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Ramadan fasting in insulin-treated patients is associated with potentially unfavourable changes in glucose metrics: A flash glucose monitoring (FGM) study

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ABSTRACT

Aim(s): Ramadan fasting (RF) can represent various challenges to glycaemic control especially in insulin-treated patients with diabetes. We aimed to assess the effect of RF on several glucose metrics using flash glucose monitoring (FGM).

Methods: Complete FGM data for 29–30 days before, during and after Ramadan were available for 40 patients with type 1 (n = 13) and type 2 diabetes (n = 27) on insulin (with or without oral hypoglycaemic) treatment. Indicators of mean glucose, glucose variability (GV) and time in different glycaemic ranges were analysed.

Results: RF was associated with increase in time in hyperglycaemia (38.5 ± 18.2 vs 48.7 ± 20.7%; P < 0.001) and decrease in time in hypoglycaemia (3.2 ± 2.8 vs 2.1 ± 2.1%; P = 0.003), and time in target range (56.3 ± 17.2 vs 47.9 ± 19.7%, P < 0.001). There were no significant differences in markers of GV with RF; however, RF was associated with a significant reduction in GV during the day but not night time with an increase in the ensuing non-fasting period.

Conclusions: In insulin-treated patients, RF is associated with an increase in time in hyperglycaemia, a reduced time in target range and nocturnal increase in GV, indicating a need for more refined management algorithms.

1. Introduction

Insulin-treated Ramadan-fasting patients with diabetes present a unique population. Ramadan invokes a state of altered physiology, with daily fast from sunrise to sunset, primarily due to combinatory changes in patterns of feeding, sleeping and physical activity [1–3]. There is much inter-individual variability in different biological parameters due to the geographically-induced differences in fasting hours, cultural influences on dietary habits at *iftar* (sunset meal) and *suhoor* (pre-dawn meal), as well as the nocturnal feeding often involving high-calorie and high-fat consumption [4,5]. In patients with chronic conditions such as diabetes this is further complicated by pharmacokinetics and pharmacodynamics of treatment which may include insulin. The Ramadan fast (RF) has been shown to be associated with a higher risk of complications such as hypoglycaemia and sustained

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hyperglycaemia [6]. Previous CGM studies, including those from our group [7,8] have also shown increased glycaemic variability (GV) with RF. These can potentially lead to a multitude of both acute and chronic complications. Although some of the short-term complications, particularly in high risk groups have been demonstrated over the last few years, the extent, if any, of long-term complications remains unknown [6,7]. Therefore, assessment of glycaemic control parameters in high-risk patient cohorts plays a crucial role in clinical management, primarily aiming at minimizing potential negative health outcomes related to fasting.

Supported by the landmark Diabetes Control and Complications Trial (DCCT) [9] and the UK prospective diabetes study (UKPDS) [10], HbA1c has been routinely used as a treatment target, to monitor glucose control and to assess clinical response to therapeutic interventions. However, many studies suggest that HbA1c does not provide complete and comprehensive information on short-term glycaemic excursions and fluctuations, and is therefore a poor predictor for imminent risks of severe hypoglycaemia [11].

Glycaemic variability, characterized by the amplitude, frequency and duration of glycaemic fluctuations [11,12], plays a central role in diabetes-associated complications such as hyperglycaemia, hypoglycaemia and cardiovascular risk [13–15]. Furthermore, there is now a consensus that GV is a valuable clinical marker of glycaemic control [16,17].

Continuous glucose monitoring (CGM) technologies, such as real-time CGM (rtCGM) and intermittently scanned Continuous Glucose Monitoring (isCGM), also known as Flash Glucose Monitoring (FGM), have facilitated the capability to digitally trace GV and produce continuous patient glucose profiles. This has therefore complemented HbA1c-centred approaches by providing several key glycaemic parameters such as mean glucose (mG), estimated A1c (eA1c), time in target range and in different range of hypo- and hyperglycaemia, to assess glycaemic control [12]. CGM technologies are thus able to provide patients and healthcare professionals with valuable and tangible information in real-time, making it a powerful tool in the management of diabetes.

FGM is a more recent glucose monitoring system which has been gaining popularity among patients. FGM differs from rtCGM [18] in several aspects. In particular, it requires active scanning of the sensor to access glucose data rather than passive display of glucose continuously (updated at 5-minute intervals [19]). FGM is factory-calibrated and the currently used generation does not have an alarm function [20]. Because of its ease of use, it has good patient satisfaction scores [21]. Additionally, FGM has the advantage of extended sensor wear time of 14 days when compared to 7–10 days for rtCGM and data can be stored for up to 90 days [12].

As stated above, patients on insulin therapy are at a particularly high risk of complications with the Ramadan fast. We have therefore adopted FGM technology to compare glucose profiles of patients with diabetes on insulin therapy before, during and after Ramadan fasting periods. We have used different metrics for a detailed assessment of the Ramadan fast in these patients to provide further insight into these potential risks.

2. Research design and methods

2.1. Subjects

Adult (age >18 years) patients with type 1 or type 2 diabetes and on insulin therapy using flash glucose monitoring (FGM-FreeStyle Libre, Abbotts Diagnostics, Illinois, USA) were recruited based on the patient's ability, willingness and intention to fast during the month of Ramadan in 2018 (17 May to 14 June). Exclusion criteria included pregnancy, mental disorders and moderate to severe renal impairment. Patients were recruited from the Imperial College London Diabetes Centre (ICLDC) in Abu Dhabi and ethics approval was obtained from the ICLDC Research Ethics Committee (IREC ref no. 042).

3. Materials and methods

3.1. FGM procedure and glycaemic parameters

3.1.1. Data acquisition

FGM (FreeStyle Libre, Abotts Diagnostics) was used for subcutaneous interstitial glucose monitoring for ≥14 days during each study period: a. 30 days Pre-Ramadan (PR); b. 29 days Ramadan (R) and c. 30 days Post-Ramadan (PoR). Each sensor was inserted at day 0 on the lateral aspect of the left upper arm and removed after 14 days. Two sensors were used per study period. With a sensor value being recorded every 15 min, a total of 96 sensor values were generated per day. Informed consent was obtained and all patients were instructed on the insertion of the FreeStyle Libre sensor and the use of FGM. They were asked to scan the sensor using the reader, at least every 8 h, to guarantee complete data acquisition.

3.1.2. Data processing

Data were pre-processed and analysed following the international consensus recommendations on the use of continuous glucose monitoring [12]. To be included in this study, data points from ≥14 consecutive days during each of the study periods were required with ~70% of FGM data capture. Per patient, one continuous FGM curve containing all daily records was constructed for each of the study periods.

The following parameters were calculated from each FGM curve to asses glycaemic control during (R) and outside Ramadan (PR and PoR) fasting periods using methods previously described [12]: 1. mean glucose, 2. glucose management indicator (GMI), 3. percentage of time in level 1 (<3.9 mmol/L) and level 2 (<3.0 mmol/L) hypoglycaemic range, 4. percentage of time in target range (3.9–10.0 mmol/L), 5. percentage of time in level 1 (>10.0 mmol/L) and level 2 (>13.9 mmol/L) hyperglycaemic range, 6. coefficient of variance (CV), 7. standard deviation (SD), 8. low blood glucose index (LBGI), 9. high blood glucose index (HBGI) and 10. area under the curve (AUC).

The GMI, previously termed estimated A1c (eA1c), is calculated by converting the mean glucose from glucose readings, using the following formula: GMI (mmol/mol) = 12.71 + 4.705 87 × [mean glucose in mmol/L] or GMI (%) = 3.31 + 0.02392 × [

mean glucose in mg/dl] [22]. The coefficient of variance is the SD (standard deviation) divided by the mean. HBGI and LBGI are calculated to measure the frequency and extent of high and low blood glucose readings. The higher the LBGI or HBGI index, the higher the risk of hypoglycaemia or hyperglycaemia respectively.

In order to quantify nocturnal (5 PM to 5 AM) and diurnal (5 AM to 5 PM) GV, the following metrics were calculated: CV, SD, and mean absolute glucose (MAG) [23]. For every patient, the mean of each parameter was calculated for all days included. The results of these time frames were compared to 24 h values.

3.2. *Flash glucose monitoring profiles*

We constructed an average glucose trace for non-Ramadan and Ramadan periods by including all collected days for all patients. By calculating the 50th (median), 25th and 75th (IQR) frequency percentiles of all collected data over multiple days and plotting them according to time (without regard to date - starting and ending at midnight), the 24 h average glucose trace was created.

Data pre-processing, parameters extraction and average glucose trace construction was done in MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States).

3.3. *Statistical analysis*

SPSS 25 software was used for the statistical analysis. Normality of the data was analysed using the Shapiro-Wilk test. As the data were not normally distributed, non-parametric statistics (Mann-Whitney test) were performed to compare Ramadan and non-Ramadan parameters. Statistical significance were considered when P values were $\leq$0.05. Data will be described as mean ± SD unless otherwise stated.

4. Results

Full FGM data was available on 40 patients (mean age = 47.4 ± 11.5 years; BMI = 30.3 ± 5.5 kg/m^2, baseline HbA1c = 7.9 ± 1 .2% (63 ± 13.1 mmol/mol). Thirteen (all male) had type 1 diabetes; twenty-seven (21 male) patients had type 2 diabetes and were on a combination of insulin plus oral hypoglycaemic agents. Baseline characteristics of the study group are listed in Table 1. FGM records interstitial, rather than blood glucose, but for simplicity, the terms “blood glucose” and “interstitial glucose” are used interchangeably when describing FGM-derived data. Fig. 1 shows the median glucose trace for non-Ramadan and Ramadan periods derived from all patients (~3136 days of FGM readings) along with the inter-quartile range-IQR (25%-75%) for: (1) Pre-Ramadan (2) Ramadan fasting and (3) Post-Ramadan. During Ramadan fasting, the FGM curve showed, a small peak (~11 mmol/L) at *suhoor* time (4 AM), stabilization (~10 mmol/L) of BG (9 AM to 1 PM) before a gradual decline (from 10 mmol/L to 7 mmol/L) during the last four hours of fasting (3 PM to 7 PM) which then increased rapidly after *iftar* (~7:15 PM) to 13 mmol/L. During non-fasting periods, the blood glucose dropped overnight to 7 mmol/L at 4 AM before Ramadan, showed a slow rise between breakfast and lunch time followed by a small peak (~10 mmol/L) at dinner time.

4.1. *Changes in glycaemic parameters*

For Ramadan fasting and non-fasting periods, four groups of glucose metrics were calculated and compared (Table 2); 1. Markers of overall glucose control (mean glucose, GMI and AUC), 2. Markers of GV (CV, SD and MAG), 3. Percentage time in different ranges (target, level 1 and level 2 hyper- and hypoglycaemia) and 4. Hyperglycaemia and hypoglycaemia risk HBGI and LBGI). Comparison of various parameters for different periods in type 1 and type 2 diabetes was also made separately (Supplementary Table 1).

4.1.1. *Markers of overall glucose control*

Significant increases were seen in mean glucose (9.5 ± 1.9 vs 10.6 ± 2.2 mmol/L; P < 0.001, Fig. 2A) , GMI (7.4 ± 0.8 vs 7.9 ± 0.9% (57.2 ± 8.9 vs 62.6 ± 10.3 mmol/mol); P < 0.001) and AUC (36.6 ± 7.3 vs 41.2 ± 8.6 mmol*h/L; P < 0.001) during Ramadan with a significant decrease in these parameters one month post-Ramadan without returning to baseline pre-Ramadan values (Table 2).

4.1.2. *Glucose variability (GV)*

Analysis of GV measures over the 24 h periods showed small changes that were only statistically significant for SD and MAG (Table 2). Mean CV pre-Ramadan was 0.37 ± 0.08 with no statistically significant difference during or after Ramadan. There was a statistically significant increase in SD from 3.6 ± 1.1 mmol/L pre-Ramadan to 3.8 ± 1.1 mmol/L in Ramadan (P = 0.004). MAG decreased significantly from 2.1 ± 0.5 mmol/L before Ramadan to 1.9 ± 0.4 mmol/L in Ramadan (P = 0.002); (Fig. 2C, Table 2).

Further analysis with quantification of nocturnal and diurnal glucose variance or SD, MAG and CV revealed a reduction

Table 1 – Study population characteristics.

	N	Male	Age [year]	Weight [Kg]	BMI [Kg/m^2]	HbA1c [%] (mmol/mol)
All	40	34	49.4 ± 11.5	87.5 ± 17.0	30.3 ± 5.5	7.9 ± 1.2 (63 ± 13.1)
Type 1 diabetes (T1D)	13	13	37.2 ± 9.8	82.2 ± 16.0	27.0 ± 4.9	7.6 ± 0.7 (60 ± 7.7)
Type 2 diabetes (T2D)	27	21	55.2 ± 6.7	90.0 ± 17.2	31.9 ± 5.1	8.1 ± 1.3 (65 ± 14.2)

Full FGM data was available on 40 patients; thirteen (all male) had type 1 diabetes; twenty-seven (21 male) patients had type 2 diabetes. Baseline characteristics included mean age, weight, BMI and HbA1c. Data tabulated via SPSS v25.

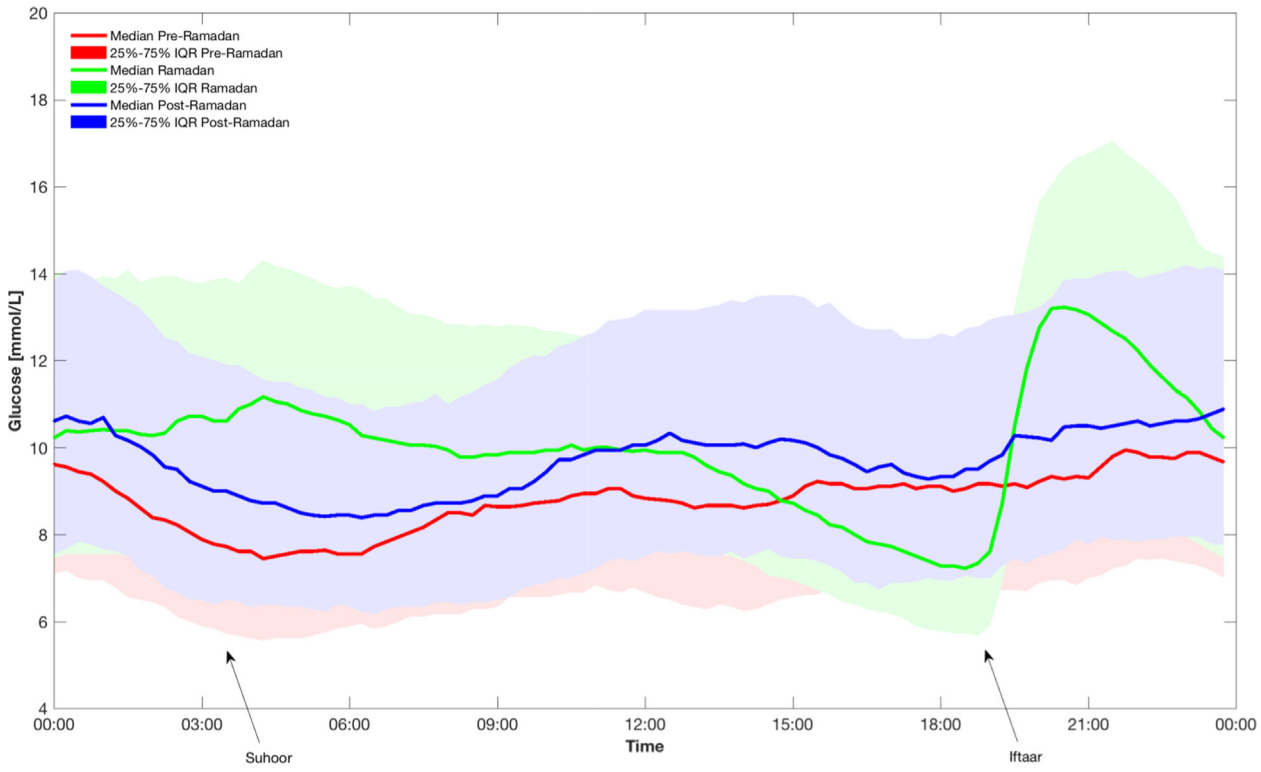

Fig. 1 – Median FGM profiles along with the interquartile range (25–75%) from all participants (~3136 days of FGM readings) during Ramadan and non-Ramadan periods: Pre-Ramadan: red curve and light red shaded area; Ramadan fasting: green curve and light green shaded area; Post-Ramadan: blue curve and light blue shaded area. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2 – Glycaemic parameters during and outside Ramadan in the study population.

	Pre-Ramadan (PR)	Ramadan (R)	Post-Ramadan (PoR)	P-value PR vs R	P-value R vs PoR	P-value PR vs PoR
MG [mmol/l]	9.5 ± 1.9	10.6 ± 2.2	10.0 ± 1.8	<0.001	0.006	0.008
GMI (%)	7.4 ± 0.8	7.9 ± 0.9	7.6 ± 0.8	<0.001	0.006	0.008
GMI [mmol/mol]	57.2 ± 8.9	62.6 ± 10.3	59.8 ± 8.4	<0.001	0.006	0.008
AUC [mmol*h/L]	36.6 ± 7.3	41.2 ± 8.6	38.8 ± 7.4	<0.001	0.007	0.007
CV	0.37 ± 0.08	0.36 ± 0.08	0.36 ± 0.07	0.205	0.908	0.066
SD [mmol/l]	3.6 ± 1.1	3.8 ± 1.1	3.7 ± 1.0	0.004	0.027	0.184
MAG [mmol/l]	2.1 ± 0.5	1.9 ± 0.4	2.0 ± 0.5	0.002	0.250	0.034
TILO1 [%]	3.2 ± 2.8	2.1 ± 2.1	2.4 ± 2.0	0.003	0.230	0.042
TILO2 [%]	1.9 ± 2.5	1.3 ± 2	1.1 ± 1.5	0.094	0.632	0.014
TIR [%]	56.3 ± 17.2	47.9 ± 19.7	51.9 ± 17.9	<0.001	0.033	0.006
TIHI1 [%]	38.5 ± 18.2	48.7 ± 20.7	44.6 ± 18.3	<0.001	0.042	0.002
TIHI2 [%]	13.7 ± 12.9	21.0 ± 16.4	17.1 ± 13.1	<0.001	0.009	<0.001
LBGI	1.3 ± 1.2	0.8 ± 0.9	0.9 ± 0.8	0.012	0.656	0.018
HBGI	9.4 ± 6.0	12.8 ± 7.3	10.9 ± 5.7	<0.001	0.005	0.011

Data are means ± SD. MG: mean glucose; GMI: glucose management index; AUC: area under the curve; CV: coefficient of variance; TILO1: Percentage of time in hypoglycaemia [3.0–3.9 mmol/L]; TILO2: Percentage of time in hypoglycaemia [<3 mmol/L]; TIR: Percentage of time in range [3.9–10.0 mmol/L]; TIHI1: Percentage of time in hyperglycaemia [>10 mmol/L]; TIHI2: Percentage of time in hyperglycaemia [>13.9 mmol/L]; LBGI: low blood glucose index; HBGI: high blood glucose index.

in the assessed GV markers during the day (5 AM-5 PM; 2.7 ± 0.9 vs 2.1 ± 0.7 mmol/L; 2.1 ± 0.6 vs 1.4 ± 0.4 mmol/L; 0.29 ± 0.07 vs 0.21 ± 0.07 respectively) and increase during the night (5 PM-5 AM; 2.7 ± 0.7 vs 3.4 ± 0.9 mmol/L; 1.7 ± 0.6 vs 2.3 ± 0.6 mmol/L; 0.29 ± 0.06 vs 0.31 ± 0.07 respectively) (Fig. 2B and 2C).

4.1.3. *Time in different ranges*

Percentage of time in target range (3.9–10.0 mmol/L) decreased significantly (P < 0.001) from 56.3 ± 17.2% Pre-Ramadan to 47.9 ± 19.7% during Ramadan in all participants and increased significantly (P = 0.033) to 51.9 ± 17.9% one

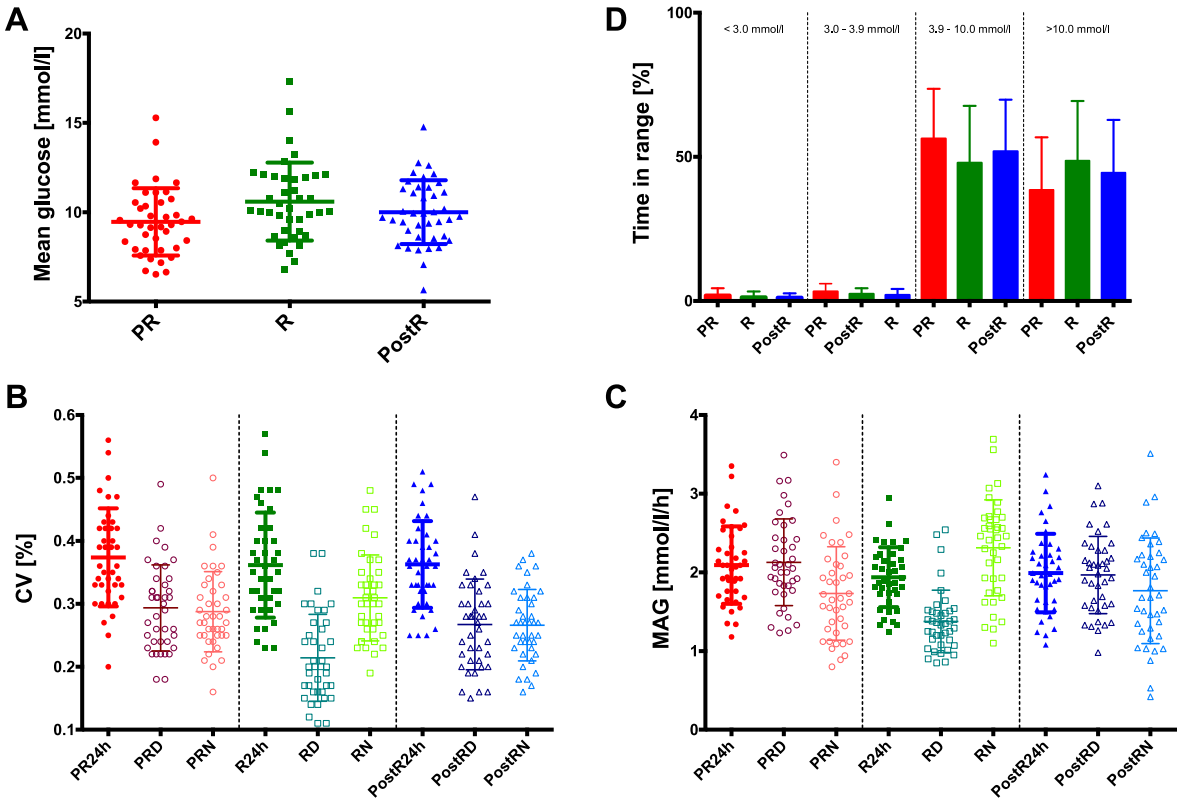

Fig. 2 – Glycaemic parameters extracted from FGM data before (Pre-Ramadan: PR), during (Ramadan: R) and after Ramadan (Post-Ramadan: PostR): A. Mean glucose; B. Coefficient of variance (CV); C. Mean absolute glucose (MAG); D. Percentage of time in different ranges (Time in range). PR24h: Pre-Ramadan 24 h; PRD: Pre-Ramadan day; PRN: Pre-Ramadan night; R24h: Ramadan 24 h; RD: Ramadan day; RN: Ramadan night; PostR24h: Post-Ramadan 24 h; PostRD: Post-Ramadan day; PostRN: Post-Ramadan night.

month after Ramadan but did not return to pre-Ramadan baselines (Table 2, Fig. 2D).

Percentage of time spent in level 1 hypoglycaemia (3.0–3.9 mmol/L) decreased significantly (P = 0.003) during Ramadan from 3.2 ± 2.8% to 2.1 ± 2.1% and increased slightly to 2.4 ± 2.0% but did not return to pre-Ramadan value. No significant changes for level 2 hypoglycaemic range (<3.0 mmol/l) during Ramadan were observed (1.9 ± 2.5 vs 1.3 ± 2.0%).

Percentage of time spent in hyperglycaemia increased significantly during Ramadan from 38.5 ± 18.2% to 48.7 ± 20.7% (P < 0.001) in level 1 hyperglycaemia (>10 mmol/L) and from 13.7 ± 12.9% to 21.0 ± 16.4% (P < 0.001) in level 2 hyperglycaemia (>13.9 mmol/L) but did not return to pre-Ramadan values.

4.1.4. *Hyperglycaemia and hypoglycaemia risk (high- and low- blood glucose index (HBGI and LBGI))*

The risk of hypoglycaemia (LBGI) decreased significantly during Ramadan from 1.3 ± 1.2 to 0.8 ± 0.9 (P = 0.012) with no significant change post-Ramadan. A reverse trend was seen for the risk of hyperglycaemia (HBGI) whereby the value of 9.4 ± 6.0 increased to 12.8 ± 7.3 (P = 0.005) during Ramadan and decreased significantly to 10.9 ± 5.7 (P < 0.001) post-Ramadan.

4.1.5. *Type 1 vs type 2 diabetes*

Trends in markers of overall glucose control were similar in type 1 and type 2 diabetes with increases in mean glucose, GMI and AUC in both groups. However, the values for all parameter for the type 1 diabetes patients did return to pre-Ramadan baselines. Differences were observed between the two groups in some of the other indicators in the context of the Ramadan fast (Supplementary Table 1). Patients with type 1 diabetes showed no significant changes in time in target during the periods studies whereas type 2 diabetes patients show a significant decrease only during Ramadan (59.5 ± 18.5% vs 49.0 ± 22.0%; P < 0.001). In addition, between type 1 and type 2 diabetes patients, there was a significant difference in level 1 (P = 0.005) and level 2 hypoglycaemia (P = 0.031) post-Ramadan. However, no significant difference in hyperglycaemia trends, LBGI and HBGI between type 1 and type 2 diabetes patients were observed during the periods assessed.

5. Discussion

In the current study, we have used large FGM data to generate important parameters indicative of glucose variability as well as hypo- and hyperglycaemia risk during the Ramadan fast. We have also derived robust indicators of overall glucose control including GMI, MAG and AUC for the continuous FGM curve. Importantly, the population studied was of insulin-treated diabetes patients who have been shown to be a higher risk group; more so should they choose to fast against medical and religious advice.

The Holy Quran exempts the sick from fasting Ramadan. Many patients with diabetes, including those on insulin, make a personal decision guided by social, cultural and religious norms, to proceed with the Ramadan fast in spite of this exemption. We have shown that Ramadan fasting, in insulin-treated patients with diabetes, even in a setting guided by best practice guidelines, can lead to adverse changes in markers of glucose variability, overall glucose control and time spent in hyperglycaemia.

Our study showed that Ramadan fasting was associated with statistically significant increases in markers of hyperglycaemia risk, mean glucose and time spent in hyperglycaemic range. There were observed increases in hyperglycaemia risk overall which occurs mostly, but not exclusively, after *iftar* but the risk of hypoglycaemia which is traditionally more of a clinical concern, was notably small even in insulin-treated patients. There was an observed reduction in time spent in target range, time spent in hypoglycaemia and in hypoglycaemia risk. Significant increases were also seen in markers of overall glycaemic control during Ramadan with a significant decrease one month post-Ramadan (Table 2). Both type 1 and type 2 diabetes patients followed the same trend, however the values for all parameters for the type 1 diabetes patients did return to pre-Ramadan baselines.

Previous studies of Ramadan fasting including large questionnaire-based studies have reported increased risk of hypo- and hyperglycaemia in patients with type 1 diabetes compared with type 2 diabetes [6]. Our group has previously reported real world quantitative data demonstrating important differences in glucose profiles [8], excursions [7] and variability during Ramadan fasting and through CGM work established that insulin-treated patients are at a particularly high risk. This is exacerbated in patients with unsatisfactory diabetes control during pre-Ramadan periods, and/or patients poorly compliant with lifestyle recommendations [24].

In recent years, CGM technology has allowed for more objective measurements of glucose fluctuations. However, patient numbers in Ramadan CGM studies have been typically small since the technique is relatively invasive and unwelcome by patients focusing on other aspects of the Ramadan fast. FGM is a more recent, more patient-friendly and less cumbersome technology [25]. It has an extended sensor use of 14 days and can store glucose data for several months, making it better suited for studying Ramadan glucose changes. It is important to note for all studies utilizing this technology that both CGM and FGM measure tissue (interstitial), rather than blood glucose, and that there is a significant lag phase of several minutes between these two. Furthermore, for any time point, there may be a difference between interstitial and blood glucose the magnitude of which depends on blood glucose stability.

Mitigating the risk of hypoglycaemia is one of the priorities for insulin-treated patients with diabetes, who decide to fast, and their treating healthcare professionals. Typical changes in therapy in the context of the Ramadan fast range from judicious use of intermediate or long-acting insulin preparations plus a short-acting insulin administered before meals [26,27] or use of a rapid-acting insulin analogue instead of regular human insulin before meals to reduce hypoglycemia and postprandial glucose excursions [28,29]. Guidelines also suggest daily doses of short-acting insulin secretagogues may be reduced or redistributed to two doses during Ramadan according to meal size [30]. Our data suggest that the magnitude of reduction in insulin dose in anticipation of hypoglycaemia during the fast may be inappropriate. This emphasizes the need for focused pre-Ramadan patient education including advice on dietary and medication issues. Moreover, the findings indicate that current practice in insulin dose adjustments may require further optimization and suggest the need for modified treatment algorithms for this high risk group of patients during the Ramadan fast.

Further detailed analysis of our data highlighted that markers of glucose variability over a 24 h span are little different between Ramadan and non-Ramadan periods. Indeed, the major differences in glucose variability patterns actually occur at different time intervals of the day and night. Glucose variability patterns during daylight hours (5 AM – 5 PM) are different from evening and night-time (5 PM – 5 AM). In part, this is due to falling glucose levels in the last few hours of fasting followed by a carbohydrate-consumption induced glucose rise at *iftar* (Fig. 2). Our current data show this was paralleled by statistically significant changes in markers of glucose variability; reduction during the day and increase during the night. In terms of the consequences of these observations, our study indicated that during Ramadan, time spent in level 1 hypoglycaemia was decreased significantly in all participants and that this increased significantly one month after Ramadan but did not return to pre-Ramadan baselines while level 2 hypoglycaemic ranges showed no significant changes. We also observed that between type 1 and type 2 diabetes patients, there was a significant difference in level 1 and level 2 hypoglycaemia but only during the post-Ramadan period. Patients with type 1 diabetes showed no significant changes in time in target during the periods studied whereas type 2 diabetes patients show a significant decrease only during Ramadan (Table 2). We observed a similar trend in indicators of overall glucose control which were shown to deteriorate during Ramadan; an increase in calculated HbA1c (Glucose Management Indicator - GMI) was noted; although there was a decrease after Ramadan without returning to pre-Ramadan values for the type 2 diabetes patients only. Such detailed observations and differences in glycaemic patterns have significant clinical implications for diabetes patients.

As per consensus guidelines [12], for the analyses, we have included complete data (>=14 consecutive days of data points, >70% of data captured). Thus, our stringent inclusion criteria excluded many women not fasting during menstruation days. It is generally assumed that there is no difference between men and women in physiological aspects of fasting. This assumption may not be strictly valid. Studies on changes in appetite and hunger scores indicate women tend to adapt better as Ramadan progresses with less pronounced hunger by the end of the fasting day and as *iftar* time gets closer. This adaptation does not seem to happen in men to the same extent. As such, caution should be applied when generalizing findings. Nonetheless, whilst the final data analysed came from a relatively small patient number (40 patients from 321 patients recruited) can be seen as a limitation, it is also a true strength of the study due to the robust data collection and analysis.

The current study has generated a large volume of clinically relevant glucose data in a high risk group. It is acknowledged that CGM technology comes with limitations. Nevertheless, our real world data adds to the past body of evidence and can contribute to a positive review of current therapy guidelines for the Ramadan fast. The current study further emphasizes the importance of appropriate changes to medication as well as dietary advice in well-timed pre-Ramadan consultations with trained healthcare professionals. Our findings also indicate that current clinical practice guidelines can incorporate improved insulin schedules, and perhaps more novel therapeutic and technological approaches, to allow more stable glycaemic control during the Ramadan fast.

Author Contributions

IS conducted the research, analysed the data, and contributed to the writing of the manuscript. TA contributed to the structure and interpretation of results, writing and editing of the manuscript. AEL contributed to the analysis of the data, writing and editing of the manuscript. NL designed the research, reviewed and analysed the data, contributed to the writing, and edited the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2020.108592.

REFERENCES

[1] Finch GM, Day JE, Razak DA Welch, Rogers PJ. Appetite changes under free-living conditions during Ramadan fasting. Appetite 1998;31(2):159–70.
[2] BaHammam A, Alrajeh M, Albabtain M, Bahammam S, Sharif M. Circadian pattern of sleep, energy expenditure, and body temperature of young healthy men during the intermittent fasting of Ramadan. Appetite 2010;54(2):426–9.
[3] Lessan N, Saadane I, Alkaf B, Hambly C, Buckley AJ, Finer N, et al. The effects of Ramadan fasting on activity and energy expenditure. Am J Clin Nutr 2018;107(1):54–61.
[4] Maislos M, Abou-Rabiah Y, Zuili I, Iordash S, Shany S. Gorging and plasma HDL-cholesterol–the Ramadan model. Eur J Clin Nutr 1998;52(2):127–30.
[5] Vasan SK, Karol R, Mahendri NV, Arulappan N, Jacob JJ, Thomas N. A prospective assessment of dietary patterns in Muslim subjects with type 2 diabetes who undertake fasting during Ramadan. Indian J Endocrinol Metab 2012;16(4):552–7.
[6] Salti I, Benard E, Detournay B, Bianchi-Biscay M, Le Brigand C, Voinet C, et al. A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. Diabetes Care 2004;27 (10):2306–11.
[7] Lessan N, Hannoun Z, Hasan H, Barakat MT. Glucose excursions and glycaemic control during Ramadan fasting in diabetic patients: insights from continuous glucose monitoring (CGM). Diabetes Metab 2015;41(1):28–36.
[8] Lessan N, Hasan H, Barakat MT. Ramadan fasting: a study of changes in glucose profiles among patients with diabetes using continuous glucose monitoring. Diabetes Care 2012;35 (5):e37.
[9] Diabetes Control and Complications Trial (DCCT): results of feasibility study. The DCCT Research Group. Diabetes Care. 10 (1): 1987; 1-19.
[10] King P, Peacock I, Donnelly R. The UK prospective diabetes study (UKPDS): clinical and therapeutic implications for type 2 diabetes. Br J Clin Pharmacol 1999;48(5):643–8.
[11] Kovatchev BP, Otto E, Cox D, Gonder-Frederick L, Clarke W. Evaluation of a new measure of blood glucose variability in diabetes. Diabetes Care 2006;29(11):2433–8.
[12] Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International consensus on use of continuous glucose monitoring. Diabetes Care 2017;40 (12):1631–40.
[13] Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 2006;295(14):1681–7.
[14] Kovatchev B. Glycemic variability: risk factors, assessment, and control. J Diabetes Sci Technol 2019;13(4):627–35.
[15] Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. Lancet Diabetes Endocrinol 2019;7(3):221–30.
[16] DeVries JH. Glucose variability: where it is important and how to measure it. Diabetes 2013;62(5):1405–8.
[17] Bergenstal RM. Glycemic Variability and Diabetes Complications: Does It Matter? Simply Put, There Are Better Glycemic Markers!. Diabetes Care 2015;38(8):1615–21.
[18] Edelman SV, Argento NB, Pettus J, Hirsch IB. Clinical implications of real-time and intermittently scanned continuous glucose monitoring. Diabetes Care 2018;41 (11):2265–74.
[19] Liebl A, Henrichs HR, Heinemann L, Freckmann G, Biermann E, Thomas A. Continuous glucose monitoring: evidence and consensus statement for clinical use. J Diabetes Sci Technol 2013;7(2):500–19.
[20] Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Flash Glucose-Sensing Technology as a Replacement for Blood Glucose Monitoring for the Management of Insulin-Treated Type 2 Diabetes: a Multicenter. Open-Label Randomized Controlled Trial. Diabetes Ther 2017;8(1):55–73.
[21] Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kroger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-

masked, randomised controlled trial. Lancet 2016;388 (10057):2254–63.
[22] Bergenstal RM, Beck RW, Close KL, Grunberger G, Sacks DB, Kowalski A, et al. Glucose management indicator (GMI): a new term for estimating A1C from continuous glucose monitoring. Diabetes Care 2018;41(11):2275–80.
[23] Service, F.J., G.D. Molnar, J.W. Rosevear, E. Ackerman, L.C. Gatewood, and W.F. Taylor. Mean amplitude of glycemic excursions, a measure of diabetic instability. Diabetes 1970;19(9):644–55.
[24] Monnier L, El Azrak A, Lessan N, Rochd D, Colette C, Bonnet F. Ramadan and diabetes: what we see, learn and understand from continuous glucose monitoring. Diabetes Metab 2015;41 (6):456–62.
[25] Heinemann L, Freckmann G. CGM Versus FGM; or, continuous glucose monitoring is not flash glucose monitoring. J Diabetes Sci Technol 2015;9(5):947–50.
[26] Al-Arouj M, Assaad-Khalil S, Buse J, Fahdil I, Fahmy M, Hafez S, et al. Recommendations for management of diabetes during Ramadan: update 2010. Diabetes Care 2010;33 (8):1895–902.
[27] Al-Arouj M, Bouguerra R, Buse J, Hafez S, Hassanein M, Ibrahim MA, et al. Recommendations for management of diabetes during Ramadan. Diabetes Care 2005;28(9):2305–11.
[28] Mattoo V, Milicevic Z, Malone JK, Schwarzenhofer M, Ekangaki A, Levitt LK, et al. A comparison of insulin lispro Mix25 and human insulin 30/70 in the treatment of type 2 diabetes during Ramadan. Diabetes Res Clin Pract 2003;59 (2):137–43.
[29] Akram J, De Verga V. Insulin lispro (Lys(B28), Pro(B29) in the treatment of diabetes during the fasting month of Ramadan. Ramadan Study Group. Diabet Med 1999;16(10):861–6.
[30] Hassanein M, Al-Arouj M, Hamdy O, Bebakar WMW, Jabbar A, Al-Madani A, et al. Diabetes Res Clin Pract 2017;126:303–16.