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Review

Ramadan and diabetes: What we see, learn and understand from continuous glucose monitoring

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Abstract

Abstinence from eating and drinking from dawn to sunset characterizes the holy month of Ramadan. For the 50 million Muslims worldwide with diabetes who adhere to this religious fast, the practice results in marked changes in glucose homoeostasis. The sunset meal (*Iftar*) that breaks the fasting state is followed by exaggerated surges in blood glucose and sustained overnight hyperglycaemia in cases of nocturnal overfeeding. The predawn meal (*Suhoor*) frequently results in prolonged glucose decay over the daylight hours. These glycaemic disturbances are particularly marked in insulin-treated patients, in those with unsatisfactory diabetes control during the pre-Ramadan period and in patients who are poorly compliant with lifestyle recommendations. Whether such patients should be exempt from the Islamic fast remains an open debate, which might be partially resolved by long-term controlled studies using the technology of continuous glucose monitoring in large populations of patients with diabetes.

Keywords: Diabetes; Dietary and pharmacological concerns; Glycaemic patterns; Ramadan

1. Introduction

Among the 1.6 billion Muslims in the world's population, 5% (approximately 80 million) are affected by diabetes [1,2]. Considering that two-thirds of them fast during Ramadan [3], it may be estimated that more than 50 million Muslim people with diabetes participate in the religious fast every year [4]. Although all religions provide recommendations to their congregations for spiritual fasting periods [5], Islam is probably the only one that sets its adherents upon such long periods of fasting, characterized by abstinence from eating and drinking from dawn to sunset during the holy month of Ramadan. In people with diabetes, such periods of intermittent fasting affect both the regularity and contents of meals. At least in insulin-treated patients, any disruption of the recommended stable dietary planning [6] is at risk of triggering adverse effects on glycaemic control, as the timing and doses of insulin injections are set according to mealtimes and amounts of carbohydrates ingested at each consistent meal. When the fasting state during Ramadan exceeds several hours, striking metabolic disorders, characterized by an increased mobilization of fatty acids from adipose tissue, can arise [7]. In type 2 diabetes (T2D), the release of fatty acids contributes to an increase of insulin resistance in muscles and other target sites [8], as well as to an additional impairment of glucose homoeostasis.

Bringing all these observations together, it appears that either permission for or exemption from fasting should be decided upon after carefully weighing the respective advantages and disadvantages. In 1995, experts at an international consensus meeting held in Casablanca [9] stated that patients with stable T2D without progressive comorbid pathology and treated with oral antidiabetic agents could safely receive authorization for undertaking the Islamic fast. Nevertheless, many other situations

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were left open to debate. The present review aims to revisit the usual guidelines by integrating new scientific findings that have arisen from recent studies using the technology of continuous glucose monitoring [10–12].

2. Chronic Ramadan dysglycaemia: lessons from observational studies

Acute adverse events such as severe hyperglycaemia or hypoglycaemia are usually reported during Ramadan [3]. Such events are probably due to inappropriate handling of dosages of oral or injectable agents and dietary intakes [4,13,14]. Beyond acute events, there arises the question of whether Ramadan can result in sustained chronic glucose disorders—so-called 'ambient hyperglycaemia'. In this case, it should first be borne in mind that the Ramadan period has a 1-month duration and, second, that any abnormally prolonged exposure of several weeks to high glucose levels can result in deleterious effects, such as a sustained increase in HbA_{1c} levels and excess glycation of the structural proteins in blood vessel walls [15,16]. The latter can have a subsequent 'legacy' effect, with the development of adverse cardiovascular outcomes several years later [17]. In fact, a 1-month exposure to abnormally high glucose levels, if repeated every year, can produce, after 24 years, the same deleterious vascular damage as sustained hyperglycaemia over a continuous 24-month period. For this reason, our recently published reports [12,18] merit particular attention.

2.1. Continuous 24-h glucose profiles during Ramadan when pre-Ramadan diabetes control is satisfactory

In 56 patients with relatively well-controlled diabetes (mean ± SD non-Ramadan HbA_{1c} levels = 55 ± 9 mmol/mol, 7.2 ± 1.2%) investigated by continuous glucose monitoring during Ramadan, interruption of the fasting state coupled with sudden refeeding at the sunset meal (*Iftar*) was marked by a rapid rise in glucose of approximately 5 mmol/L above premeal values (Fig. 1) [12]. This increase persisted overnight until dawn. The predawn meal (*Suhoor*), taken before sunrise, then contributed by reactivating the hyperglycaemia and maintaining glucose at abnormally high levels. During daylight hours, glucose concentrations returned to baseline levels, which were near-normal in the population as a whole, but remained elevated in those using insulin regimens (Fig. 1) [12]. Glucose nadirs were only observed at the end of the afternoon after a slow progressive glucose decline at a constant rate throughout the period of abstinence from eating and drinking. In this observational study, it is noteworthy that insulin-treated patients behaved differently from those treated with either oral antidiabetic agents or diet alone. This was particularly evident when the prescription of oral antidiabetic agents was limited to metformin and/or dipeptidyl peptidase (DPP)-4 inhibitors, drugs without risk of triggering hypoglycaemia.

2.2. Continuous 24-h glucose profiles during Ramadan when pre-Ramadan diabetic control is unsatisfactory

A few years ago, our team investigated a patient with a body mass index (BMI) of 31 kg/m^2, an HbA_{1c} level of 68 mmol/mol (8.4%) and T2D treated with insulin [18]. Ambulatory continuous glucose monitoring during the Ramadan period showed that the dietary intake at the sunset meal was followed by rapid and exaggerated glucose increments that were similar over the three consecutive study days (Fig. 2). Within a time interval of < 2 h, glucose concentrations rose from premeal levels of between 5.5 and 7.2 mmol/L to postmeal peaks ranging from 16.7 to ≥ 22.2 mmol/L. However, nocturnal glucose patterns were markedly different on study days 2 and 3 (Fig. 2). On study day 2, the postmeal peak was quickly followed by a decrease in glucose concentrations that further fluctuated around an average level of 11.1 mmol/L overnight until the predawn meal taken at 07:00 h. On study day 3, glucose concentrations plateaued at an average level of 22.2 mmol/L overnight until dawn. On both study days, slow progressive decays of glucose

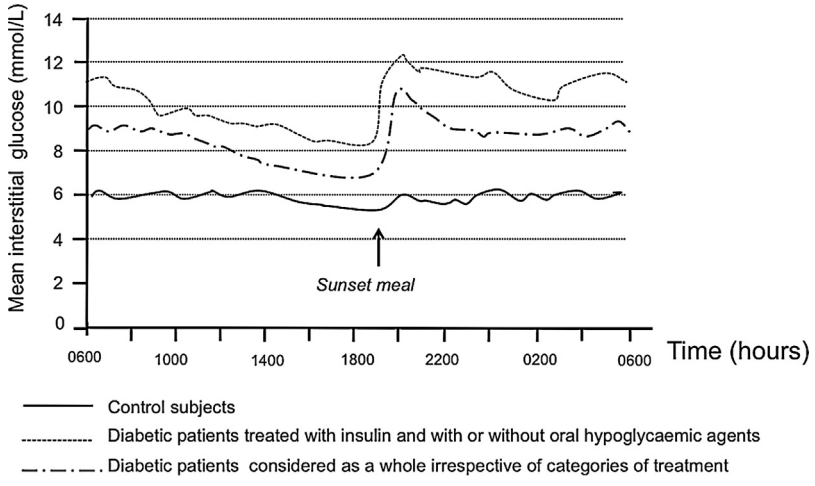

Fig. 1. Mean 24-h glycaemic profiles during Ramadan. Seven healthy, nondiabetic subjects (solid line) and 56 diabetic patients (broken and dotted lines), irrespective of treatment categories, were investigated. Among these patients, 13 (dotted line) were treated with insulin: six had type 1 diabetes and seven had type 2 diabetes [12].

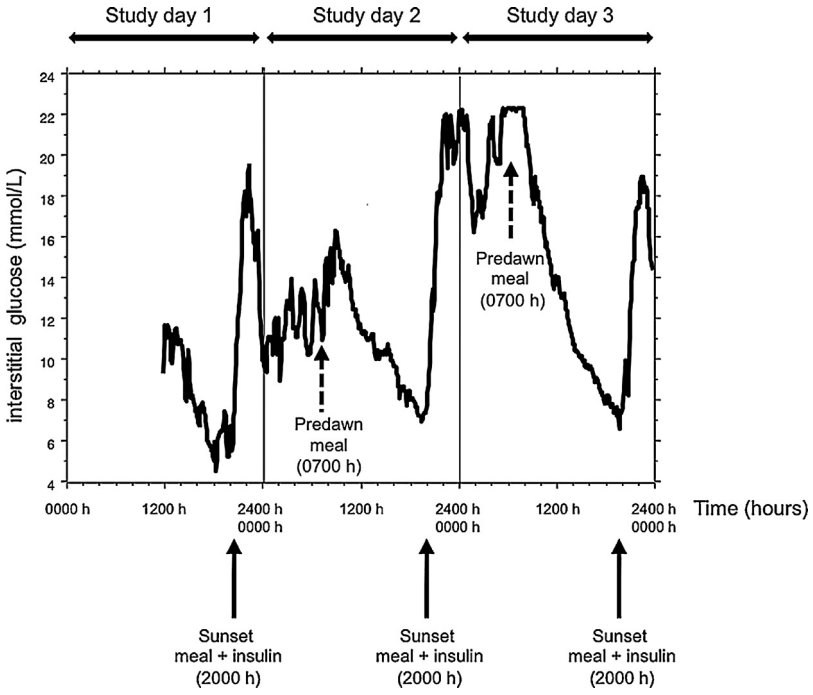

Fig. 2. A typical 24-h glycaemic profile. A patient with insulin-treated type 2 diabetes was investigated during Ramadan over three consecutive days (study days 1, 2 and 3). The arrows indicate when the sunset and predawn meals were taken. A once-daily dose of insulin (44 U of long-acting insulin glargine and 16 U of short-acting insulin glulisine) was injected before the sunset meal [18].

concentration at constant rates were observed throughout the daylight hours. Near-normal glucose values (7.0 mmol/L) were only achieved late in the afternoon, just before the sunset meal (Fig. 2). Because of Ramadan, this patient, who was usually treated during non-Ramadan periods with a twice-daily glargine regimen (58 U and 20 U before breakfast and dinner, respectively), was instructed by his healthcare practitioner to take a once-daily 44 U dose of long-acting insulin glargine and 16 U of short-acting insulin glulisine before the sunset meal. In addition, the patient was also taking dual oral antidiabetic treatment with daily doses of metformin (2 g) and glibenclamide (10 mg).

This case report clearly indicated that the Ramadan fast can be associated with major glucose disturbances when two essential requirements are not achieved:

- satisfactory glycaemic control in the pre-Ramadan period;
- the patient's clear willingness to comply with a structured nutritional and pharmacological programme during Ramadan.

Moreover, the report highlighted two other major issues:

- the long time interval required to obtain near-normal glucose concentrations during the period of total abstinence from eating and drinking in the face of abnormally high plasma glucose levels at sunrise;
- the major deterioration of overnight glycaemic control after a rapid and marked rise in glucose levels on interruption of fasting at sunset.

The latter prompted a commentary on patient compliance with dietary measures. Although the dietary intakes of our patient were not recorded between the sunset and predawn meals, the differences in nocturnal glucose profiles between days 2 and 3 (Fig. 2) were probably due to marked day-to-day fluctuations in eating behaviours, with moderately exaggerated casual food intakes on study day 2 and highly sustained overfeeding on study day 3.

3. Pathophysiological considerations

In healthy, nondiabetic people, total body glucose uptake capacity during the postabsorptive state—the 6 h following the 4-h postprandial period [19,20]—is approximately 2 $mg.kg^{-1}.min^{-1}$ (0.66 $mmol.kg^{-1}.h^{-1}$) [8]. For someone with a body weight of 96 kg (as in our case report above), this corresponds to a glucose utilization rate of 64 mmol/h. On considering the diurnal glucose profile of our patient on study day 3, given that he had ingested a predawn meal at 07:00 h, he was then in a postabsorptive state between 11:00 and 17:00 h (Fig. 2). During this time interval, the glucose disappearance rate was relatively constant, with a glucose decrement from 15.3 mmol/L at 11:00 h to 9.3 mmol/L at 17:00 h. Glucose distribution is usually depicted as a single-compartment open system (the exchangeable glucose pool), with equivalent inflow and outflow rates corresponding to endogenous hepatic glucose production and glucose disappearance in peripheral target tissues, respectively. As the volume of the exchangeable pool is commonly set at 0.150 L/kg body weight [21], it may be estimated that the total amount of glucose in the exchangeable compartment of our patient with a body weight of 96 kg was

220 mmol (0.150 × 96 × 15.3) when his plasma glucose value was 15.3 mmol/L. Consequently, it may be assumed that a normal plasma glucose concentration (5.55 mmol/L) could only be attained when the total amount of exchangeable glucose was reduced to 80 mmol (0.150 × 96 × 5.55). Thus, the patient had to metabolize 140 mmol of glucose (220 minus 80 mmol), a quantity that represents the amount of excess glucose when plasma glucose is as high as 15.3 mmol/L.

Applying this assumption to our patient, it may be suggested that a near-normal glucose value would have been achieved within approximately 2 h (at 13:00 h), provided that the outflow of glucose from the single open compartment was maintained at a physiological constant rate of 64 mmol/h (0.66 mmol.kg^{-1}.h^{-1}) [8]. Yet, in fact, in our patient, a near-normal glucose value of 7.0 mmol/L was reached only late in the afternoon, just before the sunset meal at 20:00 h (Fig. 2) [18]. This clearly indicates that, despite the absence of any food intake from dawn to sunset, glucose utilization remained markedly impaired throughout the daylight hours, an alteration probably due to poor coverage of the patient's insulin requirements during this period. In other words, the insulin dose (60 U, corresponding to around 0.6 U/kg/day) administered on the preceding day before the sunset meal was insufficient to ensure appropriate coverage of his insulin needs. Thus, an insulin bolus injection before the predawn meal (*Suhoor*) would not only have been appropriate but, in fact, even necessary or mandatory for accelerating glucose disposal over the diurnal period.

4. Dietary intakes during Ramadan: a matter of concern?

The sudden and rapid glucose rise observed on interruption of fasting in patients with T2D and the presence of more or less marked subsequent glycaemic disorders from sunset to dawn [12,18] (Figs. 1 and 2) raise the question of whether or not compliance with nutritional intakes should be the cornerstone of glycaemic control. This is particularly true when T2D patients wish to comply with their religious duty to fast. Before proceeding to additional recommendations, it should be remembered that, during Ramadan, several meals are spread throughout the nocturnal refeeding period from sunset to dawn, two of which are clearly identified [22]. The first meal is taken at sunset (*Iftar*) to break the fasting state whereas the second one, taken during the predawn period (*Suhoor*), aims to cover requirements for water, carbohydrates and energy during the daytime hours to come. The sunset meal alone, with its average estimated supply of 150 g of carbohydrates and 1400 kcal in total [12], would appear to achieve appropriate coverage of any major nutritional requirements during the transition from fasting to refeeding.

However, the meal that breaks the fasting state would remain just a minor dietary setback were it not followed by supplementary meals or snacks during Ramadan [22]. Among those extra meals, the most traditional one is the additional dinner eaten 2 or 3 h after the sunset meal. Coupled with nocturnal nibbling, this contributes adversely by, first, creating a state of overeating characterized by overconsumption of calories and carbohydrates and, second, by maintaining overnight sustained hyperglycaemia. Several recent publications have shown that the nutritional changes observed during Ramadan are more and more commonly accompanied by an increased frequency to gain weight [13,14] whereas, several years ago, weight gain was exceptionally observed [23]. Yet, although the impact of fasting on body weight is still controversial during Ramadan, it has recently been demonstrated that the holy month, with its marked changes in lifestyle and dietary habits, is associated with approximately 2-kg increases in body weight in healthy Egyptians [13]. The nutritional assessment conducted in that study revealed that fasting during Ramadan was associated with average increases of 250 kcal in mean daily energy intakes.

Determining how this excess is distributed throughout the nocturnal period is not easy, as dietary habits can differ considerably according to country, families and season. For instance, in Morocco, despite substantial heterogeneity across different social classes, the nocturnal food intake appears to be

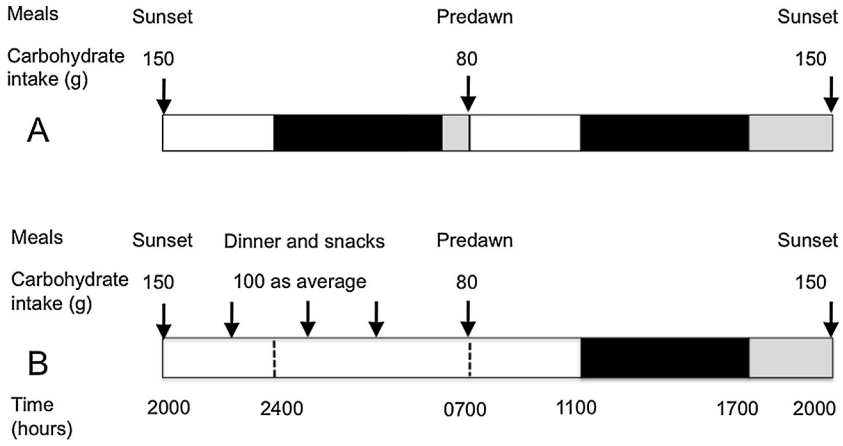

Fig. 3. Schematic theoretical distribution of carbohydrate intakes over a 24-h period during the holy month of Ramadan, when the duration of daylight hours is approximately 12 h. Nutritional states are indicated as postprandial (white area), postabsorptive (black area) and fasting (grey area). Usually, the durations of postprandial and postabsorptive states are 4 h and 6 h, respectively. The true fasting state occurs after the postprandial and subsequent postabsorptive periods—in other words, 10 h after the beginning of a meal. Two situations are depicted, depending on whether carbohydrate intakes are limited to the sunset (*Iftar*) and predawn (*Suhoor*) meals (A) or extended to include supplementary nocturnal dinners and/or snacks (B).

essentially distributed between two main meals taken at sunset and then a dinner taken 2–3 h afterwards, consisting of a wide variety of typical Moroccan dishes. In the Arab peninsula, the most consistent meal is probably the predawn meal [14]. Fig. 3 presents an example of what could be considered the average distribution of carbohydrate intake throughout the nocturnal period, depending on whether the intakes are limited to the sunset (150 g) and predawn (80 g) meals [12] or extended to include additional and unpredictable dinners and snacks after the sunset meal. Taken as a whole, those additional dinners and snacks may well increase the mean overall carbohydrate consumption by roughly 100 g, with an upper value as high as 300 g. As a consequence, the near-normal 230 g/day (150 + 80) of carbohydrate intake is shifted up to 530 g/day (150 + 80 + 300). In addition, it should be noted that the overall duration of the postprandial state (4 h after each meal) [19,20] is restricted to only 8 h when food intakes are limited to sunset and predawn meals, but rises up to approximately 15 h, or around two times longer, when supplementary meals are taken as dinner and snacks during the nocturnal period (Fig. 3). Thus, it is easy to understand why undesirable changes in body weight are seen in some patients with diabetes and why such people also exhibit poor overnight glycaemic control when additional meals are taken.

5. Adjusting antidiabetic drug treatments during Ramadan

An abundance of reports in the literature [4,22,24–30] has been devoted to the pharmacological management of diabetic patients who wish to fast during Ramadan, and a patient-centred approach is the most common recommendation made to healthcare professionals. However, when it comes to specific patients, this message is difficult to deliver, as the considerations that should be taken into account are usually general and non-specific. The first step is to separate patients according to whether or not they are treated with insulin.

5.1. Non-insulin-treated patients with type 2 diabetes

Pharmacological treatment can be maintained at its usual level when the iatrogenic risk of hypoglycaemia is either low or absent. All blood glucose-lowering therapies with no stimulatory effect on endogenous insulin secretion, such as metformin, glitazones and alpha-glucosidase inhibitors, can safely be maintained at their usual tolerated doses. The same can be said of incretin-based therapies such as DPP-4 inhibitors and glucagon-like peptide (GLP)-1 receptor agonists [31,32], which stimulate endogenous insulin secretion in a glucose-dependent manner [33]. However, as the latter agents have inhibitory effects on glucagon secretion [33], they may cause hypoglycaemia or impair recovery from hypoglycaemic episodes if used together with insulin and/or sulphonylureas (SUs).

In contrast, the precautionary principle should be applied when patients are treated with non-glucose-dependent insulin secretagogues such as SUs and glinides. SUs are not contraindicated during Ramadan, even though some authors suggest replacing them with glinides, which have a lower risk of hypoglycaemia than SUs [34]. When either SUs or glinides are maintained during Ramadan, patients should be carefully instructed on the risk of hypoglycaemic episodes with their use. In the end, the physician's role is to help patients titrate these medications to a dose that allows them to avoid hypoglycaemic events. This goal can be achieved by using the blood glucose value measured in the late afternoon before the sunset meal. In most patients [35] and, more specifically, in those who practice the Islamic fast, this glucose value is usually at its lowest during the daytime hours [12,18]. This means that doses of SUs and glinides should be adjusted according to this glycaemic nadir and yet remain > 3.9–4.4 mmol/L.

Although still lacking official guidelines, the new class of sodium–glucose co-transporter 2 (SGLT2) inhibitors, which bring a risk of dehydration and, thus, of hypovolaemia [36], should be contraindicated during Ramadan, or at least for those diabetic patients living in very hot countries or when the holy month coincides with a very hot season.

5.2. Insulin-treated patients with either type 1 or type 2 diabetes

The best strategy is to intensify insulin regimens [37–40] in patients who fail to exhibit satisfactory glycaemic control before Ramadan. Injections of short-acting insulin analogues before any meal (preprandial) that contains consistent carbohydrate loads [38] should aim to achieve greater flexibility and improve glycaemic profiles, especially during postprandial periods. From a practical point of view, any carbohydrate intake > 40–50 g, and especially those with a high glycaemic index, should be preceded by a bolus injection of a short-acting insulin analogue. However, guidelines for initiating these preprandial insulin doses are either lacking [41] or loosely formulated (4 U, 0.1 U/kg body weight, 10% basal insulin dose) [40], with no consideration of carbohydrate loads. Algorithms for setting these premeal doses may be based simply on either the amount of ingested carbohydrates or postmeal glucose concentrations, depending on whether an anticipatory or compensatory treatment algorithm is applied [38,42]. Using the anticipatory method, the average dose of premeal boluses may be calculated according to the carbohydrate load of the meal (mean insulin-to-carbohydrate ratio = 1 U/10 g, approximately) [42]. The dose is usually larger for the predawn meal because insulin resistance and hepatic glucose production reach their highest levels in the early morning hours [43].

During Ramadan, ingestion of the predawn meal with its relatively high carbohydrate load contributes to acceleration of the blood glucose rise at the end of the nocturnal period, and further renders the glucose decay even more hazardous during the daytime period to come.

From these observations, it is possible to assess, for example, a T2D patient, with unsatisfactory glycaemic control despite insulin treatment for several months, who is being treated with a pre-dinner injection of long-acting insulin analogue and who wishes to practice the religious fast of Ramadan. In this case, it would be better to initiate a basal-plus or basal-bolus insulin regimen. To achieve this, a stepwise procedure should be implemented to first reduce the basal insulin dose

by 10–20%. Boluses of rapid-acting insulin analogues should be delivered at the meal breaking the fast, at the dinner following the sunset meal and at the predawn meal, with doses calculated using the anticipatory method based on carbohydrate load. The starting doses should be further titrated according to the results of self-monitoring of postprandial blood glucose values. In addition, the basal-bolus or basal-plus regimens should be initiated a few weeks before Ramadan to test the patient's responses; this is particularly relevant for patients with unsatisfactory glycaemic control treated with a twice-daily biphasic insulin regimen. Patients who do not accept escalation of their insulin regimen to a basal-bolus strategy should be dissuaded from participating in the Islamic fast. For those who comply with the basal-bolus regimen, the final decision to fast or not to fast should be taken according to whether satisfactory or unsatisfactory glycaemic control is achieved, respectively, at the end of the 2- or 3-month period that precedes Ramadan, during which the patient's responses have been carefully evaluated.

6. Conclusion

According to the present review, which includes data from observational studies using continuous glucose monitoring [12,18], it appears that the decision-making process should be more finely modulated. Non-insulin-treated patients with satisfactory diabetes control can be authorized to practice the Islamic fast. However, severe drug-induced hypoglycaemia can arise in patients treated with non-glucose-dependent insulin secretagogues such as SUs and glinides [34]. Consequently, in such patients, both education and empowerment are fundamentally important, including teaching them how to recognize, manage and preferentially prevent clinical manifestations of hypoglycaemia. Education sessions should be undertaken several weeks before the beginning of Ramadan. In insulin-treated patients who have been well-controlled for long periods before Ramadan, the Islamic fast should be authorized provided that certain conditions are fulfilled, including sufficient adherence to a structured dietary programme, and a complete understanding of both the insulin regimen and self-monitoring of blood glucose. In contrast, any unsatisfactory glycaemic control during the pre-Ramadan period, especially in those treated with insulin, should raise the question of whether it might be preferable to discourage the Islamic fast. In such patients, decisions should be taken on an individual basis after discussion with healthcare practitioners. This latter recommendation may also be extended to certain groups of 'vulnerable' diabetes patients, including pregnant women and, more generally, all those at high risk of adverse cardiovascular events. It should be borne in mind that the vascular walls of patients with diabetes retain the 'memory' of month-long episodes of high glucose exposure repeated every year and that this 'legacy' effect is most likely cumulative [17].

Consequently and finally, it is suggested that long-term trials in large populations be conducted to more accurately test the impact of the Islamic fast on either glycaemic profiles or such other 'hard' endpoints as the development of vascular complications. However, it is highly likely that such complex and costly trials would be difficult to conduct.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

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