglycemia, and should not interfere with the outcomes.

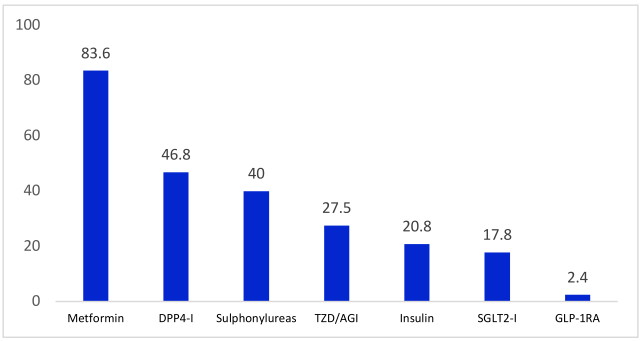

FIGURE 2 Total use of glucose-lowering agents (percentage).

During the study, the number of hypoglycemic episodes in participants in the intervention group was less than in those who received the usual care. The intervention protected participants from episodes of severe hypoglycemia significantly compared with the control group with an OR of 0.2 (95% CI 0.1–0.8). However, it had no significant effect on the risk of having a hypoglycemia below level 3 or requiring hospitalisation with OR 0.7 (95% CI 0.4–1.2) (Table 2; Figure 3).

The frequency of glucose measurement did not modify the outcome of hypoglycemic episodes (Sumppleentary Material). At the end of the trial, the odds of participants in the intervention group reaching the composite endpoints of no hypo/no weight gain or no severe hypo/no weight gain were 1.7–2 times higher than the usual care group. However, the intervention effect was not significant for the main secondary composite outcome (Table 3). Results were unaffected when adjusting for age, sex, insulin use and study site (Suppleamentry Tables 2a and 2b).

The mean change from baseline in the clinical and biological parameters was calculated to assess the effects between the usual care and the intervention group (Table 4). A significant improvement in HbA1c was observed within each group with a decrease of 0.5% (95% CI −0.6 to −0.3) [−5.3 mmol/mol (95% CI −6.8 to −3.7)] in the intervention group and 0.4% (95% CI −0.5 to −0.2) [−3.8 mmol/mol (95% CI −5.9 to −1.9)] in the usual care group; the difference between groups was statistically significant −0.2% (95% CI −0.4 to 0.0) [−2.3 mmol/mol (95% CI −4.5 to −0.1)].

Comparing the two groups, the intervention had no significant effect on any other clinical outcome. By the end of Ramadan, participants from both groups had significantly lost weight with a mean drop of 1.0 kg (95% CI −1.4 to −0.6) in the intervention group and 0.7 kg (95% CI −1.0 to −0.3) in the usual care group. Also, in the intervention group, patients had a significant increase in their high-density lipoprotein (HDL)-cholesterol with a mean increase of 3.0 mg/dl (95% CI 0.0–5.9) [0.1 mmol/l (95% CI 0.0–0.2)].

The number of hypoglycemic episodes observed among the participants who reported blood glucose measurement at least three times a day was lower in the intervention group than in the usual care group, 1 versus 11 episodes, respectively, OR 0.14 (0.04–0.57) (Supplementary Table 3). The intervention effect on composite outcomes observed among such participants was in favour of the intervention group (SupplementaryTable 4).

TABLE 2 Number of hypoglycemic episodes by the treatment group

	Intervention group (n = 231)	Control group (n = 221)	Total (n = 452)
Number of severe HEs[a]	1	11	12
Number of participants with one or more severe hypo[a] (%)	1 (0.4)	5 (2.3)	6 (1.3)
Severe hypo[a]—odds ratio (95% CI)	0.2 (0.1–0.8)* (p = 0.02)	1.0	NA
Number of hypos[b]	85	167	252
Number of participants with one or more hypo[b] (%)	32 (13.9)	41 (18.6)	73 (16.1)
Hypo[b]—odds ratio (95% CI)	0.7 (0.4–1.2) (p = 0.18)	1.0	NA

[a]Severe hypoglycemic episode defined as level 3 or requiring hospitalisation.
[b]Hypoglycemic episode defined as self-monitored blood glucose <70 mg/dl with/without symptoms.
**p < 0.01, *p < 0.05.

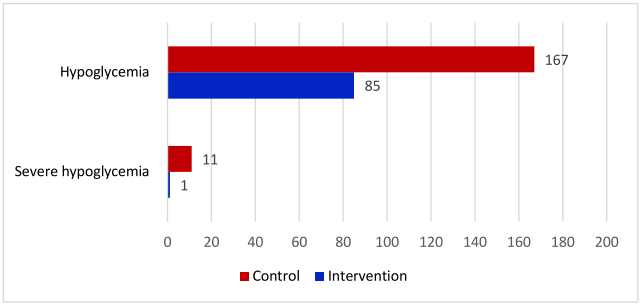

FIGURE 3 Number of hypoglycemic episodes (HE) by the treatment group.

As per recommendations some glucose-lowering drugs were stopped before Ramadan, replaced during fasting and/or modified. Almost all participants who were on metformin, DPP4-inhibitors, or insulin maintained their treatment regimen. However, the sulfonylurea treatment was reduced by 10% in the intervention group (from 39.2% at baseline to 29.7% at follow up) versus 3.2% in the control group (from 42.2% at baseline to 38.8% at follow up). Also, the use of alpha-glucosidase inhibitors (AGI) and thiazolidinediones (TZD) dropped in both groups during Ramadan. The prescription of SGLT-2I in both groups almost tripled with a 23% increase in the intervention group and 27% increase in the control group. The distribution of glucose-lowering drug uses in both groups at baseline and follow up is shown in (Table 5; Figures 4 and 5).

4 | DISCUSSION

During Ramadan, people fast intermittently with changes in their meal schedule and sleep patterns and no intake of food, water, or fluid during the day and eating is shifted to the nighttime. This eating pattern in people with diabetes carries a high risk of acute complications such as hypoglycemia, hyperglycemia, dehydration and diabetic ketoacidosis.[5–8] In this RCT, the effect of pre-Ramadan education coupled with a treatment adjustment in agreement with the updated ADA/EASD Ramadan-focussed consensus was evaluated. By the end of fasting, participants in the intervention group experienced a significantly reduced risk of developing severe episodes of hypoglycemia. Also, pre-Ramadan counselling resulted in more participants achieving the composite outcome of weight loss and no hypoglycemic event and also improved glycaemic control in the intervention arm versus usual care.

The recruited participants mostly had no contra-indications to fasting, which partly explained the low incidence of severe hypoglycemia during Ramadan (2%). In this study, the intervention that provided a significant risk mitigation for severe hypoglycemia and improved the composite outcome consisted of two complementary elements: treatment adjustment and patient education. Glucose-lowering drugs may also contribute to the occurrence of hypoglycemia. A recent review has summarised the potential benefits and problems of glucose-lowering agents during Ramadan.[9] Such drugs can induce hypoglycemia during Ramadan also in people who have received Ramadan-focussed education.[10] The CREED study in 3250 patients showed that during Ramadan 5.3% and 16.8% of patients experience hypoglycemia with oral glucose-lowering drugs and insulin use, respectively.[11] The 2020 recommendation states that during Ramadan metformin is safe; however, sulfonylureas, especially the older generation, could be associated with the risk of hypoglycemic events and therefore such drugs may be preferably withheld or the dose to be adjusted.[2] Other glucose-lowering therapies, such as SGLT-2 inhibitors, DPP4-inhibitors, GLP1-RA, AGI, and TZD, are associated with a low risk of hypoglycemia and can be continued. It also advised that SGLT-2 inhibitors should not be introduced within 4 weeks of the start of fasting and that attention should be paid to any signs of dehydration. In this study, health personnel in both groups had access to the 2020 diabetes management recommendations and their application during Ramadan.

Throughout fasting, participants were taking at least one glucose-lowering drug, but in several patients, the treatment regimen was modified. Participants were switched from sulfonylureas to safer agents like SGLT2 inhibitors or DPP4 inhibitors as deemed appropriate. At the end of the study, the percentage of participants continuing sulfonylurea was higher in the usual care group (38.8%) than in the intervention group (29.7%), which may explain the higher incidence of hypoglycemic events in the usual care group. In a systematic review of randomized clinical trials and observational studies

TABLE 3 Intervention effect on different outcomes

	Participants achieving outcome, *n* (%)		Intervention effect[c]		
	Intervention group	Control group	OR (95% CI)	*p*	*N*
No severe hypo[a], sustained HbA1c of ≤7.0% or reduction in HbA1c, and weight maintenance/reduction	126 (66.3)	97 (58.4)	1.4 (0.9–2.2)	0.13	356
No severe hypo[a], reduction in HbA1c	105 (54.8)	79 (46.5)	1.4 (0.9–2.2)	0.12	362
No severe hypo[a], reduction in weight	119 (51.5)	75 (33.9)	2.1 (1.4–3.1)**	0.0002 (<0.01)	452
No hypo[b], reduction in HbA1c	89 (46.4)	69 (40.6)	1.3 (0.8–2.0)	0.23	362
No hypo[b], reduction in weight	100 (43.3)	68 (30.8)	1.7 (1.2–2.5)**	0.0061 (<0.01)	452
Reduction in HbA1c, reduction in weight	58 (30.1)	39 (22.7)	1.5 (0.9–2.3)	0.09	365

[a]Severe hypoglycemic episode defined as level 3 or requiring hospitalisation.

[b]Hypoglycemic episode defined as self-monitored blood glucose <70 mg/dl with/without symptoms.

[c]Difference between treatment groups.

*$p < 0.05$, **$p < 0.01$.

TABLE 4 Intervention effect on changes in clinical outcomes

	Mean change from baseline				Intervention effect[a]		
	Intervention group		Control group				
	Coefficient (95% CI)	*N*	Coefficient (95% CI)	*N*	Coefficient (95% CI)	*p*	*N*
HbA1c, % [mmol/mol]	−0.5 (−0.6 to −0.3)** [−5.3 (−6.8 to −3.7)]	193	−0.4 (−0.5 to −0.2)** [−3.8 (−5.9 to −1.9)]	172	−0.2 (−0.4 to 0.0)* [-2.3 (−4.5 to - 0.1)]	0.05	365
Weight, kg	−1.0 (−1.4 to −0.6)**	230	−0.7 (−1.0 to −0.3)**	213	−0.3 (−0.8 to 0.2)	0.24	443
Systolic blood pressure, mmHg	−1.6 (−3.4 to 0.2)	208	−2.9 (−4.7 to −1.1)**	193	1.0 (−1.1 to 3.2)	0.35	401
Diastolic blood pressure, mmHg	0.3 (−1.2 to 1.8)	210	−0.1 (−1.5 to 1.3)	195	0.4 (−1.3 to 2.1)	0.64	405
Total cholesterol, mg/dl [mmol/l]	−4.1 (−9.8 to 1.6) [−0.1 (−0.3 to 0.0)]	153	−5.6 (−11.6 to 0.4) [−0.1 (−0.3 to 0.0)]	140	1.2 (−5.8 to 8.2) [0.0 (−0.2 to 0.2)]	0.74	293
LDL cholesterol, mg/dl [mmol/l]	−3.8 (−8.9 to 1.3) [−0.1 (−0.2 to 0.0)]	154	−1.2 (−6.8 to 4.4) [0.0 (−0.2 to 0.1)]	139	−3.0 (−9.0 to 2.9) [−0.8 (−0.2 to 0.1)]	0.33	293
HDL cholesterol, mg/dl [mmol/l]	3.0 (0.0 to 5.9)* [0.1 (0.0 to 0.2)]	148	3.0 (−1.1 to 7.0) [0.1 (0.0 to 0.2)]	131	−0.9 (−5.9 to 4.1) [0.0 (−0.2 to 0.1)]	0.72	279
Triglycerides, mg/dl [mmol/l]	−2.1 (−10.7 to 6.4) [0.0 (−0.1 to 0.1)]	146	−9.4 (−20.1 to 1.3) [−0.1 (−0.2 to 0.0)]	133	2.6 (−9.6 to 14.8) [0.0 (−0.1 to 0.2)]	0.68	279

[a]Difference between treatment groups.

*$p < 0.05$ **$p < 0.01$.

assessing the impact of fasting on hypoglycemia, sulfonylureas were more likely to increase the risk of hypoglycemia.[8] It is known that there is heterogeneity among sulfonylureas regarding this detrimental effect. In fact. A meta-analysis showed no increase in the incidence of hypoglycemia between gliclazide and DPP4-I.[12] Despite suggesting that TZDs and AGIs are suitable options during Ramadan, such treatments were withheld in 21% of the subjects in this study. The increased prescription of DPP4-inhibitors is compatible with the evidence from the literature; DPP4-inhibitors are recommended as an add-on therapy to metformin and do not require dose change during fasting. A review of DPP4-inhibitors use during Ramadan showed that DPP4-inhibitors can reduce the risk of hypoglycemia compared with other glucose-lowering drugs.[6,13–15] Liraglutide is the only GLP1-RA evaluated during the Ramadan period with a favourable effect on weight and hypoglycemic events.[16] In the treat 4 Ramadan trial, liraglutide compared with sulphonylurea was well-tolerated, and in combination with metformin during Ramadan, more patients were able to achieve target HbA1c and lose or maintain weight with no severe hypoglycemia.[17] Also, liraglutide can significantly diastolic blood pressure.[18] However, in our study, the use of GLP1-RA was reduced from 2.2% to 1.3%.

In this study, the medical management plan focussed on withholding sulfonylureas and using SGLT2-inhibitors as a substitute despite recommendations discouraging the first prescription of the latter close to or during Ramadan. With SGLT-2 inhibitors in warm climates, the risk of dehydration should be considered.[19–22]

TABLE 5 Use of glucose-lowering drugs at baseline and follow-up by the treatment group

	Intervention (n = 232)		Control (n = 219)		Total (n = 451)	
Glucose-lowering drug, n (%)	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**
Any glucose-lowering medication	229 (99.6)	229 (99.6)	217 (100.0)	217 (100.0)	446 (99.8)	446 (99.8)
Oral medication	221 (95.3)	222 (95.7)	210 (97.2)	213 (98.6)	431 (96.2)	435 (97.1)
Metformin	193 (83.2)	188 (81.0)	182 (83.1)	177 (80.8)	375 (83.2)	365 (80.9)
Sulphonylurea	91 (39.2)	69 (29.7)	92 (42.0)	85 (38.8)	183 (40.6)	154 (34.2)
DPP-4 inhibitor	110 (47.6)	114 (49.4)	98 (45.0)	109 (50.0)	208 (46.3)	223 (49.7)
SGLT2 inhibitor	32 (16.8)	76 (40.0)	36 (21.1)	82 (48.0)	68 (18.8)	158 (43.8)
TZDAGI[a]	55 (23.7)	14 (6.0)	67 (30.6)	14 (6.4)	122 (27.1)	28 (6.2)
Insulin	50 (21.6)	46 (19.8)	44 (20.1)	41 (18.7)	94 (20.8)	87 (19.3)
(GLP-1RA) non-insulin injectable	6 (2.6)	4 (1.7)	4 (1.8)	2 (0.9)	10 (2.2)	6 (1.3)

Note: Includes participants who reported data on use of each medication at both baseline and follow-up.

Abbreviations: AGI, alpha glucosidase inhibitors; DPP-4, *dipeptidyl peptidase 4*; GLP-1RA, glucagon-like peptide-1 receptor; SGLT2, sodium-glucose cotransporter-2; TZD, thiazolidinedione.

[a]In light of the small number of participants enroled in the alpha glucosidase inhibitor study group, this study group was combined with the thiazolidinedione group. These two drug classes have been deemed to have an acceptably similar risk of hypoglycemia, and should not interfere with the outcomes.

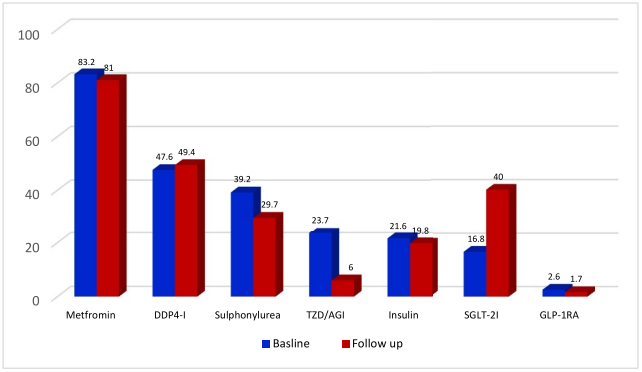

FIGURE 4 Percentage of participants using glucose-lowering drugs at baseline and follow-up by the treatment group (Intervention group).

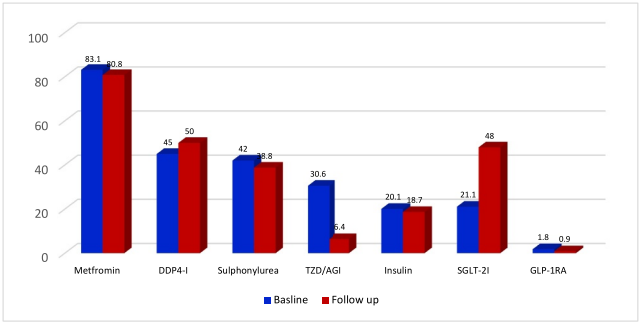

FIGURE 5 Percentage of participants using glucose-lowering drugs at baseline and follow-up by the treatment group (Control group).

Insulin use increases the risk of hypoglycemic events.[11] However, in the present study, most patients were maintained on insulin with a drop of insulin prescription by only 1.5%. Any change in the type, the dose, and the timing of insulin injections might alter the risk of hypoglycemia; however, the adjustment to the insulin regimen in these patients has not always been reported.[23,24] The risk of hypoglycemia with glucose-lowering drugs is not only drug class related, it can be also affected by drug combinations.[25–29] It is true that glucose-lowering agents and their different combinations may modulate the risk of hypoglycemic events; however, in this study, drug treatment differences between groups cannot alone explain the reduction in the hypoglycemic events in the intervention group. Counselling patients on how to address different risk factors may limit the risk of hypoglycemic events.

A meta-analysis of randomized educational interventions with T2D showed an improvement in HbA1c with patient education.[30] A systematic review on the effectiveness of self-management training in people with T2D showed improved glycaemic control with a variable effect on weight reduction.[31] According to the American Association of Diabetes Educators (AADE), pre-Ramadan education improves diabetes knowledge, medication adherence and blood glucose monitoring, which prevents severe hypoglycemic events and improves BMI and glycaemic control.[32] In our study with individualised patient education, the intervention showed a significant reduction in HbA1c of 0.2% (2.3 mmol/mol) compared with the usual care group, in keeping with results observed in a previous study.[33] However, inconsistent results were seen in a recent systematic review and meta-analysis on the effect of Ramadan-focussed education in people with T2D.[34] Educating people with diabetes reduced HbA1c by 0.46% (5.3 mmol/mol) but increased serum TG by 6.2 mg/dl (0.07 mmol/l), and increased the mean weight by 0.44 kg, but had no effect on hypoglycemic events or blood pressure. In our study, more participants in the intervention group achieved the composite

primary outcome, that is, a reduction in HbA1c with a reduction in severe hypoglycemic episodes, and a reduction in weight as the secondary endpoint. In contrast, another study showed that despite an alteration in drug dosage and an increase in blood glucose monitoring, there was no difference in hypoglycemic episodes between those who did and did not receive pre-Ramadan education.[35] It is important to note that the Ramadan-focussed education programs are variable in their duration and content and will likely impact the outcomes differently.[34] Also, the effects of such programs on other biological parameters such as HDL cholesterol and blood pressure were shown to vary.

Our study had some limitations, including the fact that the collected data lack some information that could affect the outcome assessment. Data on comorbidities, medical treatment other than glucose-lowering drugs, adherence to treatment, changes in the insulin regimen including doses of insulin, and changes in diet and exercise were not reported. Acquiring data on side effects associated with glucose-lowering drugs could have helped in understanding changes in treatment plans. Patients and physicians were not blinded to the aim of the study as well as to the group allocation, which can introduce a selection and a performance bias. Also, the participants in this study were mostly without major health problems besides T2D; therefore, it would be difficult to extrapolate the results to the general T2D population that also includes patients with several comorbidities. We do not have information about possible changes participants may have made during the study period in their diabetes management, but this issue was the same for both groups. Strengths include that this was a large multicenter trial, and the definition of hypoglycemia was based on objective findings. The recommended treatment regimen was uniform, based on the 2020 Ramadan-focussed recommendations.

In conclusion, Ramadan-focussed education and raising awareness of the potential complications empower people with T2D to self-manage their diabetes and improve their glycaemic control. A pre-Ramadan assessment of people with T2D coupled with pre-Ramadan education and an adjustment of glucose-lowering treatment as per the updated 2020 recommendations can contribute to the prevention of acute complications and allow a safer fast for people with T2D. We have shown that such an approach reduces the risk of developing severe hypoglycemia and improves the metabolic outcomes. There is a need to assess the safety of this approach in more challenging populations of people with T2D and to objectively measure the effect of comprehensive pre-Ramadan education addressing not only glycaemia but also associated cardiometabolic risk factors.

AUTHOR CONTRIBUTIONS

Mahmoud Ibrahim and Ebtesam M. Ba-Essa determined the study protocol and manuscript strategy, delivered study instruction to investigators, wrote the first draft, comments on each version; Melanie J. Davies, Ehtasham Ahmad and Mary Moffett Barker commented on the protocol, conducted the statistical analysis and tables and commented on the final draft. Pamela Houeiss, wrote sections in the introduction and discussion sections; Firas A. Annabi, Asma Ahmed, Shehla Shaikh, Shabeen Naz Masood and Hyam Tantawi supervised the collaborating centres and provided the results sheets; Jaakko Tuomilehto helped in the initial recruitment of the samples, provided intellectual content in interpreting data and critically reviewed the manuscript. All authors revised and approved the final version of the manuscript.

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CONFLICT OF INTEREST

MI received honorarium from Novo Nordisk, Boehringer Ingelheim, Pfizer and Medtronic; MJD has acted as consultant, advisory board member, and speaker for Boehringer Ingelheim, Lilly, Novo Nordisk and Sanofi; advisory board member and speaker for AstraZeneca; advisory board member for Janssen, Lexicon, Pfizer and ShouTi Pharma Inc and as a speaker for Napp Pharmaceuticals, Novartis and Takeda Pharmaceuticals International Inc. She has received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, AstraZeneca and Janssen. SNM: Nouman Lateef, Chief Commercial Officer Martin Dow Marker Pvt. Ltd provided financial and logistic support to the Department of Diabetes, Al-Ibrahim Eye Hospital, Isra University for the study and Suhail Chughtai for telemedicine support. JT owns stocks in Orion Pharma.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to patient-level data and related documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants.

ETHICS STATEMENT

This study was conducted in accordance with the guidelines for Good Epidemiology Practice and the Declaration of Helsinki of 1964 and subsequent amendments. The study protocol was reviewed and approved by the Institutional Review Board/Institutional Ethics Committee in accordance with the local regulations in each participating country/study centre. All participants provided written informed consent.

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PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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