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Original Article

A pilot study using flash continuous glucose monitoring in patients with type-2 diabetes on multiple anti-diabetic agents during Ramadan

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ABSTRACT

Background: This study aims to examine the incidence of hypoglycaemia, based on activity, during Ramadan in patients with type 2 diabetes mellitus who were on were on three or more anti-diabetic medications.

Methods: Type 2 diabetes patients who fasted during Ramadan and were on three or more anti-diabetic medications were studied for two weeks using flash glucose monitoring. The patients were asked to document all episodes of hypoglycaemia and were classified as active or sedentary according to their daytime activity.

Results: The study included 16 patients of whom 10 were active and 6 were sedentary. There were 13 males and 3 females; mean age was 53.4 ± 6.4 years; mean diabetes duration was 15 ± 5.9 years, and mean HbA1C was 7.9 ± 1.3%. Over the two weeks; there were 7.9 episodes of hypoglycaemia recorded per patient; 50% of which were asymptomatic. There was no difference at baseline in age, BMI, HBA1C, diabetes duration, and anti-diabetic medications between the active and sedentary groups. The active group had better glucose control; median blood glucose was (7.1 (5.1–8.5) vs 10.6 (9.6–11.5) mmol $p < 0.01$), mean estimated HBA1C was (6.2 ± 1.2% vs 8.3 ± 1.0%; $p = 0.047$). The active group had more episodes of hypoglycaemia compared to the sedentary group (11.6 vs 1.8 hypo episode per patient/two weeks; $p = 0.019$); most of which were asymptomatic.

Conclusion: Patients with type 2 diabetes mellitus who are on three or more anti-diabetic medications should be warned about the increased risk of asymptomatic hypoglycaemia during Ramadan. Anti-diabetic medication adjustments during Ramadan should take into account the degree of activity. Flash glucose monitoring system can help patients to fast safely during Ramadan and detect asymptomatic hypoglycaemia.

1. Introduction

Ramadan is the ninth month of the Muslims' lunar calendar during which Muslims fast during the day by abstaining from food and drinks from dawn till dusk. All adult Muslims must fast during this month with some exemptions like people with chronic disorders. While exempted from fasting during Ramadan; the EPIDIAR (Epidemiology of Diabetes and Ramadan) study showed that 42.8% of patients with type 1 diabetes (T1DM) and 78.7% with type 2 diabetes (T2DM) fasted for at least 15 days [1].

The rising number of Muslims with diabetes has raised a concern about the safety of fasting during Ramadan. A large observational study showed that the incidence of hypoglycaemia among patients with T2DM who fasted during Ramadan ranged between 7.1% to 13.8% [2]. Besides, the incidence of hypoglycaemia varied widely between regions ranging between 4.1% in the Middle-East to 13.0% in North Africa, and between 6.1% in the Middle-East to 38.5% in North Africa in high-risk patients [2]. Another study showed that the rate of hospital admission with diabetic ketoacidosis was increased during Ramadan compared to the previous months [3].

Studying diabetes management during Ramadan is challenging. In addition to the heterogeneity of diabetes; the nature of the Muslim lunar year means that Ramadan comes at various times of the year and at different seasons. The length of fasting hours in the

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same year can be as low as 6 h to as high as 22 h in different regions of the globe. Hence what applies to one region, does not necessarily apply to other regions. Besides, the degree of activity of patients during the fasting hours is an important, often overlooked, factor in the risk of hypo and hyperglycaemia during Ramadan. Most of the published guidelines are driven by observational studies and do not take into account these crucial factors in their recommendations [4,5].

With the recent rise in the classes of anti-diabetic medications, more T2DM patients are on three or more anti-diabetic agents than before. This group is under-represented in most studies; for example, only 9.5% of the patients in the CREED study (Multi-country retrospective observational study of the management and outcomes of patients with Type 2 diabetes during Ramadan in 2010) were on three anti-diabetic agents [6]. Besides, most of the studies that reported on hypoglycaemia during Ramadan have relied on the self-reporting [2,7–9]. Fasting can inevitably cause fatigue, tiredness, and hunger, which are very similar to the symptoms of hypoglycaemia.

The PROFAST study (the PROspective study of dose adjustment of multiple anti-Diabetic therapy for type-2 diabetic patients FASTing the month of Ramadan) is an observational study that investigated the incidence of hypoglycaemia in T2DM on three or more anti-diabetic medications who fasted Ramadan during the summer of 2017 in Qatar. This pilot study aims to examine the incidence of hypoglycaemia, based on activity, in a subgroup of patients who were studied with a flash glucose monitoring system over a period of two weeks.

2. Methods

This is a prospective pilot observational study. Inclusion criteria were patients with T2DM on stable treatment that included three or more anti-diabetic medications; planning to fast the whole month of Ramadan; age between 18–79 years; HbA1c $\leq$9.9%; and estimated glomerular filtration rate (eGFR) >30 ml/min. Exclusion criteria included history of recurrent hypoglycaemia or hypoglycaemia unawareness; admission with more than 2 episodes of diabetic ketoacidosis (DKA) or with hyperosmolar non-ketotic coma in the preceding year or with an episode of (DKA) within the previous 3 months prior to the start of Ramadan; active coronary artery disease, congestive cardiac failure, or those with advanced co-morbidities and/or advanced diabetes microvascular complications; patients with newly diagnosed cancer or those who are undergoing cancer treatment.

Before the start of Ramadan, the adjustment of anti-diabetic medications was based on the recent IDF guidelines with few modifications [5]. These modifications included; 50% reduction in the dose of sulphonylurea and capping of the Metformin dose to less than 2 g per day. Both changes were based on local experience to avoid undue hypoglycaemia. Patients received IDF-based standard advice about diet, exercise, and lifestyle modifications 4–8 weeks before Ramadan. Data were collected 4–8 weeks before and after Ramadan and included patient's weight, height, BMI, blood pressure, HBA1c, creatinine and fasting lipids. Patients were provided with a flash glucometer monitoring system (Freestyle Libre) and were asked to use it for two weeks during Ramadan. They were asked to record all episodes of symptomatic hypoglycaemia. Based on the current day job of each patient, patients were classified as sedentary or active. Sedentary patients were those who were unemployed or were doing office-based work during the fasting hours. Active patients were those who did fieldwork or prolonged standing during the fasting hours.

The primary outcome was the incidence of symptomatic and CGMS-documented hypoglycaemia. Secondary outcomes were the differences between the active and sedentary groups in the incidence of symptomatic and CGMS-documented hypoglycaemia; the difference in estimated HBA1C; and the difference in the percentage of time spent within the glycaemic target. The blood glucose target was set between 4.4–8.3 mmol/l (80–150 mg/dl). In 2017, Ramadan occurred in June, and the length of fasting in Qatar was 15 h. Clinical hypoglycaemia was defined as the presence of symptoms of hypoglycaemia plus capillary blood glucose of <4.0 mmol/l while CGMS hypoglycaemia was defined as glucose of <3.9 mmol/l (70 mg/dl). All patients received standard education on hypoglycaemia recognition and were instructed to break their fast at any point if hypoglycaemia occurred or capillary glucose readings were <4.0 mmol/l. Routine capillary glucose monitoring was not part of the protocol.

Statistical analysis was performed using STATA 15 software (College Station, TX: Stata Corp LP). Variables are expressed as a percentage (%) for frequencies, mean and standard deviation for normally distributed continuous variables, and median plus interquartile range for the non-normal distributed continuous variable. Comparison between the groups was made using the Student t-test, and Wilcoxon rank test for normally and non-normally distributed continuous variables, respectively. Fisher's exact test was used to compare categorical variables. A p-value <0.005 is considered as significant.

The study was approved by Institutional Review Board of Hamad Medical Corporation (HMC), Doha, Qatar, (reference number **16437/16**). The CGMS flash glucometers (Freestyle Libre) and the sensors were provided by Abbott (Ben-Mahmoud-Doha, Qatar) through an educational grant. Abbott had no access to the data and was not involved in the statistical analysis or the writing of the manuscript.

3. Results

A total of 16 patients were enrolled in the study; of which 13 were males, and 3 were females. The mean age was 53 $\pm$ 6.4 years, the mean duration of diabetes was 15 $\pm$ 5.9 years, and the mean HBA1C was 7.9 $\pm$ 1.3% (Table 1). As shown in Table 1, most of the therapeutic regimens had metformin −15(93.7%), followed by DPP-IV inhibitors −12(75%), and basal insulin analogues −11 (68.5%).

As shown in Table 2, over the two weeks period; 43.8% of the patients reported at least one episode of hypoglycaemia. The average number of reported hypoglycaemia-episodes was 1.9 episodes per person over two weeks. On the other hand, hypoglycaemia was detected on the CGMS in 81.3% (13/16) of the patients. The average number of documented episodes of hypoglycaemia was 7.9 episodes per person over two weeks. There were no episodes of severe hypoglycaemia, DKA or hospital

Table 1
Baseline characteristics. Data is expressed as percentages and mean $\pm$ standard deviation.

Mean Age (years)	53 $\pm$ 6.4 (40–64 years)
Gender	13 Males, 3 Females
Mean Duration of DM (years)	15 $\pm$ 5.9 years
Mean HBA1C (%)	7.9 $\pm$ 1.3
Mean weight (kg)	82.4 $\pm$ 16.8
Mean BMI (kg/m^2)	27.5 $\pm$ 4.0
Metformin	15 (93.7%)
DPP-IV	12 (75.0%)
Basal Insulin	11 (68.5%)
SGLT-2i	8 (50%)
Sulphonylurea	4 (25.0%)
TZDs	3 (18.75%)
GLP-1	2 (12.5%)
Bolus Insulin	1 (6.25%)
Mixed insulin (70/30)	1 (6.25%)

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Table 2
Main Outcomes Data are expressed as percentages, mean ± standard deviation, and median (Interquartile range).

Symptomatic hypos	7 (43.8%)
Average episodes of symptomatic hypos	1.9 episodes
CGMS Documented hypos	13 (81.3%)
Average CGMS Documented hypos episodes (Episodes/patient/two weeks)	7.9 ± 8.7
Average BG	8.4 ± 2.4 mmol/l
Estimated HBA1c	6.9 ± 1.5 %
Percent of time spent above targets (%)	40 (25–70)
Median time within target (%)	47 (24.5–55)
Percent of time spent below targets (%)	7 (1–23)

admissions. Most of the hypoglycemic episodes occurred in the last 3–4 h of fasting.

Ten (10) patients were classified as physically active and 6 patients were classified as sedentary. As shown in Table 3, there was no difference in age, weight, BMI, HBA1C, duration of diabetes and anti-diabetic medications used between the two groups. As shown in Table 4, there was no statistical difference in the frequency of reported hypoglycaemia between the two groups (60% in the active group vs 16.7% in the sedentary group; p = 0.128). All the patients in the active group, 10(100%), had CGMS-documented hypoglycaemia while only 3(50%) in the sedentary group had CGMS-documented hypoglycaemia (p = 0.036). The average number of symptomatic hypoglycemic episodes per patient was 2.9 and 0.3 episodes in the active and sedentary groups respectively (p = 0.213). The average number of CGMS-documented hypoglycaemia episodes was 11.6 and 1.8 in the active and sedentary groups respectively (p = 0.0019). The active group had significantly lower CGMS-estimated HBA1c compared to the sedentary group (6.2 ± 1.2% vs 8.3 ± 1.0%, p = 0.004). Furthermore, the active group spend more time within targets and less time above targets compared to the sedentary group (50% vs 20%; p = 0.0017) and (29% vs 79%; p = 0.003).

4. Discussion

This pilot study shows that hypoglycaemia is quite frequent in patients with T2DM who were on three or more anti-diabetic agents during Ramadan. CMGS-documented hypoglycaemia was seen in 81.3% (13/16) of the patients while only 43.8% (7/16) had reported symptomatic hypoglycaemia. Furthermore, 75% of the CGMS-documented hypoglycaemic episodes were asymptomatic. Despite no difference at baseline characteristics and anti-diabetic medications between the active and sedentary groups, the active group spent more time in target glucose range and less time in hyperglycaemia and was more vulnerable to hypoglycaemia

Table 3
Baseline characteristics of active versus sedentary groups. Data are expressed as percentages and mean ± standard deviation.

	Physically active (10)	Sedentary (6)	p value
Age (Years)	51.2 ± 6.4	57.2 ± 5.0	0.128
Weight (Kg)	86.3 ± 6.12	75.9 ± 3.98	0.173
BMI (Kg/m^2)	27.4 ± 4.6	28.4 ± 1.8	0.707
HBA1C (%)	7.5 ± 1.0	8.7 ± 1.6	0.128
Duration of DM (Years)	13.6 ± 1.4	20 ± 14	0.180
Metformin	9 (90%)	6 (100%)	0.625
Sulphonylurea	2 (20%)	2 (33.3%)	0.489
DPP-IV	7 (70%)	5 (83.3%)	0.511
GLP-1	2 (20%)	0 (0%)	0.375
SGLT-2i	6 (60%)	2 (33.3%)	0.304
TZDs	3 (30%)	0 (0%)	0.214
Basal insulin	7 (70%)	4 (66.7%)	0.654
Bolus insulin	1 (10%)	0 (0%)	0.625
Mixed Insulin	1 (10%)	0 (0%)	0.625

compared to the sedentary group. Furthermore, most of the hypoglycaemic episodes were asymptomatic.

To our knowledge, this is the first study to report a 14 days CGMS results in patients with T2DM who are treated with three more anti-diabetic agents during Ramadan. All the previous studies have used retrospective CGMS for a maximum of 3 days [10–12]. It is also the first study to quantify the rate of asymptomatic hypoglycaemia during long fasting hours. Lessan et al. studied 23 patients with T2DM using retrospective CGMS devices for three days [10]. In this study, the treatment ranged from diet alone to combined oral therapy. None of their 23 patients recorded any symptomatic hypoglycemic episodes while the CGMS detected at least one hypoglycemic episodes in 14/23 patients. Oueslati et al studied five patients with T2DM who were on metformin and glimepiride using 72 h retrospective CGMS [11]. The study reported 1.3 episodes of hypoglycaemia per day in 2 patients, but it was not clear if the hypoglycaemic episodes were symptomatic or not. Another study performed 3 days retrospective CGMS in 50 patients with type 2 diabetes and reported no changes in the incidence of hypoglycaemia before and after Ramadan [12]. The study did not report on the rate of symptomatic and asymptomatic hypoglycaemia.

The degree of activity during fasting is a critical risk factor for hypoglycaemia that is not addressed in guidelines. This study shows that active patients are more vulnerable to symptomatic and asymptomatic hypoglycaemia than sedentary patients. While there were no episodes of severe hypoglycaemia reported in our study, the high incidence of asymptomatic hypoglycaemia puts active patients at higher risk of severe hypoglycaemia. Asymptomatic hypoglycaemia also puts patients at risk of accidents at the workplace; e.g. among the active group, there was a patient who operated heavy machinery at a construction site, two patients who

Table 4
Main outcomes of physically active versus sedentary group. Data are expressed as percentage, mean ± standard deviation, and median (Interquartile range).

	Physically active (10)	Sedentary (6)	p value
Symptomatic Hypos	6 (60%)	1 (16.7%)	0.121
CGMS-documented Hypos	10 (100%)	3 (50%)	0.036
Symptomatic hypo episodes/patient	2.9	0.3	0.213
CGMS-documented hypo episodes/patient	11.6	1.8	0.019
Mean estimated HBA1C (%)[a]	6.2 ± 1.2	8.3 ± 1.0	0.004
Median blood glucose (mmol/l)[b]	7.3 (5.1–8.5)	10.3 (9.6–11.5)	0.004
Median time within target (%)[b]	50 (45–56)	20 (11–27)	0.017
Median time above target (%)[b]	29 (6–35)	79 (64–89)	0.003
Median time below target (%)[b]	21 (2–36)	1 (0–4)	0.016

[a] Mean ± SD.
[b] Median (IQR).

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drive for a living and a site construction engineer. The high rate of asymptomatic hypoglycaemia in this group during fasting could be masked by the overlap between the symptoms of hypoglycaemia and the general feeling of tiredness and hunger.

Our study has several limitations. There was no data available before Ramadan to assess the incidence of CGM-documented hypoglycaemia before Ramadan. Hence it is not clear if fasting increases the incidence of asymptomatic hypoglycaemia or unmasks the symptoms. Patients carbohydrates intake before and after Ramadan was not assessed. There was no self-monitoring blood glucose data to confirm the episodes of symptomatic hypoglycaemia. The assessment of activity was merely based on the type of day job done by patients during the day. In Qatar and most of the nearby Gulf countries, the working hours are reduced during Ramadan, which perhaps has reduced the frequency and severity of hypoglycaemia. However, in other countries, the working hours are not reduced. Hence the results cannot be generalised to other regions.

In conclusion, T2DM patients on three or more anti-diabetic medications are at high-risk of symptomatic and asymptomatic hypoglycaemia during Ramadan. We recommend that the activity during the fasting hours be considered as a crucial factor in the adjustment of anti-diabetic medications. Furthermore, patients on three or more anti-diabetic medications should be cautioned about the risk of asymptomatic hypoglycaemia and should take this into account in their decision to fast Ramadan. They should also be educated about the overlap of symptoms of general tiredness and fatigue of fasting and hypoglycaemia and should be directed to monitor their blood glucose regularly throughout the fasting hours. Flash glucose monitoring could be a useful tool in the monitoring of the blood glucose during Ramadan and in the detection of asymptomatic hypoglycaemia. Prospective studies are needed to confirm the findings of this pilot study.

Disclosures

The authors have nothing to disclose.

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