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Invited review

The value of Continuous Glucose Monitoring and Self-Monitoring of Blood Glucose in patients with Gestational Diabetes Mellitus during Ramadan fasting

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ABSTRACT

Introduction: In order to achieve the recommended glycemic control, women with Gestational Diabetes Mellitus (GDM) are instructed to self-monitor blood glucose (SMBG) regularly. The purpose of this study was to evaluate glucose readings provided by Continuous Glucose Monitoring (CGM) and SMBG in GDM patients during Ramadan fasting.

Methods: This is a prospective observational study that recruited GDM patients treated with diet ± metformin were enrolled. They agreed to wear the iPro®2 Professional CGM device and to do SMBG by glucose reading meters, during fasting and after meals. We evaluated the rates of hypoglycemia and hyperglycemia in each approach. The frequency and timing of SMBG was investigated.

Results: Twenty-five patients were recruited. A total of 36,628 readings by CGM device and 408 readings using glucose meters and were captured. Average glucose level was 103 ± 8 mg/dl (5.7 ± 0.4 mmol/l) and 113 ± 14 mg/d (6.28 ± 0.8 mmol/L) on CGM and glucose meters respectively. The rate of hyperglycemia was 5.65% and 14.2% and hypoglycemia was 4.35% and 1.5% using CGM and glucose meters respectively.

While all hypoglycemic episodes occurred between 16:00–19:00 in both approaches, only 38 readings (9%) of SMBG readings were done in that time frame.

Conclusion: Although the frequency of SMBG using glucose meters for women with GDM and fasting Ramadan was acceptable, the timing was not. CGM detected more hypoglycemia and less hyperglycemia than SMBG. Relying on Intermittent SMBG in the management of GDM patients during Ramadan fasting might be misleading.

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1. Introduction

The impact of Ramadan fasting on glucose fluctuations in women with Gestational Diabetes Mellitus (GDM) has not been fully investigated. Eating and sleeping patterns in Ramadan, without food/fluids from dawn to sunset, differ from those during the rest of the year. Consequently, sleep patterns are also disturbed as many fasters wake up pre-dawn for a meal. While glucose levels may improve during early fasting hours, there are serious concerns about the possibility of prolonged periods of hypoglycemia in the late fasting hours and postprandial hyperglycemia during eating hours. Generally, diabetes and Ramadan guidelines advise against fasting for pregnant women with GDM or diabetes [1,2]. However, many insist on fasting despite medical advice [3]. We previously reported that GDM patients treated with diet only or with diet plus metformin have lower mean glucose levels and higher rates of hypoglycemia during fasting the month of Ramadan [4].

There is ample clinical evidence that maintaining strict glycemic control and early treatment with insulin to avoid postprandial hyperglycaemia are highly beneficial in patients with GDM [5]. In order to achieve the recommended tight glycemic control, women with GDM are instructed to self-monitor blood glucose (SMBG) regularly according to their specific needs and glycemic goals. A recently published study found that the actual frequency of glucose monitoring in women with GDM was sub-optimal and that this could be linked to poor pregnancy outcomes [6]. During Ramadan, SMBG timing need to be intensified to prevent and detect any hypoglycemia during the long fasting hours. Yet, this could be difficult at the pre-dawn meal (Suhour) as many GDM patients are asleep and skip checking SMBG post-meal.

New technologies to monitor glucose levels continuously are less invasive and more convenient to patients, however these expensive devices measure the interstitial glucose levels and hence they are not instantaneous and, the accuracy of Continuous Glucose Monitoring (CGM) during fasting has not been properly validated yet.

Benefits of CGM use have been proven in patients with type1 diabetes [7–10], type 2 diabetes [11] and GDM [12–15] patients, however, patients using CGM are still required to measure blood glucose using glucose meters to make treatment decisions.

Intermittent SMBG underestimates the number of hyperglycemic events in patients with GDM. In contrast, CGM may facilitate the detection of all postprandial peaks, includ-

ing those due to unscheduled meals, and thus provide opportunities for better intervention by providing the complete glucose profile [12].

The purpose of this study was to evaluate the frequency and timing of glucose readings provided by CGM and SMBG using Glucose Reading Meters in GDM patients treated with diet or diet plus metformin during Ramadan fasting. Data could lead to more accurate risk stratification and it could help in avoiding significant glucose swings and in timely intensification of treatment whenever indicated.

2. Methods

This is a prospective observational study. The study was approved by our Institutional Research Ethics Committee (CRD517/17 Protocol NO 17-46). Twenty-five GDM patients who insisted on fasting during the month of Ramadan 2017 were recruited from Tawam Gestational Diabetes Program. The diagnosis of GDM was made in the second or third trimesters. Only patients on diet ± metformin were enrolled. All Patients were considered well controlled on their original treatment before Ramadan fasting.

All participants provided written consent to participate. Patients who signed the consent form agreed to wear the iPro®2 Professional (blinded) CGM device for a minimum of three days. This sensor checks the glucose every 10 s, and averages the level every 5 min with a total of 288 readings every 24 h.

All patients were interviewed by their physicians, diabetes educators and nutritionists before fasting. All patients were instructed to check and keep records of their blood glucose using glucose reading meters with a minimum of three, preferably six, times daily. Emphasis was placed on including the late fasting hours of the day (16:00–19:00) as well as the 1 h after the two main meals (Iftar and Sohour). All patients were interviewed after the monitoring period to discuss their experience. Hyperglycemia was defined as glucose level more than 140 mg/dl (7.8 mmol/L), hypoglycemia was defined as glucose level below 70 mg/dl (3.9 mmol/L).

Severity of hypoglycemia during fasting was classified as mild, moderate or severe when glucose levels were 60–69 mg/dl (3.30–3.85 mmol/L), 50–59 mg/dl (2.80 ± 3.25 mmol/L), <50 mg/dl (2.80 mmol/L), respectively.

Data was merged and saved in MS Excel (2010), then uploaded to IBM SPSS (version 20). For data analysis, we used descriptive analysis. For statistical analysis, Kruskal Wallis and Mann-Whitney tests were used to compare percentages

of time spent in normal, high or low BG. A significance level of 0.05 was used throughout.

3. Results

Ramadan 2017, started on May 26th and ended in the evening of June 24th, fasting started from around 04:00am, and ended around 07:00 pm i.e. maximum eating hours were 9 h versus 15 h of fasting. Out of 27 screened patients, one refused participation and was excluded because of misdiagnosis. Twenty-five GDM patients, 14 treated with diet only and 11 treated with diet plus metformin 500 mg bid, were recruited. Mean age 31 ± 3.8 , mean BMI $29.3 \pm 4\%$, parity 2.3 (0–10), personal history of GDM was present in 12 patients (48%) and diabetes family history in 15 patients (60%). Mean monitoring period was 5.1 ± 0.4 days. Glucose level <70 mg was noted in 56% of patients (50% for the diet only group and 63% for the metformin group). All hypoglycemic episodes occurred between 16:00–19:00.

Patients in our cohort had a total of 36,628 glucose readings using the CGM device, averaging 288 readings/patient/day, and 408 SMBG readings using glucose meters, averaging 4 ± 0.8 readings/patient/day.

The average glucose level was 103 ± 8 mg/dl (5.7 ± 0.4 mmol/l) and 113 ± 14 mg/d (6.28 ± 0.8 mmol/L) by CGM and SMBG respectively, $p < 0.0001$. 90% and 84.3% of glucose level readings were normal using CGM and SMBG respectively (Table 1). The rate of hyperglycemia was 5.65% using CGM and 14.2% by SMBG.

Hyperglycemia analysis shows that 4.8% of all CGM readings were in the range of 140 (7.8 mmol/L)–180 mg/dl (10 mmol/L) and the rate of glucose >180 mg/dl (10 mmol/L) was $<1\%$. In contrast, for SMBG 12.2% of all readings were between 140 (7.8 mmol/L) and 180 mg/dl (10 mmol/L) and the percentage of glucose of >180 mg/dl (10 mmol/L) was 2.0% (Table 2).

The rate of hypoglycemia using CGM and SMBG was (4.35% and 1.5%, respectively; $p 0.004$) (Table 1). Analysis of glucose levels during hypoglycemia measured by CGM showed that 65%, 14% and 21% were mild, moderate and severe, respectively. In contrast, 100% of low blood glucose readings captured by SMBG using glucose meters were between 60 and 69 mg/dl (3.30–3.85 mmol/L) (Table 3).

Finally, we evaluated the timing of blood glucose readings provided SMBG. Only 38 readings (9%) of SMBG readings were done in the late fasting hours of the day (16:00–19:00), compared to 244 readings (60%) readings between (19:00–04:00) and 126 readings (31%) between (04:00–16:00).

Table 2 – Frequency and severity of hypoglycemia.

Glucose Level	CGM	SMBG
<70 mg/dl (3.9 mmol/L)	4.35%	1.5%
Mild hypoglycemia 60–69 mg/dl (3.30–3.85 mmol/L)	65%	100%
Moderate hypoglycemia 50–59 mg/dl (2.80–3.25 mmol/L)	14%	0
Severe hypoglycemia < 50 mg/dl (2.80 mmol/L)	21%	0

Table 3 – Frequency and severity of hyperglycemia.

Glucose Level	CGM	SMBG
>140 mg/dl (7.7 mmol/L)	5.65%	14.2%
140–180 mg/dl (7.7–10 mmol/L)	4.8%	12.2%
>180 mg/dl (10 mmol/L)	0.85%	2%

4. Discussion

Glucose monitoring is essential in both the long term and “real time” management of patients with Gestational Diabetes Mellitus (GDM). Current treatment guidelines recommend that fasting blood glucose should not exceed 95 mg/dl (5.3 mmol/L) and the one-hour postprandial level not to exceed 140 mg/dl (7.8 mmol/L). Medical treatment is indicated when patients do not achieve targets while on diet therapy [16].

Many Muslim ladies with GDM insist on fasting Ramadan against medical advice. In a previous study, we found that 59% of women with GDM treated with metformin or insulin, insisted on fasting [3]. While blood glucose levels may improve during early fasting hours, there are serious concerns about the possibilities of having long episodes of hypoglycemia during the late(r) fasting hours and postprandial hyperglycemia that might persists during and after eating hours [4].

Hence, diabetes and Ramadan guidelines categorize Ramadan fasting in women with diabetes or gestational diabetes as very high risk and advise against it [1,2,17]. However,

Table 1 – Glycemic levels by CGM and SMBG.

	CGM	SMBG	P value
Total readings	36,628	408	
Average Glucose Level	103 ± 8 mg/dl (5.7 ± 0.4 mmol/l)	113 ± 14 mg/d (6.28 ± 0.8 mmol/L)	<0.0001
Hypoglycemia Glucose below 70 mg/dl (3.9 mmol/L)	4.35%	1.5%	$P = 0.004$
Normoglycemia	90%	84.3%	0.0001
Hyperglycemia Glucose more than 140 mg/dl (7.8 mmol/L)	5.65%	14.2%	<0.0001

this seems not to be strictly enforced by healthcare professionals and many pregnant women with diabetes are not clear whether to fast or not [18].

Yogev et al. have shown that pregnant women seem to have up to 20% lower blood glucose level than non-pregnant women without having symptoms of hypoglycemia [19]. This is further supported by CGM study comparing blood glucose levels in non-pregnant with those in pregnant women. Surprisingly, those data showed that blood glucose levels below 60 mg/dl were common, both among non-diabetics and diabetic gestational women, but such levels of hypoglycemia were not seen in non-pregnant women [20]. In contrast, A Study from Al-Ain city on pregnant women without diabetes or GDM showed that the mean random blood glucose level after 1 h of breaking the fast was significantly higher in the Ramadan fasting group than in the nonfasting control group, and this was not affected by the number of fasting days. There was no significant difference in the fasting blood glucose level [21]. Similarly, Kiziltan et al. observed no significant changes in fasting glucose levels in Turkish pregnant women fasting for Ramadan. However, changes in postprandial glucose levels, when levels are expected to be highest; were not investigated in that study [22].

Here, we report that 56% of our patients had at least one episode of glucose below 70 mg/dl. All of these episodes were presumably asymptomatic and occurred between 16.00 and 19.00 h which are the last three hours of fasting. CGM detected almost 3 times the rates of hypoglycemia by SMBG. This reflects the low rate of readings during these times despite being advised to do so during the pre-Ramadan visit, as only 9% of SMBG were carried out during that time. It is possible that GDM patients treated with diet ± metformin were much more concerned about postprandial hyperglycemia than with hypoglycemia as 60% of SMBG readings were performed during eating hours (19.00–04.00).

The severity of hypoglycemic episodes is of concern as 14% of the hypoglycemic episodes were between 50 and 59 mg/dl and 21% were below 50 mg/dl and all of these episodes were asymptomatic. As mentioned above, mild rates of hypoglycemia are commonly seen in pregnant women with or without diabetes.

This is the first reported data of glucose levels <50 mg/dl in GDM patients. It is not clear whether this is a result of long fasting hours in our cohort or inaccuracy of CGM data during fasting due to mild dehydration affecting the accuracy of interstitial glucose levels. Consequently, such data should be validated using SMBG.

CGM in routine care of GDM is not recommended, and, the accuracy of these data during fasting is not yet confirmed. If, confirmed, then CGM could improve our understanding of the impact of Ramadan fasting in women with GDM. Specifically, such data could help to better compare fasting and non-fasting blood glucose level during Ramadan and thus empower GDM patients to break their fast when hypoglycemic and prevent postprandial hyperglycemia with diet or treatment modifications.

Our patients did not regularly perform SMBG during the late fasting hours, thereby masking the incidence of frequent hypoglycemia and instead focused more on their post prandial readings, thus exaggerating the incidence of hyper-

glycemia. This indicates the need to reinforce the message to GDM patients who insist on fasting to be aware of the possibility of hypoglycemia while fasting and the need to check between 16.00 and 19.00 h to detect and interrupt hypoglycemia.

Our data show that relying on SMBG in the management of GDM patient fasting Ramadan might be misleading to both patients and physicians, and give rise to incorrect patient classifications and delays in necessary treatment.

5. Conclusion

CGM detected much more episodes of hypoglycemia and less hyperglycemia than SMBG in GDM patients during Ramadan fasting. SMBG timing during fasting seems to focus more on times to detect postprandial hyperglycemia than on times to detect and prevent hypoglycemia. Relying on intermittent SMBG in the management of GDM patients during Ramadan fasting might be misleading. The accuracy of CGM data during Ramadan fasting need to be further studied.

6. Author's contributions

B.A. Planned and submitted study for approval, interviewed and recruited patients, researched data, wrote and revised manuscript.

M.H. Planned study, researched data, wrote and revised manuscript.

S.R. Recruited and followed patients, obtained consents, contributed to discussion.

N.N. Analyzed data, edited manuscript.

Acknowledgment

BA takes full responsibility for the work.

This material has not been published previously and is not under consideration for publication elsewhere.

The authors have no relevant conflict of interest to disclose.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.diabres.2019.01.036>.

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