Incidence of hypoglycaemia in patients with type-2 diabetes taking multiple glucose lowering therapies during Ramadan: the PROFAST Ramadan Study

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Abstract

Objective To assess the incidence of hypoglycemia in people with type-2 diabetes mellitus (T2DM) on three or more anti-diabetic medications during Ramadan.

Study design methods We have studied people with T2DM on three or more glucose-lowering drugs during Ramadan of H1438 (May–June 2017). The dose of each drug was adjusted according to a pre-specified protocol. The incidence of symptomatic or blood glucose confirmed hypoglycemia was recorded during the study.

Results We enrolled 228 people with T2DM; 181 completed the study, and data on hypoglycaemia was available in 172 subjects. There were 115 males and 66 females, (mean age $\pm$ SD) 53.6 ± 9.7 years, diabetes duration 10 ± 6 yrs. The incidence of hypoglycaemia was 16.3% (28/172). Univariable logistic regression analysis showed that the risk of hypoglycaemia was increased in Arab subjects compared to Qatari; in those with longer duration of diabetes; and in those on four or more anti-diabetic medications compared to those on three anti-diabetic medications.

Conclusion Despite the tailored advice, there is a high incidence of hypoglycemia in people with T2DM taking multiple glucose lowering therapies whilst fasting during Ramadan. Guidelines should address the increased complexity in anti-diabetic medications in patients who fast during Ramadan. Healthcare providers should individualize the modifications in anti-diabetic medications during Ramadan.

Keywords Type 2 diabetes · Ramadan · Hypoglycaemia · IDF

Background

Patients with Type-2 diabetes (T2DM) who fast during Ramadan, are at increased risk of hypoglycemia. Indeed, the EPIDIAR study showed that the patients with T2DM are more

vulnerable to hypoglycaemia than those with Type-1 diabetes [1]. Most studies assessing the risks of hypoglycemia in patients with T2DM during Ramadan have studied patients on monotherapy or dual therapy, usually with metformin [1–9]. Very few studies have assessed people with T2DM on insulin and have primarily assessed mixed insulins or basal insulin versus insulin secretagogue or postprandial glucose regulators [6–8]. The CREED study (Multi-country retrospective observational study of the management and outcomes of patients with Type 2 diabetes during Ramadan) is the only available one that reports on the incidence of hypoglycaemia in patients on multiple drugs during Ramadan [10].

Guidelines for the management of diabetes during Ramadan have relied heavily on studies of older and newer anti-diabetic agents, used either as monotherapy or dual therapy to treat T2DM during Ramadan [11–16]. However, with the rise in anti-diabetic classes, the number of patients on

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multiple medications have swollen placing them at higher risk of hypoglycaemia, especially during Ramadan. To date, there are no published studies on the incidence of hypoglycaemia in T2DM patients using three or more glucose-lowering therapies during Ramadan. Recent recommendations advocate structured education programs and dose-adjustment to limit hypoglycaemia while fasting during Ramadan [11]. The PROspective study of dose adjustment of multiple anti-Diabetic therapy for type-2 diabetic patients FASTing the month of Ramadan (PROFAST Ramadan Study), was designed to prospectively assess the incidence of hypoglycaemia in patients with T2DM after dose adjustment of their complex oral and injectable glucose-lowering therapies.

Patients & methods

This is a prospective observational cohort study that was undertaken in Hamad Medical Corporation, Doha, Qatar during Ramadan of 2017. 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 and 79 years; HbA1c $\leq 9.9\%$; and estimated glomerular filtration rate (eGFR) >30 ml/min. Exclusion criteria included history of recurrent hypoglycaemia (more than two episodes of symptomatic hypoglycaemia per week) 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.

Four to eight weeks before Ramadan, we advised subjects on diet modifications and exercise and we adjusted the anti-diabetic medications doses- based on the most recent recommendations by the DAR-IDF and ADA guidelines [10, 11] (Visit A). Besides, the dose of sulphonylurea was reduced by 50%. The dose of basal insulin was reduced by 25% and patients were advised to take this at Iftar (when breaking the fast in the early evening). The morning premixed insulin dose was given at Iftar and the evening dose was reduced by 25% - 50% and taken at Sohoor (the meal before dawn). Those on basal-bolus regimens, basal plus or more complex insulin regimens were provided flexible advice to reduce their basal insulin by 30% and to omit the afternoon bolus dose together with increased self-monitoring of home blood glucose. The dose of metformin, pioglitazone, DPP-4i, SGLT-2i or GLP1-RA were not altered. During Ramadan, patients were contacted by phone to reinforce guidance given during visit A. Participants were reviewed 4–8 weeks after the completion

of Ramadan and data on the episodes of symptomatic and confirmed hypoglycemia the number of days fasted and any visit to the emergency room (ER) were collected (visit B). Confirmed hypoglycaemia is defined as capillary blood glucose of <3.9 mmol/l with or without symptoms while symptomatic hypoglycaemia was defined as occurrence of typical hypoglycemic symptoms that responded to corrective measures with or without confirmed capillary blood glucose. Patients were placed into four groups: Group A included patient on a sulphonylurea (SU) (minimum of two drugs); Group B included those on insulin; Group C included those on both insulin and an SU; and Group D included patients taking neither insulin or a SU and were taking other agents. Ethical approval for the study was granted from the Institutional Review Board of Hamad Medical Corporation (HMC), Doha, Qatar, (reference number 16437/16), as well as from the appropriate local hospital as per the Bylaws of HMC.

Statistical analysis was performed using STATA 15 software (College Station, TX: Stata Corp LP). Variables are expressed as a percentage (%) for frequencies, mean $\pm$ standard deviation for normally distributed continuous variables. Chi-2 test was used to analyse categorical data. Univariable logistic regression analysis was used to explore the risk factors for hypoglycaemia. To identify the combination of medications with the highest risk of hypoglycaemia, we identified the two most common combinations of anti-diabetic medications and had sequentially added a third agent. We considered a P value <0.05 as statistically significant.

Results

We were enrolled 228 patients with T2DM in the study (Visit A) and 181 returned for visit B and completed the study. Table 1 shows the baseline characteristics of the study subjects. There were 115 males (63.5%) and 66 females (36.5%) with a mean age of 53.5 ± 9.7 years, mean weight of 83.3 ± 14.5 kg, mean diabetes duration of 10.6 ± 6.5 years, and mean HBA1C of $7.8 \pm 1.0\%$. The majority of the study group were Middle Eastern/Arab [74 (40.9%)]. Supplementary table 1 shows the demographics of the study based on the ethnic distribution. Group A (SU+) had 97 patients (53.6%), Group B (insulin +) had 55 patients (30.4%), group C (Insulin and SU) had 17 patients (9.4%) and group D (neither insulin or SU) had 12 patients (6.6%). Most of the patients were on Metformin 95.3%, followed by DPP-IV inhibitors 82.9% and Sulphonylurea 63.0% (Fig. 1).

Data on hypoglycaemia was available in 172 subjects. The incidence of hypoglycaemia was 28/172 (16.3%). Figure 2 shows that the hypoglycaemia was recorded in 13/93 (13.98%) in group A, 10/41 (19.61%) in group B, 5/16 (31.25%) in group C and 0/12 (0%) in group D; $p = 0.125$. There were no episodes of severe hypoglycaemia, diabetic

Table 1 Baseline characteristics

	Total (181)			
Mean age	53.5 ± 9.8 Years			
Gender (%)	Males		Females	
	115 (63.5%)		66 (36.5%)	
Ethnicity (%)	Qatari	Arab	Asian	
	51 (28.2%)	74 (40.9%)	56 (30.9%)	
Mean Duration of Diabetes	10.6 ± 6.5 Years			
Mean Weight	83.3 ± 14.5 kg			
Mean HBA1C	7.8 ± 1.0%.			
Groups	A	B	C	D
	97(53.6%)	55(30.4%)	17(9.4%)	12(6.6%)
Number of Medications	3 Medications		≥ 4 Medications	
	101 (56.4%)		78 (43.6%)	

Data is expressed as mean ± standard deviation and percentages

ketoacidosis of hyperglycemic hyperosmolar state. Among those with hypoglycaemia, the average episodes of hypoglycaemia was 3.7 episodes per patient.

Metformin plus DPP-IV, and Metformin plus sulphonylurea combination were the most common combination used in 80.1% and 59.7%. We found that the combination of Metformin, DPP-IV inhibitors and basal insulin was associated with significantly increased risk of hypoglycaemia compared to other combination occurring in 7/22 (31.8%), $p = 0.035$ (Supplementary table 2).

Table 2 shows Univariable logistic regression analysis for hypoglycemic risk. Diabetes duration was associated with increased risk of hypoglycaemia (OR 1.07, 95% CI 1.00–1.13; $p < 0.036$). Patients on four or more medications were at higher risk for hypoglycaemia compared to those on three medications (OR 3.43, 95% CI 1.42–8.42; $p < 0.007$). Compared to the Qatari nationals, Non-Qatari Arab patients

were at higher risk of hypoglycaemia (OR 4.69, 95% CI 1.30–16.97; $p < 0.018$).

Discussion

This is the first study -to prospectively- follow T2DM patients on a complex regimen of anti-diabetic medications during Ramadan. Despite patients' education and anti-diabetic medications' dose adjustment- according to international (DAR/ADA) guidelines- the incidence of hypoglycemia was relatively high at 16.3%. Most of the study population were on either SU, insulin OR both; and 43.6% were on four or more anti-diabetic medications. There was no difference in the risk of hypoglycaemia between the four pre-specified groups.

The reported rate of hypoglycaemia in this study is higher than that recorded in the CREED study- the largest diabetes

Fig. 1 Anti-diabetic medications frequencies

Fig. 2 Incidence of hypoglycaemia in the pre-defined study groups

study in Ramadan so far [10]. The CREED study reported a hypoglycaemia rate of 7.1% in the cohorts from four different regions; and 4.1% in the cohort from the Middle East. Several factors can explain the high risk of hypoglycaemia reported in our study. Compared to the CREED study; more patients were on insulin (39.8% vs 21.9% respectively) and sulphonylurea (63.0% vs 47.3% respectively). Besides, only 9.5% of the cohort in the CREED study were on three or more anti-diabetic medications [17]. It is critical to note that we have reduced the dose of sulphonylurea by 50% during Ramadan- which is not part of the current recommendations- and the resulting rate of hypoglycaemia would have been probably higher otherwise.

Our study is in tandem with others that showed an increased risk of hypoglycaemia with the increased duration of diabetes [18]. We have shown that the risk of hypoglycaemia was three folds higher in patients on four or more anti-diabetic medication compared to those on three medications only. Most of the hypoglycaemia episodes occurred in the study groups that contained SU, insulin or both. Monotherapy drugs such as metformin, DPP-IV, SGLT-2 and pioglitazone have minimal risk of hypoglycaemia compared to sulphonylurea [14–16, 19–21]. However, in combination during Ramadan,

the risk of hypoglycaemia might be increased. Indeed, we have shown in a subgroup of 16 patients from our cohort utilizing CGMS technology that subclinical hypoglycemia is highly prevalent in such patients [22]. Patients from an Arab background were at higher risk compared to the Qatari population in this cohort. The Qatari population were predominantly females (71.6%) compared to 77% males in the Arab group. The increased risk of hypoglycaemia is likely due to the difference in activity during the fasting hours. In a subgroup analysis of 16 subjects from this cohort, we have shown that active patients during Ramadan have more episodes of hypoglycaemia compared to sedentary patients [22]. The combination of metformin, DPP-IV inhibitors and basal insulin was associated with significantly higher risk of hypoglycaemia compared to other combinations, yet due to the small number in this group, this finding warrants further studying.

The main limitation of our study is the reliance on self-reporting of hypoglycemia in our study group. Besides, no data was available on the incidence of hypoglycaemia before Ramadan. The main strength of the study is a large number of participants and the uniformity of dose adjustments of anti-diabetic medications.

In conclusion; patients with type 2 diabetes, who are on three or more anti-diabetic medications, are at high risk of hypoglycaemia. With the rise in the number of anti-diabetic classes and the global increase in the prevalence of diabetes in countries, more Muslim patients are expected to be on complex anti-diabetes regimen while fasting Ramadan. Despite following the latest DAR-IDF guidelines to adjust the dose of various glucose-lowering therapies the unacceptably high incidence of hypoglycemia calls for a revision of the current guidelines to address patients on multiple anti-diabetic medications. Both healthcare providers and patients with diabetes should factor the increased risk of hypoglycaemia in the

Table 2 Results of Univariable Logistic regression analysis for associations with hypoglycaemia

	Odds ratio	95% CI	P value
Age (years)	1.00	0.96–1.04	0.932
Gender (Males vs females)	0.77	0.33–1.78	0.54
Diabetes duration (years)	1.07	1.00–1.13	0.036
Number of medications (≥ 4 vs 3)	3.43	1.40–8.42	0.007
Arab vs Qatari	4.69	1.30–16.97	0.018
Asian vs Qatari	2.18	0.52–8.97	0.280

decision to fast Ramadan; particularly in those with long standing diabetes. While we cannot recommend any specific medication adjustments, we recommend an individualized approach that considers the mechanisms of action of the anti-diabetic medications and other risks of hypoglycaemia.

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Compliance with ethical standards

Conflict of interest None declared

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