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Impact of optimum diabetes care on the safety of fasting in Ramadan in adult patients with type 2 diabetes mellitus on insulin therapy

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ABSTRACT

Aim: We aimed at evaluating the safety of fasting Ramadan for insulin treated type 2 diabetes patients by assessing the biochemical, biometric parameters, flash glucose monitoring (FGM) data as compared to pre-Ramadan and hospital admissions with diabetes or non-diabetes conditions. The risks of fasting between those treated with basal insulin vs intensive insulin during Ramadan was also assessed.

Methods: We included insulin treated patients with type 2 diabetes and we excluded those with co-morbidities. Patients were provided with Ramadan-focused education, FGM before and during Ramadan and medical advice for treatment adjustment. We measured biologic and biometric data before and after Ramadan.

Results: HbA1c reduced from 7.9 ± 1.20 pre-Ramadan to 7.7 ± 1.5% post Ramadan ($p = 0.023$). Average peak glucose reading was 330.1 ± 79.8 mg/dl before Ramadan improved significantly to reach 289.3 ± 77.7 mg/dl ($p = 0.013$). Average number of hypoglycemic episodes was higher in intensive insulin group between 1200 and 1800 h ($p = 0.028$).

Conclusion: People with type 2 diabetes treated with insulin who fast Ramadan and who are provided with Ramadan focused patient education, individualized treatment adjustment and FGMS were not at increased safety risks as measured by biochemical, biometric and FGM data.

1. Introduction

Fasting Ramadan might be associated with an increased risk of hypoglycemia, dehydration and thrombosis in patients with diabetes. The consumption of high-carbohydrate meals during Ramadan puts patients with diabetes at high risk of post-prandial hyperglycemia with or without diabetic ketoacidosis [1].

The IDF-DAR Practical guidelines proposed classifying patients wishing to fast into different risk groups. The

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classification is based upon scientific, clinical and practical considerations, and enjoys religious sanction from the Mofty of Egypt. The guidelines categorized people with diabetes into three risk groups – very high risk, high risk and moderate/low risk [2] Patients with high risk include those with type 2 diabetes mellitus (T2DM) treated with premixed insulin or multiple daily insulin injections. Meanwhile, the IDF-DAR guidelines include people with type 2 diabetes treated with basal insulin at moderate/low level of risk largely based on clinical experience. Patients in very high and high-risk category are advised by the medical and religious authorities not to fast during Ramadan while those in moderate/low risk level can fast if they wish [3]. Nevertheless, according to the EPIDIAR and CREED studies, a large proportion of patients with type 1 diabetes mellitus (T1DM) and (T2DM), irrespective of knowing their risk of diabetic complications, choose to observe the Ramadan fast [4,5]. Moreover, some patients may also choose to fast outside the month of Ramadan [5]. Therefore, medical guidance for these patients needs to be emphasized, especially when they are treated with insulin.

With the knowledge of the previously mentioned risks associated with insulin treatment during Ramadan fasting, it's surprising that only a small number of trials have been performed on patients fasting during Ramadan treated with insulin. We managed to identify ten trials (four randomized, and six observational) in patients with T2DM [6–15]. Three of the trials compared basal insulin to secretagogues [6–8]. One trial studies the safety of short acting insulin [9], while five trials assessed the safety of premixed insulins [10,11,13–15]. Minimal data in these trials relates to the impact of patient education, continuous glucose monitoring. In addition, none of these trials had a comprehensive comparison for pre-Ramadan to during Ramadan period to understand the safety of fasting for people with type 2 diabetes treated with insulin.

Structured patient education has been assessed in many studies. Bravis et al. has evaluated the effect of (READ) educational program on weight and hypoglycemic events during the month of Ramadan for people with type 2 diabetes treated with oral hypoglycemic agents (OHG). The hypoglycemic events were significantly less in the intervention group ($P < 0.001$) [16]. Another study conducted in Abu Dhabi, UAE that included 71 patients with type1 and type2 diabetes, 51 patients were recruited in the intervention group and 13 in the control group. The intervention included two to three diabetes educator and dietician visits. In addition, patients were advised frequent home glucose monitoring. The authors found that structured education is effective reaching glycemic targets and reducing the risk of hypoglycemia in diabetic patients who fast during Ramadan [17].

Many factors influence the use of self-monitoring of blood glucose as part of an optimum diabetes care during Ramadan. The pain and discomfort associated with the finger-stick blood samples along with accumulated trauma to the fingers is a barrier for some patients. Also, intermittent blood glucose monitoring provides only snapshots of glucose concentrations. CGM systems measure interstitial fluid glucose levels at rather closely spaced intervals to provide semi-continuous information on glucose levels, allowing identification and signaling of glucose level fluctuations. While improved glycemic control has been demonstrated with the use of CGM systems; CGM accuracy also remains a challenge and requires calibration to ensure accuracy [18–20]. The new flash glucose monitor (Free style Libre) is different in that it does not require calibration by the user. Data in the use of FGMS during the month of Ramadan is limited. Al Agha et al. have demonstrated that the use of FGMS in children and adolescents with type 1 diabetes is associated with increased number of days fasted, and less life threatening hypoglycemic events during Ramadan [21].

The current study differs from all previous studies in the fact that it included patients with type 2 diabetes on insulin who are willing to fast during the month of Ramadan, which enabled us to understand the risk of fasting, regardless of patient's baseline treatment whether basal plus oral hypoglycemic agents, basal bolus, or premixed insulin. Furthermore, this would be the first trial in patients with type 2 diabetes on insulin to use flash glucose monitoring (FGMS) through the free style Libre sensor, and the first study to compare basal versus intensive insulin groups. The use of the sensor allowed a more in-depth view of hyperglycemia as well as the frequency, duration, and severity of hypoglycemia before and during Ramadan.

2. Methodology

2.1. *Subjects*

This is a prospective interventional trial assessing the safety of fasting in patients with type2 diabetes on insulin, during the month of Ramadan. We included patients 18–75 years of age, with a known diagnosis of type 2 diabetes mellitus, who are using insulin. Those patients were recruited 1–2 months before Ramadan, counselled, and asked to sign an informed consent. Patients with concurrent renal disease, history of ischemic heart disease, Gestational Diabetes, or pregnant ladies were excluded.

3. Aim of the study

3.1. *1ry objectives*

Evaluate the safety of fasting Ramadan for patients with type 2 diabetes treated with insulin by assessing the biochemical parameters as well as flash glucose monitoring data including hypoglycaemia (glucose level < 70 mg/dl with or without symptoms) and hyperglycemia pre-Ramadan compared to during/post Ramadan

3.2. *2ry objectives*

- Severity of hypoglycaemia.
- Admission to hospital with diabetes or non-diabetes related conditions
- Biochemical and biometric parameters including BP, weight, BMI, lipids, renal parameters.
- Breaking fast when hypoglycemic or not.
- Number of days fasted
- Compare the hypoglycemic events in intensive versus basal insulin-treated groups.

3.3. Procedure

We screened patients with type 2 diabetes on insulin 4–6 weeks before Ramadan attending Dubai Hospital of Dubai health authority, diabetes clinic. Those who decided to fast were provided with Ramadan focused patient education for a 60 min (DAR SAFA program). This included information on safe fasting, when to break fasting during Ramadan, education on SMBG and use of glucometer and advice on dietary modifications during Ramadan. Patients were advised to break their fast when blood glucose drops below 70 mg/dl any time during fasting period. Furthermore, all patients were advised by their treating endocrinologist about their required treatment modification according to their own individual needs they were advised to adjust the timing of oral hypoglycemic agents as recommended by DaR-IDF guidelines. The dose and the timing of insulin injections were adjusted and patients were empowered to adjust the doses as per agreed algorithms to reduce the risk of hypoglycemia. Patients who agreed to take part in the study were asked to sign a consent form. Demographic data, baseline biometric data (blood pressure, weight, and BMI) and blood tests for HbA1c, creatinine, urea and electrolytes, eGFR, lipids profile, urinary albumin: creatinine ratio were collected. Detailed history of treatment records as well as history of hospital admission during the previous three months prior to study start were recorded.

During this visit patients were provided with freestyle libre sensors and were educated on how to use the CGM sensor that will be used before and during Ramadan fasting. Furthermore, all patients were given a free access to diabetes educator hot line. Patients were advised to attend during Ramadan to receive the second and third sensor which monitors data during Ramadan.

All patients received a telephone call to reinforce the education points on indications of breaking fasting and dose adjustment if required.

Two to four weeks after Ramadan, biometric and biochemical data were collected and sensor data we downloaded.

4. Ethical approvals

The study has been approved by the ethical committee of Dubai Health authority

5. Funding

This study was funded by a grant from Al-Jalila foundation of Dubai after competing for research grants by the foundation.

5.1. Definitions

According to diabetes and Ramadan guidelines, hypoglycemia was recognized when blood glucose was less than 70 mg/dL with or without symptoms. Severe hypoglycaemia occurred, if the person required third-party assistance or admission to emergency room or hospitalization.

5.2. Data collection and analysis

All data was then entered in 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).

6. Results

Total of 67 patients with type 2 diabetes treated with insulin were recruited to the study. All patients received freestyle flash glucose monitor with three sensors, and all received dedicated Ramadan education and minimum of two diabetes clinic visits during the study period. The mean age was 55.7 ± 9.6 years. Baseline characteristics of group in listed in Table 1.

6.1. Glycemic control

Laboratory HbA1c reduced from 7.9 ± 1.20 pre-Ramadan to 7.7 ± 1.5 percent post Ramadan. This was statistically significant (p = 0.023). For Flash glucose monitoring sensor data, we have set the target glucose in the sensors to be between 70 and 140 mg/dl. Using the sensor data, we were able to determine the percentage of blood glucose above, within and below target range (Fig. 1). The percentage of glucose readings within target range numerically increased from 27.9 ± 18.6 percent before Ramadan to 34.5 ± 21.4 percent during Ramadan (p = 0.098). The percentage of blood glucose readings above targets were numerically lower during the month of Ramadan; the average was 68.5 ± 21.1 percent before Ramadan compared to 60.8 ± 24.7 percent during Ramadan (p = 0.077). Meanwhile, average peak glucose read-

Table 1 – Baseline characteristics.

	Number	(%)
Total number of patients	67	(100%)
Gender	M: F = 1:1	
Mean Age	55.7 ± 9.6	
Medications at baseline		
Basal only	33	49.2%
Premixed insulin and or Basal/bolus	34	50.8%
Metformin	65	97%
SGLT2 inhibitors	34	50.7%
DPP4 inhibitors	46	68.7%
SU	19	28.4%
Pioglitazone	2	2.98%
GLP1 analogues	17	25.4%

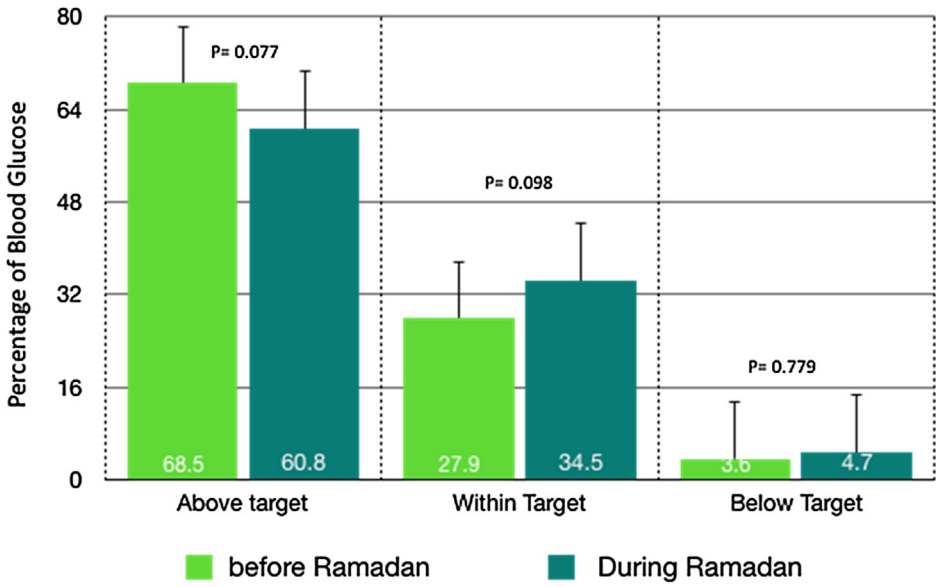

Fig. 1 – Sensor data comparing percentage of blood glucose readings above, within and below targets before and during Ramadan.

ing was 330.1 ± 79.8 mg/dl before Ramadan improved significantly to reach 289.3 ± 77.7 mg/dl (**p = 0.013**).

Similarly, the percentage of blood glucose readings below target was 3.6 ± 5.4 percent before Ramadan, this has numerically increased to reach 4.7 ± 9.9 percent during Ramadan (p = 0.779).

However, the average number of hypoglycemic episodes reduced from an average of 4.3 ± 5.7 episodes before Ramadan to 3.9 ± 4.5 episode during Ramadan (p = 0.729) as well as the duration of hypoglycemia has reduced numerically from an average of 84.4 ± 86.2 min to 71.3 ± 77.6 min during Ramadan (p = 0.344) (see Table 2). Furthermore, the Peak blood glucose during Ramadan was significantly lower when compared to peak glucose readings before Ramadan 289.3 ± 77.7 and 330.1 ± 79.8 respectively (P = 0.013) (see Table 2). It is important to note that these sensor data, were not statistically significant with the exception of peak glucose readings as mentioned above.

Table 2 – Number of hypo events and duration of hypoglycemia recorded in the freestyle Libre.

	Number of hypo events	Average hypo duration
Pre-Ramadan	4.3 ± 5.7	84.4 ± 86.2
Ramadan	3.9 ± 4.5	71.3 ± 77.6
P-value	0.729	0.344

6.2. *Basal vs intensive insulin therapy*

Sensor data for glycemic control parameters during Ramadan between those using basal insulin plus oral hypoglycemic agents were compared to those on intensive insulin therapy defined as the use of premixed insulin or multiple daily injections. The severity, timing, number and duration of hypoglycemic events in each group were shown in (Table 3). The average number of hypoglycemic episodes was significantly higher in intensive insulin group in the period between 1200 and 1800 h **(p = 0.028)**.

Table 3 – Comparison between basal and intensive Insulin therapy with regard to hypoglycemia events and severity.

	Basal (n = 26)	Intensive therapy (n = 23)	P value
Average glucose	182.1 ± 57.6	149.9 ± 35.2	0.0531
Number of hypos	2.4 ± 3.1	5.0 ± 5.4	0.168
Hypo duration (min)	47.0 ± 61.7	86.3 ± 86.9	0.056
Number of hypos <50 mg/dl	0.4 ± 0.8	1.5 ± 2.6	0.185
Number of hypos 50–60 mg/dl	0.8 ± 1.1	1.5 ± 2.1	0.295
Number of hypos 60–70 mg/dl	1.2 ± 1.9	2.0 ± 2.5	0.503
Timing of hypoglycemic events			
06:00–1200	0.3 ± 0.7	0.7 ± 1.5	0.613
12:00–1800	0.8 ± 2.0	2.6 ± 3.7	**0.028**
18:00–2400	0.5 ± 0.9	0.9 ± 1.3	0.253
00:00–0600	0.8 ± 1.4	0.8 ± 1.0	0.495

Table 4 – Shows metabolic changes from before to after Ramadan.

	Before Ramadan	After Ramadan	P-value
HbA1c	7.9 ± 1	7.6 ± 1	0.01
Weight	84.2 ± 11.9	84.2 ± 12.2	0.63
Systolic BP	124.9 ± 18.3	125.6 ± 17	0.954
Diastolic BP	69.1 ± 10	68.9 ± 10.3	0.207
LDL	84.2 ± 30.1	86.4 ± 32.3	0.687
Triglycerides	131.2 ± 58.7	135.4 ± 32.3	0.058
T. Cholesterol	157 ± 36.1	163 ± 39.4	0.602
HDL	49.1 ± 16	49.4 ± 14.3	0.705
Creatinine	0.79 ± 0.24	0.79 ± 0.23	0.180
eGFR	94.4 ± 18.2	94.3 ± 17.8	0.180
Microalbuminuria	74 ± 155.6	54.5 ± 116.5	0.123

6.3. *Biometric and biochemical Parameters:*

The weight did not significantly change from base line to after Ramadan, it dropped from 84.5 + 12.0 to 84.4 + 12.1 kg (p = 0.923). Systolic and diastolic blood pressure before and after Ramadan were not statistically significant (systolic blood pressure before Ramadan was 127.9 ± 17.9 and 127.6 ± 16.7 mmHg after Ramadan p = 0.740; while diastolic blood pressure before Ramadan was 69.0 ± 10.4 and 69.3 ± 9.9 mmHg after Ramadan P = 0.539). Other biochemical data are shown in Table 4.

6.4. *Safety data*

There was no diabetic ketoacidosis (DKA) reported during the whole study period. We did not report any hospital admission with hypoglycemia, hyperglycemia, renal impairment of cardiovascular events.

Stopping the fast when hypoglycemia during Ramadan was implemented by 83% of patients with type 2 diabetes treated with insulin. Average number of days fasted were 29.2 days and 72% of the group fasted for the whole month.

7. Discussion

Our study has proved that optimum care including structured patient education, individualized treatment adjustments, and continuous glucose monitoring using flash glucose monitoring for patients with type2 diabetes who are using insulin is safe. Indeed, this study is the first study to evaluate patients with type2 diabetes on insulin using a flash glucose monitor (Freestyle Libre) as part of an optimum treatment during the month of Ramadan. Overall, there was no worsening of hypoglycemic events nor metabolic or biometric parameters. In fact, the sensor data demonstrated numerical improvement in glucose readings during the month of Ramadan. This indicates that optimum care with Ramadan focused patient education, individualized treatment adjustments and continuous glucose monitoring with flash glucose monitoring can help people with type 2 diabetes treated with insulin to avoid worsening of the diabetes management during Ramadan fasting. Moreover, it's important to remember that this group of patients are considered in various diabetes and Ramadan guidelines as high risk or moderate risk. While this data is encouraging, more studies are required before generalizing the data to all patients with type 2 diabetes treated with insulin.

There was a reduction in the percentage of blood glucose readings above target as well as a significant reduction in the peak glucose values which dropped from 330.1 ± 79.8 mg/dl before to reach 289.3 ± 77.7 mg/dl (**p = 0.013**). Moreover, there was an increase in the percentage of blood glucose readings with in target during Ramadan compared to before Ramadan. These changes in blood glucose have resulted in reduced glucose fluctuations during the day in Ramadan.

On the other hand, the average number of hypoglycemic episodes as well as the duration of hypoglycemia was numerically lower during the month of Ramadan; the change was from an average of 4.3 ± 5.7 episodes before Ramadan to 3.9 ± 4.5 episode during Ramadan, and duration of hypoglycemia from an average of 84.4 ± 86.2 min to 71.3 ± 77.6 min during Ramadan. An explanation would be the ease with which blood glucose is monitored using the freestyle libre that allows for a more frequent and repeated testing. This will allow early detection and treatment of hypoglycemic episodes. The change is between same patient using freestyle libre in both circumstances. In fact, having hypoglycemic events showing tendency towards improvement rather than worsening, is a significant clinical achievement highlighting the importance and benefits of optimum care.

Although hypoglycemic events have reduced in number and duration, many patients did not break their fast (17%). The 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 post-prandial peaks. [21] 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. Indeed, these study needs to be replicated and revalidated to ascertain these results.

None of the trials that assessed patients with type2 diabetes who are using insulin, compared the use of the intensive versus basal insulin. Although this was not an objective in out trial, we compared the risk of hypoglycemia during Ramadan in both basal insulin and intensively treated groups. There was an improvement in glycemic control in our cohort, the HbA1c has dropped from 7.9 + 1.20 to 7.7 + 1.5 percent (p = 0.023). The risk of hypoglycemia between 1200 and 1800 h increased and was statistically significant between the intensive insulin group vs basal insulin. Shahada et al. conducted an open label trial that evaluated the use of basal insulin Levemir and NovoMix 70 in comparison to conventional therapy in insulin treated type 2 diabetes patient. They concluded that the use of Levemir and NovoMix 70 was non-inferior to standard care and was associated with less adverse events [12]. The rest of the studies compared low dose versus high dose premixed insulins [9–11].

Hui E et al. have shown a significant reduction in HbA1c of 0.48% (p = 0.0001) with the use of premixed insulin 50%, whereas low dose combination was associated with an increase in HbA1c of 0.28% [10]. Hassanein et al. in their study compared IDegAsp vs BIAsp 30 and found that, IDegAsp had similar glycemic efficacy to BIAsp 30 before, during and after Ramadan, caused significantly less overall and nocturnal hypoglycemia, and less daytime hypoglycaemia vs BIAsp 30. Both groups have demonstrated significant reductions in HbA1c ; The mean HbA1c values fell from 8.5% at baseline to 7.4% at end of Ramadan and to 7.5% at the end of 4 weeks post-Ramadan in both treatment arms. However, there were no significant differences between treatment groups [15].

This trial has some limitations. Firstly, the intervention in the trial was based on optimum care including diabetes and Ramadan patient education, individualized treatment adjustment and FGM. It is difficult to know how much the impact of every single component of these interventions is. Furthermore, we don't know how much the insulin dose adjustment during Ramadan was. Secondly, as the study did not cover areas were fasting periods exceed 16 h, this data cannot be generalized to regions with significantly longer fasting duration. Thirdly, the number of participants was limited to 67 patients and we will definitely need larger number of patients to consolidate our conclusions and to observe a statistically significant difference pre-Ramadan compared to during Ramadan. Fourthly, the study was not randomized or controlled. However, the aim of the study was to understand and observe the changes that occur during Ramadan and to minimize the risk for such high-risk group. The strengths of this trial included the fact that it is the first trial to use this comprehensive approach in patients with type2 on insulin, moreover, it is the first trial to compare the risks of hypoglycemia in patients using basal insulin compared to intensive therapy.

8. Conclusion

People with type 2 diabetes treated with insulin who fast Ramadan and who are provided with optimum care including Ramadan focused patient education, individualized treatment adjustment and FGMS were not at increased safety risks as measured by biochemical, biometric and flash glucose monitoring data. When compared with intensive insulin therapy basal insulin treated patients have numerically lower risk of hypoglycemia in general, and significantly lower risk of hypoglycemia in the period between 1200 and 1800 h. Further studies are needed to evaluate the safety of Ramadan fasting in high risk groups. Multicenter international trials are required to achieve statistical significance. We also need more studies to assess the accuracy of Flash glucose monitor (FGM) in evaluating glucose levels during Ramadan fasting in both type 1 and type 2 diabetes.

Author contribution

AB: Shared in design, data collection, analysis, writing and reviewing.
AH: Shared in data collection, writing.
FA: Shared in design and review of manuscript.
FA: Data collection, review of manuscript.
MA: Data collection, review of manuscript.
FR: Data collection, review of manuscript.
EA: Review of Manuscript.
FB: Data Collection, review of manuscript.
SA: review of manuscript.
ME: review of manuscript.
MH: Design, data analysis, review of Manuscript.

Conflict of interest

All authors declare no conflict of interest regarding this study.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.01.037.

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