Assessment of risk of fasting during Ramadan under optimal diabetes care, in high-risk patients with diabetes and coronary heart disease through the use of FreeStyle Libre flash continuous glucose monitor (FSL-CGMS)

Mohamed Hassanein, Fauzia Rashid *, Mohamed Elsayed, Alaaeldin Basheir, Maryam Al Saeed, Elamin Abdelgadir, Sona AbuelKheir, Azza Khalifa, Fatima Al Sayyah, Fawzi Bachet, Susan Jacob, Fatheya Alawadi

Endocrine Department, Dubai Hospital, United Arab Emirates

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ABSTRACT

Aim: Most of Muslims patients with diabetes and Coronary Heart Disease (CHD) elect to fast in Ramadan, but the actual risk in this subset of patients with diabetes is largely unknown.

We aimed to understand the safety of fasting in CHD patients with diabetes insisting on fasting Ramadan under optimal care. We also monitored the change in biophysical and biochemical parameters of these patients before and after Ramadan.

We conducted this prospective study in a tertiary care hospital in Dubai during Ramadan 2016, (June 6th till July 5th).

Patients and methods: 21 Patients with T2DM with stable known CHD during the three months prior to study and insisted on fasting despite advice against it were recruited for the study. All patients received continuous glucose monitoring with free style libre monitoring device (FSL-CGM) during and outside Ramadan period.

We recorded DM or CVD-related emergency visit or hospitalisation, change in BMI, systolic and diastolic BP, lipids profile, e-GFR, HBA1c, and frequency of hypoglycemia during Ramadan fasting and not -fasting period.

Results: This is first study using CGM in CHD patients with diabetes who observe fast in Ramadan. Patients had a significantly higher incidence (3.2 ± 2.8 vs 1.1 ± 1.6 episodes, $p = 0.033$) and prolonged duration of hypoglycemia (117.8 ± 87.2, 49.1 ± 59.1 min p 0.022)

during fasting compared to non-fasting respectively. No significant alteration was seen in BMI, SBP and DBP, lipid profile and renal function. There is a significant improvement in HBA1c during Ramadan.

Conclusion: We could not associate any adverse cardiovascular effects with fasting Ramadan in patients with stable CHD under optimal diabetes care. FSL-CGMS data showed higher frequency of hypoglycemia during Ramadan fasting. Studies with larger sample size are needed for further validation of these findings.

1. Introduction

Patients with cardiovascular disease are categorized as high risk for Ramadan fasting [1]. This risk stratification is based on multiple guidelines. Considering all the available scientific, clinical and practical evidences, the IDF-DAR categorizes different group of patients e.g. multiple co morbidities or advanced microvascular complications, or type of therapy, into very high risk, high risk and moderate/low risk level for fasting. Patients under category of very high and high risk are advised against fasting. This classification and medical advice received a thorough review and agreement from Mufti of Egypt [2]. However, it is repeatedly observed that despite advice of health care providers, majority of patients in all risk categories preferred to fast in Ramadan [3]. Nevertheless it is also seen that Ramadan focused education play a significant role in reducing the frequency of hospitalization due to DKA and hypoglycemia [4–7].

All the guidelines emphasize on frequent self-monitoring of blood glucose and focused education about change in timings and dose of antidiabetic medications and awareness when to break the fast as part of optimum care for these patients [8].

Based on the observation that prolonged period of fasting, possible missed doses of essential medications, consumption of sweets drinks and diet consisting of refined carbohydrate and fat content may induce unfavorable plasma coagulation and hemostatic factors. This may result in increased risk of vascular thrombosis, instability of coronary plaque and worsening of underlying CHD [9]. Numerous previous studies in patients with underlying Coronary Heart Disease (CHD), only measured the cardiovascular outcome with Ramadan fasting [10]. Many studies assessed the cardiovascular risk factors in patients and showed a beneficial or neutral effect of fasting in Ramadan on the weight, lipid profile and metabolic control [11,12]. However, no study observed these factors in the patients with established CAD. Also, there is no published data that has assessed the glycemic profile in such high-risk patients for Ramadan fasting and to correlate any following adverse or beneficial coronary outcome with the incidence of hypoglycemia and glycemic change.

Our study is a first trial done in these high-risk patients with coronary artery disease and type 2 diabetes that measured the frequency of hypoglycemia and pattern of plasma glucose by the use of FSL- CGMS, during Ramadan and non-Ramadan period under optimal diabetes care.

The outcome of our study objective can be classified into the result of glucose profile by detection of hypoglycemia,

peak blood glucose, the pattern of hypoglycemia over 24 h, overall glycemic control by the use of CGMS. Along with the measurement of cardiovascular risk markers like BMI, BP changes, renal and Lipid profile, as well as hospitalisation for any cause during the study period.

Our trial is a unique trial since very few prospective studies had focused on the high-risk patients in Ramadan, and even fewer have used a CGMS [13,14].

2. Methodology

2.1. Ethical approval and funding

2.2. Aim of the study

2.2.1. Primary objectives
To understand the glycemic changes through flash glucose monitoring data during Ramadan fasting in high- risk group of the patients with diabetes and stable cardiovascular disease and compare it with non-Ramadan. Glycemic changes including hypoglycemia (glucose level < 70 mg/dl with or without symptoms), hyperglycemia, the pattern of hypoglycemia over 24 h, and severity of hypoglycemia.

2.2.2. Secondary objectives

- To evaluate the safety of fasting Ramadan for patients with type 2 diabetes and cardiovascular disease through assessment of the cardiovascular risk factors including BP, weight, BMI, lipids, and renal parameters.
- To record admission to hospital with diabetes or cardiovascular related conditions.
- Breaking fast when hypoglycemic or not.
- Number of days fasted.

2.3. Study subjects

Patients were attending diabetes and cardiology clinics of Dubai hospital, aged between 18 and 75 years with type 2

diabetes (T2DM) and stable Coronary Heart Disease (CHD) who insisted on fasting despite advice against, were invited to join the study. Recruitment started 1 to 2 months before Ramadan 2016. Patients with any recent hospitalisation or with known chronic kidney disease or pregnancy or hypoglycemia unawareness were excluded.

2.4. Method

Those who decided to fast attended a 60 min pre-Ramadan focused educational session (DAR SAFA program that included information on safe fasting, when to breakfasting during Ramadan, education on SMBG and use of glucometer and advice on dose adjustment as well as advise on dietary changes during Ramadan). Following the session, patients were asked to sign a consent form. We also took detailed treatment record as well as the history of hospital admission during the previous three months before the study start.

Before the educational session, all patients answered a simple questionnaire to assess their knowledge of safe fasting during Ramadan and their usual behaviour during previous Ramadan. After the session, they answered two questions to assess their benefit from the educational session. Post Ramadan they also answered a questionnaire to assess their behaviour during the corresponding Ramadan. All patients had training on FreeStyle Libre flash continuous glucose monitor (FSL-CGM) insertion and understanding its functions. This glucose monitoring system works through a sensor, which is inserted under the skin of upper arm through an applicator, and it stays in place via an adhering tape. The sensor monitored the interstitial glucose level every minute for two weeks. After two weeks, it is required to reinsert another sensor This subcutaneous sensor needed to be scanned by a separate reader to keep a record of glucose measurement and pattern of glucose at the time of scan and up to 8 h before it. All subjects were instructed to check capillary blood glucose on symptoms of hypoglycemia or hyperglycemia. As this was a newer technology, so they were also advised to counter check the reading by capillary blood glucose, if flash glucose sensor showed reading less than 60 mg% or more than 250 mg% [15]. Diabetic educators downloaded data from the sensor on patients' visit and the doctors suggested the modification in the doses of their medicines according to their glucose profile in each visit. Patients were provided with questionnaires on their visits to fill about their experience of fasting and the use of the libre flash sensor.

All patients had their biophysical and biochemical profile recorded 2–4 weeks before and after Ramadan. We recorded the change in weight, Body mass index, systolic and diastolic blood pressure, HBA1c, lipids profile, renal functions, and frequency and pattern of hypoglycemia during Ramadan fasting and non-fasting period. Any third-party assistance for hypoglycemia or hospitalisation was also recorded.

3. Data collection and analysis

All data was then entered into an excel sheet and was prepared for analysis. Paired Student's t-tests were used to test the significance of differences between values for continuous variables measured at baseline and at various time points. Independent t-test, one-way analysis of variance (ANOVA) and Chi-square ($x2$) test were used to assess the significance of differences between the groups. Continuous data are presented as the mean ± standard deviation (SD), and categorical data are presented as frequencies and percentages. Differences with P-values ≤ 0.05 were considered to be statistically significant. Analyses were performed using Statistical Package for the Social Sciences (SPSS) version 23 (IBM Corp, New York, USA).

4. Results

We recruited 26 patients, two patients did not fast in Ramadan after signing consent as one of them scheduled for surgery, and another one decided later against fasting. Four patients could not complete the protocol as one patient had pacemaker and sensor did not work for him, one patient had local pain, and one another developed hematoma on sensor insertion site and one patient defaulted.

There were 21 final participants, 15 males and six females with mean age of 59.1 ± 8.7 (range 34–71). Out of 21 patients, six were on the intensive insulin-based regimen (basal-bolus or premixed), and four were on basal insulin with oral hypoglycemic agents. Total 11 patients were on multiple combined non-insulin-based antidiabetic agents, out of them 7 patients were having SU in their regimen and four patients without SU. Consequently, 17 patients (80.9%) were either on insulin and/or SU (Table 1).

4.1. Patients' behavior during Ramadan fasting

An average number of days fasting were 28. 90% patients (n = 18) completed >20 days fasting.

Although 47% patients (n = 10) experienced symptomatic hypoglycemia only 19% patients (n = 4) broke their fast.

4.2. Glycemic changes through the data from FSL-CGMS

Most patients had three sensors attached to them with average three weeks during Ramadan and three weeks outside Ramadan. Some sensors had an overlap of Ramadan and non-Ramadan period and hence for accuracy the compared data relates to one sensor of (maximum 14 days) in Ramadan vs one sensor in non-Ramadan days. The target for glycemic control was set between 70 and 130 mg/dl, and the values

Table 1 – Detail of anti-hyperglycemic treatment.

Type of Treatment	Number of patients (Total 21)
Intensive insulin therapy	6
Basal insulin + oral	4
Sulfonylurea	7
DPP4i	11
SGLT 2I	7
GLP-1antagonist	6
Metformin	18

are recorded as above or below the targets if beyond these values. The comparison was made between Ramadan and non - Ramadan period. We got the huge amount of data generated from the FSL-CGM and it was around hundred thousand of the glucose readings. The results are mentioned as mean ± SD.

There are significantly more hypoglycemic events recorded in the Ramadan monitored period compared to non-Ramadan (3.2 ± 2.8 vs 1.1 ± 1.6 episodes, p = 0.033) (Table 2). The lowest mean glucose of 74.1 ± 28.36 mg/dl recorded during non-Ramadan. While during Ramadan period the lowest mean glucose value was 62.7 ± 23.3 mg/dl, p = 0.243. The mean glucose value below 60 mg/dl recorded in 78% of patients in Ramadan and 40% of patients during non -Ramadan. The average duration for hypoglycemia was 49.1 ± 59.1 min in non-Ramadan, and it became significantly more prolonged during Ramadan with 117.8 ± 87.2 min (p 0.022) (Table 2).

The FSL-CGM data showed 5 to 10 episodes of hypoglycemia in 2% of the patients outside Ramadan. This percentage of patients experienced that many hypoglycemic episodes markedly increased to 14% during Ramadan. 5% of the patients had more than ten episodes of hypoglycemia in Ramadan that never happened in non-Ramadan period. (Fig. 1). During non –Ramadan period, most of these hypoglycemic events were either nocturnal or early hours of the day between 1200 midnight to 06:00 am, compared to Ramadan (0.3 ± 0.6 vs. 0.1 ± 0.3, p = 0.20). However, this pattern was reversed during Ramadan, and significant numbers of hypoglycemic episodes were recorded before breaking fast between 1200 and 1800 pm compared to non-Ramadan (2.0 ± 2.2 vs 0.3 ± 0.6, p = 0.005) (Table 2). None of the patients reported severe hypoglycemia.

The sensor data showed peak glucose of 271.6 ± 78.9 mean ± SD during Ramadan and non-Ramadan 270.3 ± 85.8 mg/dl, p = 0.702. (Table 2)

HBA1c showed significant improvement during Ramadan compared to non -Ramadan (7.3 ± 0.9 vs 7.8 ± 1.1, p = 0.007). (Table 3).

4.3. Cardiovascular safety of fasting Ramadan

None of the patient reported aggravation of their underlying coronary heart disease or chest pain during the Ramadan fasting, only one patient, visited emergency department with
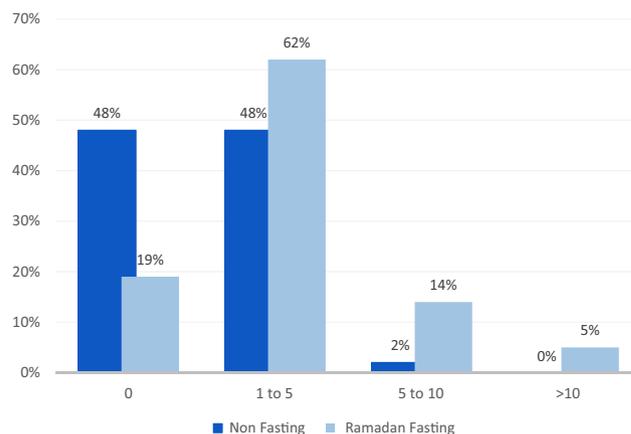

Fig. 1 – Comparison of the frequency of hypoglycemia between Ramadan and non-Ramadan.

dyspnea after Ramadan. Most importantly there was no significant change seen in blood pressure and BMI. Biochemical cardiovascular risk parameters like LDL, HDL and Renal profile remained unchanged.

4.4. Hospitalization

No hospitalization secondary to hypoglycemia, hyperglycemia or any coronary events was reported during study period.

5. Discussion

There is no previous study published so far to assess the glycemic changes by the use FSL- CGM in patients with coronary heart disease and diabetes. Though few studies with CGMS done in low-risk type diabetes [16]. and high-risk group of type 1 diabetes [13] and GDM [17].

Our results showed that most of the patients were able to observe fast more than 20 days of Ramadan despite their risk of fasting was really high as many of them were on insulin therapy with the coexisting CHD.

Table 2 – The CGMS readings non-Ramadan and during Ramadan.			
CGM data	Non-Ramadan mean ± SD	During Ramadan mean ± SD	P-value
Average glucose	168.2 ± 50.3	168.4 ± 49.0	0.33
% above target	65.4 ± 15.8	63.3 ± 18.8	0.86
% in target	32.8 ± 14.7	34.0 ± 18.1	0.87
% below target	1.8 ± 2.8	2.6 ± 5.0	0.634
Peak glucose	270.3 ± 85.8	271.6 ± 78.9	0.702
Number of HE	1.1 ± 1.6	3.2 ± 2.8	**0.033**
Average hypo duration minutes	49.1 ± 59.1	117.8 ± 87.2	**0.022**
Lowest glucose value	74.1 ± 28.3	62.7 ± 23.3	0.243
Number of HE between 00:00 and 06:00 h	0.5 ± 0.5	1.0 ± 1.2	0.162
Number of HE between 06:00 and 12:00 h	0.3 ± 0.6	0.1 ± 0.3	0.206
Number of HE between 12:00 and 18:00 h	0.3 ± 0.6	2.0 ± 2.2	**0.005**
Number of HE between 18:00 and 00:00 h	0.1 ± 0.3	0.1 ± 0.4	1.00

Table 3 – The biometric and biochemical changes before and after Ramadan.

Variables	Mean ± SD Non-Ramadan	Mean ± SD Ramadan	P value
Weight (kg)	83.7 ± 12.1	83.8 ± 12.6	0.495
Systolic BP (mmHg)	118.9 ± 18.2	121.6 ± 17.1	0.501
Diastolic BP (mmHg)	69.5 ± 9.3	68.2 ± 11.2	0.403
HbA1c (%)	7.8 ± 1.1	7.3 ± 0.9	**0.007**
Total Cholesterol (mg/dl)	142.2 ± 33.9	150.7 ± 48.9	0.629
Triglycerides (mg/dl)	134.5 ± 46.6	137.7 ± 57.6	0.952
HDL (mg/dl)	41.9 ± 10	44.1 ± 9.4	0.055
LDL (mg/dl)	44.1 ± 9.4	76.6 ± 41.1	0.872
Creatinine (mg/dl)	0.86 ± 0.26	0.87 ± 0.26	0.366
Estimated GFR (ml/min/m^2)	90.1 ± 18.9	89.1 ± 18.8	0.277

Data from FSL-CGMS showed significantly higher frequency and duration of hypoglycemia in our patients during Ramadan compared to non-Ramadan (Fig. 1). Although hypoglycemic events increased significantly both in frequency and duration (Table 2), many patients did not break their fast. This can be explained that these events might have been mild and asymptomatic, occurring at times when the reader was not accessible to patients or potentially the data could have been ignored by the patients. There is a possibility of low glucose levels being over-reported by the flash glucose monitor, as seen in a study out of Ramadan by M J Fokkert et al. who reported that use of Flash glucose monitor in both type1 and type2 diabetes patients, is associated with over estimation of low glucose values and underestimation of postprandial peaks [15]. Indeed, it is not clear if the state of fasting with the possible mild dehydration affects the accuracy of FGM results, as it is dependent on glucose levels in the interstitial fluid. Although we recommended to our patients, to countercheck the reading below 60 mg% and above 250 mg in glucometer, but those readings were not available to us as the majority simply relied on FSL-CGM. Many patients claimed that they didn't counter check as they were not severely symptomatic. We cannot say with certainty as if having FSL-CGM played a protective role against progression to severe hypoglycemia as patients through continuous check might have titrated the doses of their antidiabetic medications as per the ongoing readings. This could be the reason that though 10 patients reported symptomatic hypoglycemia in their survey questionnaire provided at the end of the study, but only 4 of them broke the fast and none felt the worsening of cardiovascular related symptoms.

FSL- CGM data did not show any significant change in peak glucose level during Ramadan and non-Ramadan. It also showed no major change for target glycaemia range (Fig. 1).

Our second aim for this trial was to assess any change in cardiovascular status and risk factors with fasting. The question about the safety of Ramadan fasting in patients with cardiovascular disease have been addressed in different previous reports, and most of these investigators showed that patients with various cardiovascular diseases including coronary heart disease were able to fast safely without any significant worsening of underlying heart conditions [18].

The adverse cardiac effect of hypoglycemia is well documented by Desouza et al. (2003) in their study using CGM, hypoglycemic episodes were associated with symptom of chest pain and ECG changes [19]. But our study subjects did not mention any adverse cardiac event despite frequent and pronounced hypoglycemic events in Ramadan. We cannot relate it objectively as no ECG recording was done during hypoglycemic events and no patient complained of chest pain or hospitalization with worsening of underlying CHD during study period though some of them had reported hypoglycemic symptoms.

Effect of Ramadan fasting on cardiovascular status have been studied in multiple studies.

A prospective observational study is recently published from the Saudi Arabia [20]. This study was done in 249 patients with heart failure and ejection fraction below 40% as inclusion criteria. 227 patients were able to fast whole month of the Ramadan while 22 patients could not fast. The results showed that patients who did not fast had significant NYHA function classification (p < 0.0001). In our study, we did not monitor the patients who did not fast as a control, and also, we did not monitor NYHA functional classification, but our cohort with stable coronary heart disease did not show any worsening of their anginal or heart failure symptom during fasting. Mossavi at al. (2014) also showed that patients with underlying stable coronary heart disease can safely observe fasting in Ramadan [21]. Similar to our result, Temizhan and colleagues (2009) showed that there is no increased incidence of acute coronary syndrome in patients who observed fasting Ramadan [22]. One retrospective observation study from Qatar done in 20,856 patients treated during the 10-year period, did not show any difference in hospitalisation with worsening of congestive heart failure in patients with heart failure who observed this religious duty [23]. None of these studies reported outcomes based on people with DM versus non-diabetics, however, all our patients are with type 2 diabetes.

Results from our study did not show any significant change in biochemical or biophysical cardiovascular risk factors among the patients during and outside Ramadan. Contrary to our findings, Nematy et al. (2012) observed a significantly lower LDL, Cholesterol, triglycerides, systolic blood pressure, body mass index and higher HDL after Ramadan. This prospective study was done in 82 patients with previous cardiovascular disease including CAD, metabolic syndrome or cerebrovascular disease rather than with type 2 diabetes [24]. Their results showed improvement in 10 years coronary heart disease risk based on Framingham risk scoring (13.0 ± 8 before Ramadan and 10.8 ± 7 after Ramadan, p < 0.001). The fasting glucose and diastolic BP was not changed significantly.

Another recently published study (2018), derived from the data of a large multi-centre heart failure registry of seven gulf countries. They prospectively observed the 4157 patients hospitalized with acute heart failure during February to November 2012. 3851 patients were hospitalized in non -Ramadan days and 306 (7.4%) were hospitalized during Ramadan days [25]. Regarding biochemical parameters, unlike to our results, patients admitted in Ramadan had significantly lower total cholesterol and comparable serum creatinine, HBA1c levels than another group.

Hypertension is an important cardiovascular risk factor for patients with an underlying CAD, and there is sparsity of data to see the effect of Ramadan fasting on blood pressure and other cardiovascular risk factors like weight and HDL in patients with cardiovascular disease. However, one previous study (2001) done in seventeen hypertensive patients showed no significant improvement or worsening of the blood pressure reading in those who observed Ramadan fast. (138.5 ± 18.5/77.2 ± 8.1 mm Hg vs 136.4 ± 20.4/75.7 ± 5.9 mm Hg) [26]. This finding is similar to our findings, with no significant difference in mean blood pressure, weight and lipids during Ramadan fasting. Though Kul et al. (2014) in their metanalysis of 30 studies done in healthy individuals found that there is a positive effect of Ramadan fasting on cardiovascular risk factors [27].

6.   Conclusion

To the best of our knowledge, this is first study done using CGM in patients with stable CHD and type 2 diabetes to objectively assess the safety of fasting in this high-risk group. The use of FSL-CGM in this study provides ample information about glycemic changes, the frequency of hypoglycemia and its correlation with any adverse CVD effect during Ramadan compared to non-Ramadan. In our study under optimal care, the majority of patients were able to fast Ramadan without any significant change in CVD risk factors or hospitalization with CVD or diabetes related conditions. Glycemic control improved, however, hypoglycaemia was significantly more frequent, more prolonged and profound compared to non-fasting state. We observed that these hypoglycemic episodes were not severe and did not cause any change or deterioration in their baseline CHD status or cardiovascular disease risk factors. These results should not be generalized to all patients with CHD and T2DM as our patients were under optimum care.

6.1.   The significance of this study

The use of FSL -continuous glucose monitoring is a relatively a newer technology, and it enabled the diabetes care provider and the patients to understand this risk of fasting more objectively. The result of this study emphasised the importance of Ramadan focus diabetes education along with close observation and continuous supervision for safer fasting in the high-risk patients. Our data also left few questions to be answered that why some patients were more prone to more hypoglycemic episodes despite sharing the similar high -risk profile.

The study needs to replicate on a larger group of the patients to further validate these results.

6.2.   Limitation of the study

Our study was conducted in small numbers of the patients, who were equipped FSL-CGM enabling them to anticipate any untoward glycemic change. They also received very close monitoring and supervision throughout the study period. This factor limits the generalizability of its result in real world setting. We suggest to further study these high-risk CHD patients with a similar control group with-out optimum care, to understand the difference in fasting risk between standard care group versus optimal care.

Availability of materials

Please contact the author for data requests.

Authors' contribution

Mohamed Hassanein: Supervision of the study, Fauzia Rashid, Organization of the study data collection, Data analysis and manuscript writing, Alaaeldin Basheir: Proposal writing, Maryam Al Saeed: Organization of the study and patients' education, Azza Khalifa: Organization of the study and patients' education, Elamin Abdelgader: data collection, Fatima Sayyah: Data collection, Fawzi Eltayb: CGMS data interpretation, Sona Abuelkheir: CGMS data interpretation and analysis, Mohammed Abdellatif: Data collection, Suad Khalifa: CGMS installation and education, Fatheya Alawadi. Manuscript review and supervision of the study.

Competing interest

The authors declare that they have no competing interests.

Consent of publication

Does not apply.

Ethics approval and consent to participate

Ethical approval was obtained from the Dubai Health Authority Ethics committee. Approval document is available upon request.

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REFERENCES

[1] Hassanein M, Al-Arouj M, Hamdy O, Bebakar WMW, Jabbar A, Al-Madani A, et al. Diabetes and Ramadan: Practical guidelines. Diabetes Res Clin Pract 2017;126:303–16. https://doi.org/10.1016/j.diabres.2017.03.003.

[2] Hassanein M, El-Sayed AA, Tayeb K, Mak O, Basit A. Chapter 5. Diabetes and Ramadan: A Medico-religious Perspective n.d.

[3] Babineaux SM, Toaima D, Boye KS, Zagar A, Tahbaz A, Jabbar A, et al. Multi-country retrospective observational study of the management and outcomes of patients with Type 2 diabetes during Ramadan in 2010 (CREED). Diabet Med 2015;32:819–28. https://doi.org/10.1111/dme.12685.

[4] Ahmedani MY, Haque MS, Basit A, Fawwad A, Alvi SFD. Ramadan Prospective Diabetes Study: the role of drug dosage and timing alteration, active glucose monitoring and patient education. Diabet Med 2012;29:709–15. https://doi.org/10.1111/j.1464-5491.2011.03563.x.

[5] Lee SWH, Lee JY, Tan CSS, Wong CP. Strategies to make Ramadan fasting safer in type 2 diabetics: a systematic review and network meta-analysis of randomized controlled trials and observational studies. Medicine (Baltimore) 2016;95:e2457. https://doi.org/10.1097/MD.0000000000002457.

[6] McEwen LN, Ibrahim M, Ali NM, Assaad-Khalil SH, Tantawi HR, Nasr G, et al. Impact of an individualized type 2 diabetes education program on clinical outcomes during Ramadan. BMJ Open Diabetes Res Care 2015;3:e000111. https://doi.org/10.1136/bmjdrc-2015-000111.

[7] Bravis V, Hui E, Salih S, Mehar S, Hassanein M, Devendra D. Ramadan Education and Awareness in Diabetes (READ) programme for Muslims with Type 2 diabetes who fast during Ramadan. Diabet Med 2010;27:327–31. https://doi.org/10.1111/j.1464-5491.2010.02948.x.

[8] Al-Arouj M, Assaad-Khalil S, Buse J, Fahdil I, Fahmy M, Hafez S, et al. Recommendations for Management of Diabetes During Ramadan. Diabetes Care 2010;33.

[9] Siegel AJ, Bhatti NA, Wasfy JH. Reprising Ramadan-related angina pectoris: a potential strategy for risk reduction. Am J Case Rep 2016;17:841–4. https://doi.org/10.12659/AJCR.900133.

[10] Salim I, Al Suwaidi J, Ghadban W, Alkilani H, Salam AM. Impact of religious Ramadan fasting on cardiovascular disease: a systematic review of the literature. Curr Med Res Opin 2013;29:343–54. https://doi.org/10.1185/03007995.2013.774270.

[11] Khatib FA, Shafagoj YA. Metabolic alterations as a result of Ramadan fasting in non-insulin-dependent diabetes mellitus patients in relation to food intake. Saudi Med J 2004;25:1858–63.

[12] Lamine F, Bouguerra R, Jabrane J, Marrakchi Z, Ben Rayana MC, Ben Slama C, et al. Food intake and high density lipoprotein cholesterol levels changes during ramadan fasting in healthy young subjects. Tunis Med 2006;84:647–50.

[13] Kaplan W, Afandi B. Blood glucose fluctuation during ramadan fasting in adolescents with type 1 diabetes: findings of continuous glucose monitoring. Diabetes Care 2015;38.

[14] Al-Agha AE, Kafi SE, Zain Aldeen AM, Khadwardi RH. Flash glucose monitoring system may benefit children and adolescents with type 1 diabetes during fasting at Ramadan. Saudi Med J 2017;38:366–71. https://doi.org/10.15537/smj.2017.4.18750.

[15] Fokkert MJ, van Dijk PR, Edens MA, Abbes S, de Jong D, Slingerland RJ, et al. Performance of the FreeStyle Libre Flash glucose monitoring system in patients with type 1 and 2 diabetes mellitus. BMJ Open Diabetes Res Care 2017;5: e000320. https://doi.org/10.1136/bmjdrc-2016-000320.

[16] Bonakdaran SH, Khajeh-Dalouie M. The effects of fasting during ramadan on glycemic excursions detected by continuous glucose monitoring system (CGMS) in patients with type 2 diabetes. Med J Malaysia 2011;66.

[17] Afandi BO, Hassanein MM, Majd LM, Nagelkerke NJD. Impact of Ramadan fasting on glucose levels in women with gestational diabetes mellitus treated with diet alone or diet plus metformin: a continuous glucose monitoring study. BMJ Open Diabetes Res Care 2017;5:e000470. https://doi.org/10.1136/bmjdrc-2017-000470.

[18] Chamsi-Pasha M, Chamsi-Pasha H. The cardiac patient in Ramadan. Avicenna J Med 2016;6:33. https://doi.org/10.4103/2231-0770.179547.

[19] Desouza C, Salazar H, Cheong B, Murgo J, Fonseca V. Association of Hypoglycemia and Cardiac Ischemia: A study based on continuous monitoring. Diabetes Care 2003;26:1485–9. https://doi.org/10.2337/diacare.26.5.1485.

[20] Abazid RM, Khalaf HH, Sakr HI, Altorbak NA, Alenzi HS, Awad ZM, et al. Saudi Med J 2018;39.

[21] Mousavi M, Mirkarimi S, Rahmani G, Hosseinzadeh E, Salahi N. Ramadan fast in patients with coronary artery disease. Iran Red Crescent Med J 2014;16:e7887. https://doi.org/10.5812/ircmj.7887.

[22] Temizhan A, Dönderici O, Ouz D, Demirbas B. Is there any effect of Ramadan fasting on acute coronary heart disease events? Int J Cardiol 1999;70:149–53.

[23] Al Suwaidi J, Bener A, Hajar H, Numan M. Does hospitalization for congestive heart failure occur more frequently in Ramadan: a population-based study (1991–2001). Int J Cardiol 2004;96:217–21. https://doi.org/10.1016/j.ijcard.2003.06.018.

[24] Nematy M, Alinezhad-Namaghi M, Rashed MM, Mozhdehifard M, Sajjadi SS, Akhlaghi S, et al. Effects of Ramadan fasting on cardiovascular risk factors: a prospective observational study. Nutr J 2012;11:69. https://doi.org/10.1186/1475-2891-11-69.

[25] Salam AM, Sulaiman K, Alsheikh-Ali AA, Singh R, Asaad N, Al-Qahtani A, et al. Acute heart failure presentations and outcomes during the fasting month of Ramadan: an observational report from seven Middle Eastern countries. Curr Med Res Opin 2018;34:237–45. https://doi.org/10.1080/03007995.2017.1376629.

[26] Perk G, Ghanem J, Aamar S, Ben-Ishay D, Bursztyn M. The effect of the fast of Ramadan on ambulatory blood pressure in treated hypertensives. J Hum Hypertens 2001;15:723–5. https://doi.org/10.1038/sj.jhh.1001262.

[27] Kul S, Savaş E, Öztürk ZA, Karadağ G. Does Ramadan fasting alter body weight and blood lipids and fasting blood glucose in a healthy population? A Meta-analysis. J Relig Health 2014;53:929–42. https://doi.org/10.1007/s10943-013-9687-0.