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Diabetes and Ramadan: Utility of flash-glucose monitoring derived markers of glycaemic control and comparison with glycosylated haemoglobin

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ABSTRACT

Aims: Flash glucose monitoring (FGM)-derived markers of glucose control and variability and laboratory measured HbA1c among patients with diabetes on insulin in context of Ramadan fasting (RF) were examined and compared.

Methods: FGM data on insulin-treated patients (n = 20, age 42.3 ± 11.4 years; 18 male, 2 female; 13 with type 1 and 7 with type 2 diabetes) who fasted during Ramadan were used to calculate Q-score as an indicator of glycaemia before, during and after RF. Post-hoc analysis in a group of patients (n = 12) who had HbA1c available and appropriate for these periods was performed. Other relevant data were extracted from patient records.

Results: Mean glucose (9.6 ± 1.32 v 10.78 ± 1.64 mmol/l; P < 0.0001) and Q-score increased significantly with Ramadan fasting and reduced after Ramadan. Post-hoc subgroup analysis showed a significant rise in eA1c (7.2 ± 0.4%; 55.0 ± 4.4 mmol/mol v 7.7 ± 0.5%; 61.0 ± 5.5 mmol/mol) but not in laboratory HbA1c with Ramadan fasting; eA1c reduced after Ramadan (P = 0.018).

Conclusions: Ramadan fasting was associated with a deterioration in overall glucose control and time in hyperglycaemia in insulin-treated patients. FGM-derived markers are useful and a preferable alternative to HbA1c in Ramadan studies.

1. Introduction

The Ramadan fast entails abstinence from eating and drinking between dawn and sunset for a whole month. Main meals -typically two- are taken between sunset and dawn. As such, the Ramadan fast represents a major shift from normal meal patterns [1]. This fundamental change also involves food content, activity, and sleep-wakefulness cycle. For individuals with diabetes, these pose challenges as the normally recommended five meals a day eating schedule [2] cannot be followed. Instead, the typical meal frequency during Ramadan will be two or three main meals [3], taken between sunset and dawn (Fig. 1). As no food can be taken during day time, there are further challenges to medication timing and dose. Drug regimens that are designed to provide adequate glycaemic control for normal non-Ramadan days will have to be adapted to the fundamentally different glucose patterns during Ramadan.

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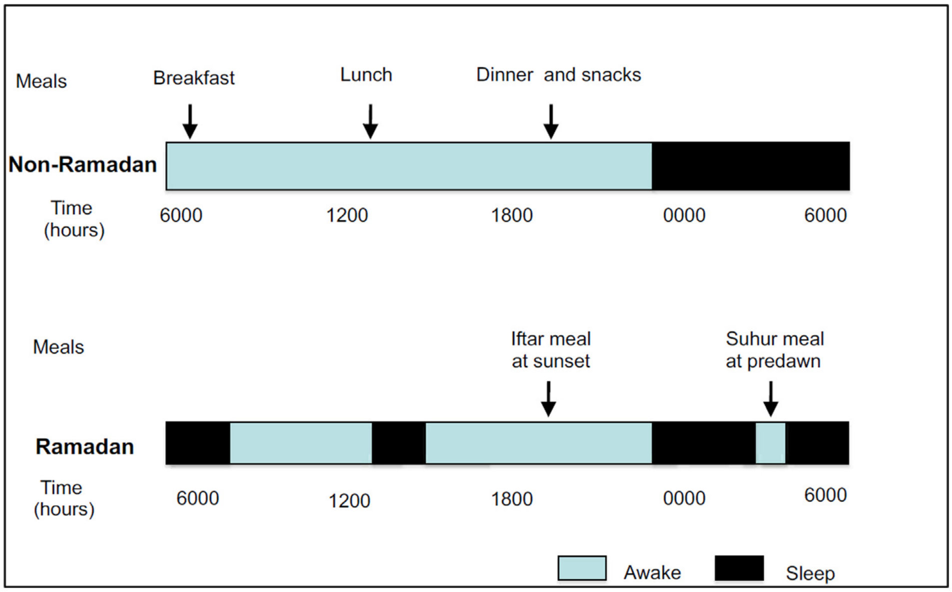

Fig. 1 – Comparison of sleep and meal patterns during Ramadan and non-Ramadan periods.

1.1. *Ramadan challenges in patients with diabetes*

For people with diabetes, the Ramadan fast has been shown to be associated with an increase in hypoglycaemia risk [4,5], mostly during the fasting hours, and hyperglycaemia risk which is most likely to occur in the evening and after the fast is broken [6] at *iftar* time. The EPIDIAR study [7] reported a 4.7 fold increase in severe hypoglycaemic events and a 3.2 fold increase in hyperglycaemic events in patients with type 1 diabetes who fasted during Ramadan. In type 2 diabetes, the increase in hypo-and hyperglycaemia events were even higher at 7.5 and 5-fold respectively.

1.2. *Measuring glycaemic control during Ramadan*

Assessing glycaemic control in the context of the Ramadan fast is not straightforward however; adequate glycaemic control should encompass optimal fasting as well as post-prandial glucose. Hypoglycaemia risk should ideally be negligible; hyperglycaemia should be minimised, glucose fluctuations should also be within acceptable limits, and overall glycaemic control has to be within targets. Glycosylated haemoglobin (HbA1c) is the most widely used and practical method of assessing glycaemic control [8,9]; accepted targets (outside Ramadan) are $\leq 7\%$, or $\leq 6.5\%$ if achievable without hypoglycaemia [10,11]. HbA1c is also used for monitoring changes in glycaemic control over periods of a few months to years. HbA1c reflects cumulative glycaemia history for the two to three months' time periods [12] which in the context of Ramadan can be more problematic as it will be difficult to separate the glycaemic changes that occur only due to, and during, Ramadan alone.

Nonetheless, HbA1c has been used in the context of the Ramadan fast in several previous studies [11,13] with variable changes reported. Other studies have used fructosamine [14] to assess glycaemic change during Ramadan. Fructosamine is a reflection of glycaemic control over the previous 2–3 weeks, and as such, it may be a preferable monitoring tool in the context of Ramadan. Fructosamine has different properties and limitations however, and can be greatly influenced by certain physiological and pathological conditions. For instance, any clinical condition that affects protein metabolism (e.g. nephrotic syndrome, thyroid disorders, decreased protein production) may alter the results [15]. Other techniques including continuous glucose monitoring (CGM) have also been used in this context by several groups [16–18], including ours [19] and have shown major changes in overall glucose profiles. CGM has the major advantage of giving a reflection on not only an overall mean, but also of glucose fluctuations, including hypo-and hyperglycaemic excursions. The CGM sensor records interstitial glucose every five minutes over periods of few days up to two weeks [20]. Although CGM is minimally invasive, our group and others found its acceptability, even in a research setting to be poor by patients practising the Ramadan fast. Flash glucose monitoring (FGM) is a newer technique. It is also minimally invasive, but has a simpler sensor insertion technique, making it more convenient acceptable for patients. [21]. It records interstitial glucose values every 15 min, and provides captured data that can be stored for several months. It is a technique better suited for clinical and research use [22] in the context of the Ramadan fast.

1.3. *Ramadan and glycaemic control in Insulin-treated patients*

Previous studies [23,24], including ours [19], show that insulin treated patients with diabetes have the poorest overall control and are at high risk of dysglycaemia during the Ramadan fast. However, the numbers of insulin-treated patients in CGM studies have been small and further elucidation of the nature and extent of the problem is warranted.

1.4. Study Aims

In the current prospective study, we have used FGM to investigate changes in overall glycaemic control in insulin treated patients with type 1 and type 2 diabetes. We have used FGM data to calculate relevant indicators of glycaemic control. In particular, we have computed estimated A1c (eA1c), otherwise known as glucose management index (GMI) [25] and Q-score [26] as previously described.

2. Subjects

2.1. Study population

Adult (age > 18 years) patients with type 1 and type 2 diabetes on insulin using flash glucose monitoring (FGM) and intending to fast during Ramadan who were able and willing to take part in the study were recruited from the Imperial College London Diabetes Centre (ICLDC) in Abu Dhabi. Exclusion criteria included pregnancy, mental disorders and significant medical condition(s) interfering with study protocol. Ethical approval was obtained from the ICLDC Research Ethics Committee (IREC-042). Relevant demographic and laboratory data on patients were extracted from their electronic records.

3. Materials and methods

This study was conducted around Ramadan 1439 in the Islamic calendar (May 17th-June 14th 2018). Patients were recruited from the out-patient clinic at the Imperial College London Diabetes Centre. Study commenced in March 2018, and continued until July 2018. Patients currently using FGM and intending to fast during Ramadan were invited to take part in the study. Written informed consent was obtained.

3.1. FGM protocol

FGM (FreeStyle Libre, Abbott, Lake Bluff, Illinois, United States) was used as per manufacturer's instructions and as previously described [27]. Patients were trained on appropriate use of FGM device and sensor use. In particular, they were asked to use the FGM reader a minimum of three times per 24 h period and that this should include a reading prior to bed time.

Subcutaneous interstitial glucose monitoring for a minimum of 14 days during each measurement period: 1. Pre-Ramadan (PR); 2. Ramadan (R); 3. Post-Ramadan (PoR). Each sensor was inserted 5 mm subcutaneously at the upper arm at day 0 and removed after 14 days. Patients were asked to scan the sensor, using the reader, generating a daily record of 96 sensor values for every measurement period of 29 (R) to 30 (PR and PoR) days.

3.1.1. Data procurement and processing

Data were pre-processed and analysed following the international ATTD consensus recommendations on use of continuous glucose monitoring [28]. A minimum of 14 consecutive days of data with approximately 70% of FGM readings were required to be included, for each measurement period. Estimated A1c (eA1c), otherwise known as glucose management index (GMI), was calculated by converting the mean glucose from glucose readings, using the following formula: eA1c (mmol/mol) = 12.71 + 4.70587 × [mean glucose in mmol/L] or eA1c (%) = 3.31 + 0.002392 × [mean glucose in mg/dl] [29]. Data pre-processing and parameters extraction was done in MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States).

FGM measures interstitial glucose (IG) with a record every 15 min, which correlates well with blood glucose with a lag phase of around 15 min. Although IG and BG are distinct with differences which may depend on various factors including rate of change in blood glucose, for simplicity, interstitial and blood glucose are used interchangeably henceforth.

3.1.2. Q-Score

The Q-score is a new patient-tailored approach for the routine clinical evaluation of CGM profiles. It allows screening for profiles that require therapeutic action and a method to identify the individual CGM parameters with improvement potential. It is calculated based on mean blood glucose (MBG), range (maximum-minimum blood glucose), duration of time in hypo- (<3.9 mmol/l) and hyperglycaemia (>8.9 mmol/l) and mean of daily difference (MODD) [26].

3.1.3. Post-hoc analysis of paired HbA1c and FGM data

Triplicate HbA1c data pertaining to pre-Ramadan, Ramadan and post-Ramadan periods were available on 12 patients and were analysed post-hoc. In order for measured HbA1c to be the best reflection of glycation during the periods of interests, HbA1c measured during the following periods were included: 1. Pre-Ramadan: 16/3/2018 to 15/5/2018; 2. Ramadan: 16/6/2018 to 15/8/2018; 3. Post-Ramadan: 16/9/2018 to 15/10/2018 (Supplementary Fig. 1: HbA1C Measurements Pre-, During and Post-Ramadan). Comparison of HbA1c with corresponding FGM-derived eA1c for (pre-Ramadan, Ramadan and post-Ramadan) each one-month block was made. HbA1c and eA1c for each of these periods were also compared.

3.2. Statistical analysis

SPSS 25 software was used for the statistical analysis. Non-parametric statistics (Mann-Whitney test) was performed to compare Ramadan and non-Ramadan parameters.

All patients (type 1 or type 2 diabetes) were on multiple insulin injections daily; treatment included other hypoglycaemic agents in patients with type 2 diabetes. Demographic, biochemical and haematological data relevant to the study, including laboratory-measured HbA1c data for specific pre- and post-Ramadan periods were extracted from patients' electronic records.

FGM data were downloaded at multiple time intervals. Data were used to calculate eA1c for specific target periods of one month before, during, and one month after Ramadan. Patients that missed fasting for >4 days, had <14 consecutive days of data, had below the minimum mark of FGM readings (<70% captured data), and did not have HbA1c measured for every period, were excluded. The HbA1c inclusion procedure is shown in Supplementary Fig. 2. We calculated the eA1c for the three periods studied and compared it to the laboratory-measured HbA1c. For comparison, laboratory-measured HbA1c data for specific pre- and post-Ramadan periods were extracted from patient records.

4. Results

FGM data were available on 20 patients (18 male, 2 female; age 42.3 ± 11.4 years, BMI 28.9 ± 5.3 kg/m^2). Female patients were under-represented since women are exempt from fasting during their menstrual periods and data during non-fasting days would need to be excluded. All patients were on insulin treatment. Treatment in patients with type 2 diabetes (n = 7) also included oral hypoglycaemic agents. Dose adjustments for Ramadan fasting period were made by the attending physicians and followed IDF/DaR guidelines.

4.1. Q-score

Baseline Q-score was 22.86 ± 4.49, indicative of inadequate overall glycaemic control in the study population (Table 1). The Q-score increased significantly (P < 0.003) to 25.07 ± 4.40 during Ramadan. This was followed by a significant (p < 0.002) reduction to 22.69 ± 4.38 after Ramadan (Fig. 2). There was no significant difference in Q-score between pre- and post-Ramadan values (P = 0.758). A Q score of < 4 is indicative of very good control, whereas a score > 20 indicates bad glucose control. Q scores between 4 and 12 indicate good to fair control. Q score is calculated using the following formula:

$$Q-Score = 8 + \frac{MBG - 7.8}{1.7} + \frac{range - 7.5}{2.9} + \frac{t_{G<3.9} - 0.6}{1.2} + \frac{t_{G>8.9} - 6.2}{5.7} + \frac{MODD - 1.8}{0.9}$$

where:

MBG = mean blood glucose

Range = glucose range

t_G = time outside glucose target range (below 3.9 mmol/l and above 8.9 mmol/l)

MODD = mean of daily differences

4.2. Post-hoc analysis: eA1c vs HbA1c

Data were available on 12 patients on insulin (5 with type 1, and 7 with type 2 diabetes, 9 male, 3 female; age = 46.1 ± 13.0 years; BMI = 31.5 ± 5.8 kg/m^2) and were included in further analysis (Table 1, Fig. 3). Compared to pre-Ramadan value (7.2 ± 0.4%; 55.0 ± 4.4 mmol/mol), eA1c showed a significant (P = 0.000) increase to 7.7 ± 0.5% (61.0 ± 5.5 mmol/mol) followed by a reduction to 7.4 ± 0.6% (57.0 ± 6.6 mmol/mol) in the month post-Ramadan (P = 0.018). In contrast, there was no significant change in measured HbA1c between pre-Ramadan (7.8 ± 0.6%; 62.0 ± 6.6 mmol/mol), Ramadan (8.0 ± 0.9%; 64.0 ± 9.8 mmol/mol) and post-Ramadan (8.1 ± 1.1%; 65.0 ± 12.0 mmol/mol) values.

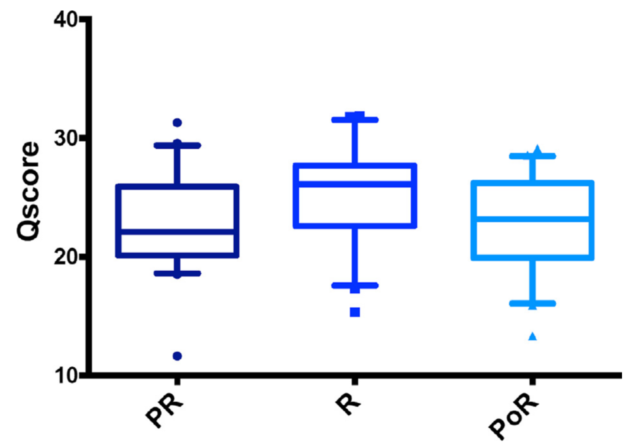

Fig. 2 – Q-score as an indicator of glycaemia pre-, during and post-Ramadan. PR = pre-Ramadan; R = Ramadan; PoR = post-Ramadan. A Q-score of < 4 is indicative of very good control, whereas a score > 20 indicates poor glucose control. Q-scores between 4 and 12 indicate good to fair control [26]

5. Discussion

Fasting has been reported to have benefits for healthy individuals. It is also of health benefits in several disease states. It is thought to be a safe practice, certainly in the short term, for most patients with diabetes, and may indeed have beneficial effects to some parameters such as weight.

Table 1 – . Changes in laboratory-measured HbA1c and Flash glucose monitoring-derived glycaemic control markers in the context of the Ramadan fast.

	N	Pre-Ramadan	Ramadan	Post-Ramadan	P-value	P-value	P-value
					PR vs R	R vs PoR	PR vs PoR
Mean glucose (mmol/l)	20	9.60 ± 1.32	10.78 ± 1.64	9.73 ± 1.41	0.000	0.000	0.489
Q-Score	20	22.86 ± 4.49	25.07 ± 4.40	22.69 ± 4.38	0.003	0.002	0.758
eA1c (%)	12	7.2 ± 0.4	7.7 ± 0.5	7.4 ± 0.6	0.000	0.018	0.272
eA1c (mmol/mol)	12	55.0 ± 4.4	61.0 ± 5.5	57.0 ± 6.6	N/A	N/A	N/A
HbA1c (%)	12	7.8 ± 0.6	8.0 ± 0.9	8.1 ± 1.1	0.402	0.43	0.308
HbA1c (mmol/ml)	12	62.0 ± 6.6	64.0 ± 9.8	65.0 ± 12.0	N/A	N/A	N/A

Q-score [26] is a marker of overall glycaemic control and was calculated from FGM data; values < 4 indicate good control, whereas a Q-score > 20 is indicative of bad control. PR = Pre-Ramadan; R = Ramadan; PoR = Post-Ramadan; BMI = body mass index; eA1c = estimated A1c; HbA1c = glycated haemoglobin.

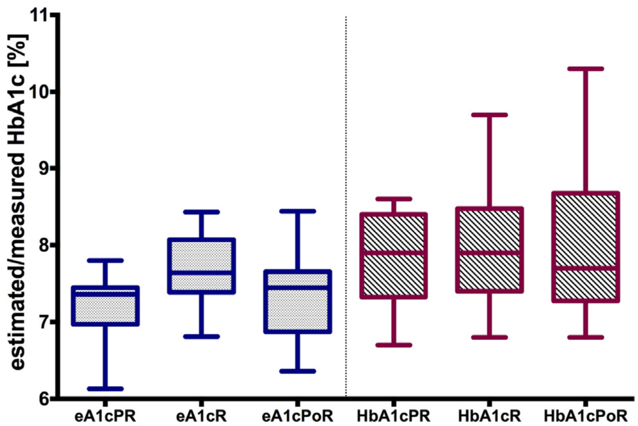

Fig. 3 – Comparison of estimated A1c (eA1c) and measured HbA1c before, during and after Ramadan. PR = pre-Ramadan; R = Ramadan; PoR = post-Ramadan.

Studying health outcomes in the context of Ramadan fasting has major challenges. Ramadan is a holy and spiritual time for those who practice the Ramadan fast and this sanctity has to be understood and respected by researchers exploring its effects on various parameters including glycaemic control. The latter is of major importance with health implications both clinically, and also in the research setting. Measuring glycaemic control and monitoring its trends around the month of Ramadan is an issue worthy of specific attention. Traditional markers of glycaemic control including HbA1c have been used in exploring Ramadan changes and have reported conflicting results with some showing glycaemic control worsening [30] and others reporting that it remains unchanged during, or soon after, Ramadan fasting [31]. Although differences in cultures and the populations studies may in part explain these variable results, we have demonstrated potential problems of using glycosylated haemoglobin in the context of Ramadan research and discourage such use. Self-monitoring of blood glucose (SMBG), is an irreplaceable useful tool for effective glycaemic monitoring [32]; however a considerable number of hypoglycaemic and hyperglycaemic events can be missed with SMBG [33]. Continuous glucose monitoring (CGM) is a valuable tool for assessing glycaemic excursion assessment [34–37] and has been used during Ramadan demonstrating major changes in glycaemic profiles and variability [19]. However, its acceptability during the Ramadan fast, even in the research setting is low.

In the current study we have used FGM data to investigate glucose changes in a group of patients with type 1 diabetes and insulin treated patients with type 2 diabetes. This is a group identified as high risk by the DaR/IDF Ramadan guidelines. FGM has its own limitations and it is well-known that FGM and simultaneous capillary blood glucose may have significant differences, especially when glucose is unstable and also in the hypoglycaemic range. FGM data frequently suffers from loss of capture and inaccuracies can occur if the reader is not used for a minimum of three times daily at appropriate times. We paid particular attention to validity of our raw data and followed advanced therapy and technology for diabetes (ATTD) guidelines in data selection and processing. In our study, we have used the Q-score, a robust marker of overall glycaemic control incorporating indicators of average glucose as well as glucose fluctuations and demonstrated a deterioration during the Ramadan fast (Fig. 4).

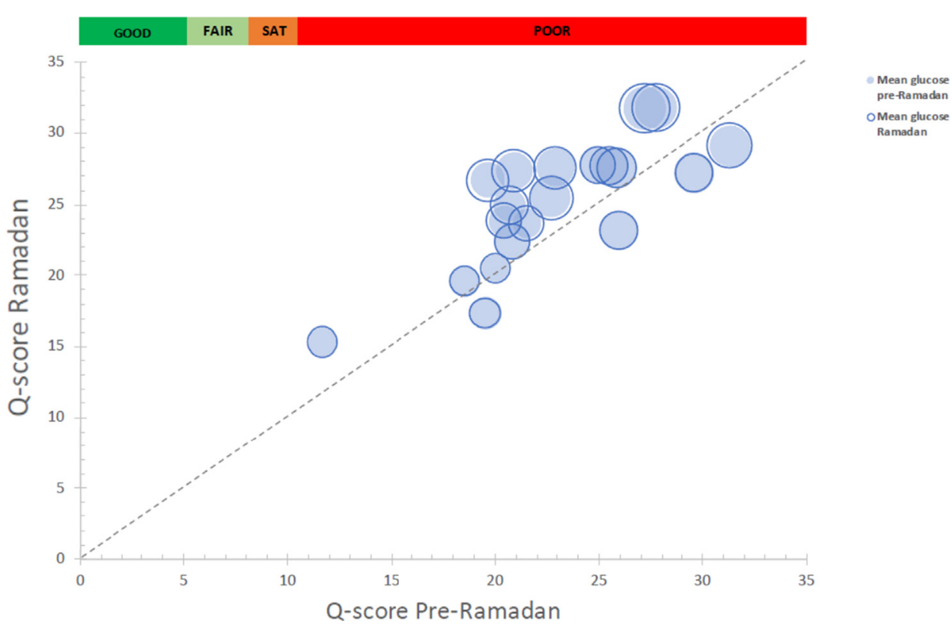

Fig. 4 – Q-score [26] pre-Ramadan vs Ramadan for the patients included in this study (n = 20). The x-coordinate of the bubble represents the Q-score pre-Ramadan, while the Y-coordinate of the bubble represents the Q-score Ramadan. The size of the bubble represents the mean glucose pre-Ramadan (shaded bubble) and during Ramadan (bubble with border but no shade). The top bar denotes level of control as indicated by Q-score. The region above the dotted line indicates deteriorating overall control with the Ramadan fast.

Interestingly, the markers we studied returned to baseline pre-Ramadan values in the month after Ramadan. We have also demonstrated the pitfalls in using the more conventional glycosylated haemoglobin in the context of the Ramadan fast and shown it to be misleading and of little value.

In summary, we report changes to glycaemic control during Ramadan fasting using FGM-derived indicators of overall control. We have shown that certain novel markers, namely, Q-score and eA1c are useful indicators of glycaemic trends and changes with Ramadan fasting. We have compared these with other markers including HbA1c that are appropriate in other settings and assert that the latter is not a good indicator of Ramadan glycaemic changes. In our group of patients with insulin-treated diabetes, our results show deterioration in overall glycaemic control with the Ramadan fast. We suggest that future studies of glycaemia with Ramadan fasting should use FGM, or CGM and suitably derived markers such as Q-score or eA1c. Our results indicate that there is much room for improvement in glycaemic control during Ramadan and we suggest that this opportunity should be used to achieve more positive outcomes.

Acknowledgements

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Conflict of Interest

None

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.05.020.

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