

Review Article

## Diabetes Mellitus and Ramadan: Physiopathological, Clinical and Therapeutic Aspects

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**Abstract** Fasting from dawn to sunset during Ramadan is one of the five pillars of Islam. A significant number of diabetic patients insist on fasting during Ramadan against the recommendations of their physicians. Fasting in diabetic subjects may be associated with increased risk of hypoglycemia and hyperglycemia, diabetic ketoacidosis, dehydration and thrombosis. Patients with uncontrolled diabetes mellitus are predisposed to major metabolic risks. Another problem is the reluctance of diabetic patients in taking their medications during the fast; therefore the timing and the dosage of anti-diabetic drugs must be adapted for each patient. It is important for diabetic patients who wish to fast during Ramadan to effect the necessary preparation to approach the fasting as safely as possible. Up to now, the management of these patients is a challenge for healthcare professionals. The aim of this minireview is that to offer a simple guide for management of Muslim diabetic patient during Ramadan.

**Keywords** *Diabetes mellitus; Fasting; Ramadan*

### 1. Introduction

With the worldwide prevalence of diabetes increasing, and the number of fasting Muslims set to rise, the importance of effective guidelines for the management of diabetes during Ramadan fasting is clear.

Ramadan is widely observed across the world. A recent survey in 39 countries involving over 38,000 Muslims reported that a median of 93% fasted during Ramadan (Ghani, 2013).

The Epidemiology of Diabetes and Ramadan (EPIDIAR) study performed in 2001 found that 42.8% of patients with type 1 diabetes mellitus and 78.7% of those with type 2 diabetes mellitus fasted for at least 15 days during Ramadan (Salti et al., 2004). More recently, the 2010 CREED study reported that 94.2% of patients with T2DM enrolled in the study fasted for at least 15 days, and 63.6% fasted every day (Babineaux et al., 2015).

Therefore, Ramadan may have a major impact on the management of diabetes in the Muslim population.

There is a paucity of evidence-based medicine in the field of diabetes management during Ramadan. Indeed, many recommendations are based on expert opinion rather than clinical evidence (IDF-DAR, 2016). Fasting during Ramadan has a number of physiological effects on endocrine processes. In patients with diabetes, these changes and the type of medication being taken to treat the condition can be associated with the development of complications such as hypoglycemia and hyperglycemia (Al-Arouj et al., 2010).

Ramadan fasting not only alters the timings of meals but it may also disturb sleeping patterns and circadian rhythms, all of which can affect a person's metabolic state. Individuals with diabetes can be stratified into different groups according to the risk that fasting would impose. Different factors, such as the type of diabetes, level of glycaemic control, medication, presence of comorbidities and personal circumstances, can be used to assess individual risk.

A cornerstone of Ramadan diabetes management is patient education, which should include information on risks, glucose monitoring, nutrition, exercise and medication (Hassan et al., 2014; Bravis et al., 2010).

Different medications to treat diabetes have varying levels of hypoglycemic risk, and Ramadan-specific treatment regimens including dose and/or timing adjustments should be produced for each patient in order to minimize the risk of complications. Implementation of guidelines requires communication and education of all those involved, including patients, health care professionals (HCPs) and religious leaders. The aim of this review is that to offer a simple guide for management of Muslim diabetic patient during Ramadan.

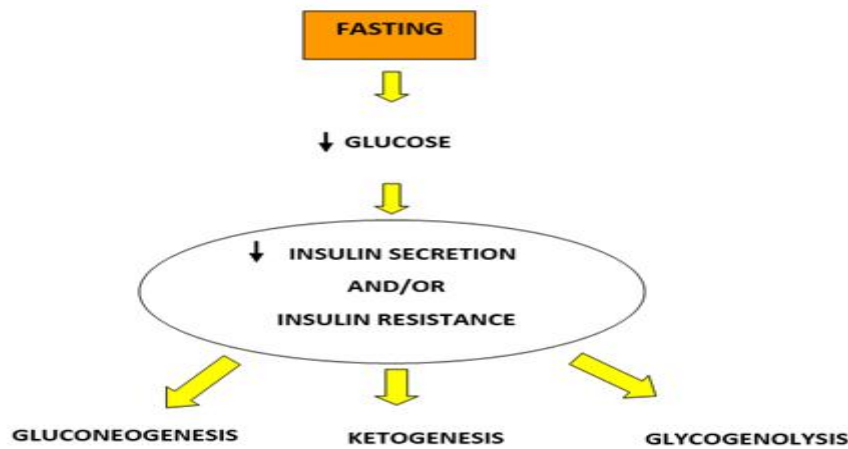
## 2. An Overview on Fasting Metabolism

Between meals and during prolonged fasting the body experiences metabolic changes due to the need to preserve glucose and the limited reserves of glycogen in the liver and muscles to supply the brain and erythrocytes, and to ensure the availability of alternative metabolic substrate of other tissues. In fact, glucose represents the only energetic substrate for the erythrocytes while the brain may metabolize ketone bodies and satisfy up to 20% of its energetic requirements (Longo and Mattson, 2014).

During fasting, the plasma levels of glucose levels, amino acids and triacylglycerol tend to decrease. The reduction of the insulin/glucagon ratio and the reduced availability of circulating substrate make fasting a catabolic period, characterised by degrading triacylglycerol, glycogen and proteins. In the first fasting phase, a small reduction of plasma glucose levels and an increase of free fatty acids is observed. In the instance of prolonged fasting, the plasma concentration of ketone bodies (acetoacetate and  $\beta$ -hydroxybutyrate) increase exceedingly (Murray Robert, 2012).

During fasting following the reduction of blood glucose levels, the secretion of insulin decreases and consequently the transport of glucose are reduced at a musculoskeletal and adipose tissue level. The glycogen represents the main reserve of carbohydrates in the liver and in the muscles. In the liver, its principal function is to supply glucose to extra hepatic tissues; as for the muscles, it represents a rapid source of energy, such that in the absence of glucose-6-phosphatase is unable to release free glucose from the glycogen. Insulin causes an inhibition of the glycogenolysis and stimulates glycogen synthesis. In the absence of other sources of glucose, the liver and muscle glycogen is exhausted after about 18 hours. If fasting is prolonged, the amino acids released as a result of protein breakdown are used in the liver and kidney for gluconeogenesis. Fasting and diabetes mellitus are characterized by an increase of the oxidation of the fatty acids, which results in the liver producing ketone bodies (ketogenesis). In poorly controlled diabetes, hyperglycaemia is due in part to the absence of insulin, which stimulates the uptake and utilization of glucose and in part to increased

gluconeogenesis from amino acids. At the same time, the absence of insulin leads to an increase of lipolysis in adipose tissue and free fatty acids which are a substrate for ketogenesis in the liver (Longo and Mattson, 2014) (Figure 1).



**Figure 1:** *Physiology of fasting in diabetic individuals*

The ketosis may be sufficiently severe such that it results in a noticeable acidosis (ketoacidosis) considering that the acetoacetate and 3-hydroxybutyrate is strong acids.

The entity of ketoacidosis is moderately low during fasting while it is noticeable in decompensated diabetes mellitus (Cahill, 2014; Kreisberg, 1978).

### 3. Diabetes and Ramadan

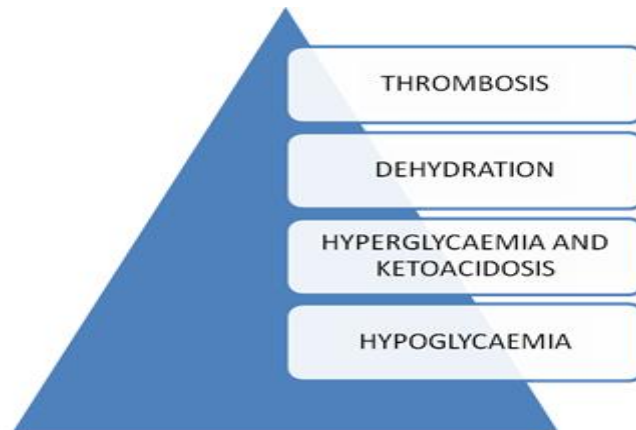
Fasting from sunrise to sunset during the holy month of Ramadan is one of the five basic pillars of Islamic worship, and it is mandatory for healthy adults. For the duration of Ramadan (29-30 days) it is forbidden to eat or drink, take oral or inject medications, from sunrise to sunset. Since the Islamic calendar is made up of 354 or 355 days (10 or 11 days less than the solar year), Ramadan does not always fall in the same season. Depending on the season and region, periods of fasting can last up to 20 hours.

During Ramadan after the announcement of the intention (niyyah), fasting begins at dawn. The iftar meal eaten at sunset is the moment when fasting temporarily stops. It is characterized by 3 courses. The first dish is an odd number of dates. The second dish is a soup (traditional in Morocco, for example, carrot and orange soup) and the third dish is the main course; cold drinks are also served, in large quantities, such as sorrel, tamarind, dates with milk, carob. A lot of salads are eaten; vegetables with a high concentration of water are preferred. The suhur is a meal that is eaten before sunrise; it is believed that it strengthens and helps the individual during fasting (Karamat et al., 2010).

Healthcare professionals need to be able to offer structured education and proper patient preparation in terms of nutrition, exercise and medication adjustments, informing them about the possible complications of diabetes during prolonged fasting. HCPs' duty is to classify patients into risk levels (mild, moderate and severe) based on their clinical history, laboratory results and general conditions, in order to determine the therapeutic strategy that suits everyone (IDF-DAR, 2016).

#### 4. Risks Associated with Fasting

The Muslim religion does not require diabetics to observe fasting, but many choose to do so themselves to risks. Prolonged fasting can cause severe alterations of glucose homeostasis mechanisms to diabetics, particularly in subjects with type 1 diabetes (DM 1). There are a number of known complications such as hypoglycaemia (the risk increases by 4.7 times in the DM 1 and 7.5 times in DM 2 during Ramadan), hyperglycaemia and diabetic ketoacidosis. Very important is also the risk of dehydration and thrombosis (Figure 2).



**Figure 2:** *The risks associated with fasting in diabetic patients*

A survey conducted in Saudi Arabia revealed for example that 30% of all cases of retinal vein thrombosis occur during Ramadan. Guidelines advise general practitioners on patients' regional and cultural differences in order to help them in their advisory task (IDF-DAR, 2016).

##### 4.1. Hypoglycaemia

Food reduction is a known cause of hypoglycaemia (Al-Arouj et al., 2005). In patients with DM 1 it causes death in 2-4% of the cases (Laing et al., 2014). It is unknown whether mortality is associated with hypoglycaemia in patients with DM 2. The study of EPIDIAR (Salti et al., 2004), conducted in 13 countries with a presence of Muslims, has studied the effects of fasting during Ramadan on 12.243 diabetics, of which 8.7% suffering from DM 1. During fasting less than 50% of patients changed drug therapy. The number of reported hypoglycaemia was relatively low. Instead there has been a number of severe hypoglycaemia, requiring hospitalization, significantly increased compared to the other months of the year, especially in those who have spontaneously changed the therapy without a prior educational process. In patients with DM 1 and DM 2, the increase in the number of severe hypoglycaemia was 4.7 and 7.5 times higher than in other months of the year, respectively.

##### 4.2. Hyperglycaemia and Ketoacidosis

A recent study has shown the influence of breakfast in the control of glucose levels; avoiding breakfast for patients suffering from DM 2 determines, in fact, a high glycaemic response, after lunch and after dinner, associated with elevated glucagon levels and to a reduced secretion of insulin, this is confirmed by the reduced plasma levels of C-peptide (Jakubowicz et al., 2015).

Although major studies such as the DCCT (The Diabetes Control and Complications Trial Research Group) (The Diabetes Control and Complications Trial Research Group, 1993) and UKPDS (UK Prospective Diabetes Study Group) (UKPDS Group, 1998) have shown a close correlation between hyperglycaemia, macro- and microvascular complications of diabetes, no study has been carried out

on the influence that repeated episodes of hyperglycaemia in a short period of a few weeks may have on the development or progression of complications. Certainly, the EPIDIAR study (Salti et al., 2004) has demonstrated the significant increase in severe hyperglycaemia with or without ketoacidosis, with need for hospitalization, during Ramadan, to the extent of 1: 5 for the DM 1 and 1: 3 for the DM 2. The causes are to be found in the increase of glycogenolysis and gluconeogenesis, in the reduction of uncontrolled drug treatment, justified by a reduction of food intake and in the insufficient glyco-metabolic control in the period preceding Ramadan. Recently, patients with type 2 diabetes were kept into observation in order to monitor their blood glucose levels during Ramadan (Lessan et al., 2012). Although they lacked any serious events of hypo- or hyperglycaemia, significant glucose excursions were observed with a high intra- and inter-individual variability, confirming the importance of the educational process in the run-up to Ramadan.

#### 4.3. Dehydration

People, living in hot and humid environments or exercising physical activity of high intensity, become dehydrated if they limit the intake of liquids for long periods, especially if combined with sweating. The osmotic diuresis, typical in hyperglycaemia, in addition involves hydro-electrolyte depletion with possible orthostatic hypotension, particularly in patients with autonomic neuropathy; the risk of syncope and falls is therefore increased. Dehydration can be associated with hypercoagulability and thrombosis. In literature to date, there is no evidence of an increase of cardiovascular accidents during Ramadan; however, a report published in 1993, describes an increased incidence of retinal vein occlusion during Ramadan in Saudi Arabia (Alghadyan, 1993).

#### 4.4. Changes in Circadian Rhythms

Changes in sleep/wake cycle and food consumption also have an impact on the circadian rhythms, including changes in body temperature and cortisol levels. Compared to periods of non-Ramadan, the study reported low cortisol levels in the morning and higher levels during the evening. The alterations of the circadian rhythm of cortisol may explain, in part, lethargy reported by some Muslims during Ramadan (Haouari et al., 2008; Bahijri et al., 2013).

#### 5. Nutritional Recommendations

The change in the timing and the widening gap between the main meals intensify the feeling of hunger, therefore an excessive caloric intake typically occurs at the time of the "iftar" leading to weight gain. A meta-analysis that evaluated the effect of fasting on body weight highlighted a weight loss among the examined healthy subjects. A sub-analysis revealed a gender difference in weight change; specifically, it has been observed that men lost weight whereas women did not (Kul et al., 2014).

The diet during this period should not differ significantly from a balanced diet for it is important not to exceed the intake of food at the end of the day. In addition, it is advisable to eat high-fibre foods especially during suhur. It is also necessary to compensate for the lack of water intake during the day by drinking 10-12 glasses a day and consuming plenty of fruits (ADI-AMD-SID "Nutrizione e diabete", 2013-14).

#### 6. The Risk Categories

Three risk categories among diabetics have been defined: very high, high, low-moderate. The first category includes people with diabetes who have experienced episodes of severe hypoglycaemia, diabetic ketoacidosis, hyperosmolar coma in the three months preceding Ramadan, pregnant women with diabetes, patients on dialysis or with end-stage renal failure, patients with acute disease and the frail elderly. The high-risk category includes patients with poorly controlled DM 2 or insulin treatment,

patients with DM 1, those with renal insufficiency stage 3, with macrovascular complications, those with DM 2 who have heavy jobs and those treated with drugs which may impair their cognitive function. These two risk categories should definitely be dissuaded from engaging in prolonged fasting (IDF-DAR, 2016).

## 7. Patients' Education

Patients' education in pre-Ramadan plays a vital role in managing diabetes. The patient should be sent information on the quantification of risk, the importance of self-monitoring blood glucose, diet and exercise, the adaptation of the anti-diabetes treatment, recognition of symptoms of complications and especially when we need to interrupt fasting. The EPIDIAR study showed that only about two-thirds of the patients received recommendations from their health care providers regarding the management of diabetes during Ramadan, and highlighted the need for intensive training before fasting (Salti et al., 2004).

In the most recent study conducted by CREED, 96% of physicians provided advice to patients during fasting, although only 63% of them followed the requirements set by the guidelines. In addition, only 67% of physicians used a proper educational programme (Babineaux et al., 2015).

## 8. Adjusting the Hypoglycaemic Therapy for Diabetic Patients during Ramadan

The scheme that involves the use of intermediate insulin or double administration of ultra-short-acting insulin with the addition of rapid-acting insulin before the two meals is risky because the possibility of hypoglycaemia is very high. Currently, it is believed that the basal-bolus scheme best stabilizes glucose levels and avoids severe hypo or hyperglycaemia. The long or intermediate analogues (glargine or detemir) should be administered in the evening. For patients with type 1 diabetes, insulin glargine resulted in an excellent glycaemic stabilizer as a basal (Mucha et al., 2004, Kadiri et al., 2001).

In a small study of five adolescents with DM 1, in the age of 15 to 19, the subcutaneous infusion of insulin during Ramadan (CSII) was associated with improved glycaemic control and fewer hypoglycaemic episodes in comparison to conventional insulin treatment. The insulin pump therapy provides a flexible treatment and it is potentially safer, but only for selected subjects, given the high cost of the procedure and the required intensive glucose monitoring (Abbas, 2007).

Insulin sensitizers (metformin and pioglitazone) do not induce hypoglycaemia; therefore, the dosage should not be modified. It is advisable to distribute the dose of metformin for 2/3 iftar (the evening meal that interrupts fasting) and the remaining dose, lower, at suhur (in the morning) (Bolen et al., 2007; Vasan, 2006).

More complex is the management of patients treated with sulfonylureas or glinides; in fact, these drugs are burdened by the risk of hypoglycaemia, especially those of the first generation such as glibenclamide. Among the sulfonylurea, however, there are minor risks with glimepiride and gliclazide, which reduce significantly major hypoglycaemic events, especially when the patients have committed to a proper preparation for the Ramadan. Even with the use of glinides minor hypoglycaemic events were reported compared with the use of other sulfonylureas (Hassanein, 2004; Sari et al., 2004; Zargar et al., 2010; Scherthaner et al., 2004).

There was no severe hypoglycaemia with the use of repaglinide. Bakiner et al. have reported that a dose of repaglinide taken before the two main meals of the day in addition to a single insulin glargine is safe and it does not provoke hypoglycaemia or changes in body weight in low-risk individuals committing to fasting (Bakiner et al., 2009).

Cesur et al. have compared the effects of glimepiride, repaglinide and insulin glargine in individuals with DM 2 during Ramadan; fasting blood glucose (FBG), postprandial blood glucose (PBG), HBA1c and fructosamine were measured before the start of Ramadan, immediately after, and one month later. No significant differences were reported amongst the three phases of the study. The risk of hypoglycaemia did not differ in the sample in the study compared to control and does not show any difference among the three treatment regimens (Bakiner et al., 2009; Cesur et al., 2007).

As for the incretin hormones, analogues of GLP-1 do not require titration, as they do not induce hypoglycaemia, but if associated with sulphonylureas or insulin, they may increase the hypoglycaemic effect (Brady et al., 2014).

DDP-IV inhibitors do not require titration thanks to their low propensity to induce hypoglycaemia, but if associated with sulfonylureas or insulin they may potentiate the hypoglycaemic effect. Vildagliptin, in particular, has demonstrated a reduction of hypoglycaemia in the course of Ramadan compared with sulfonylureas (Devendra et al., 2009; Hassoun et al., 2016).

Regarding the use of SGLT2 inhibitors during Ramadan, there is no unambiguous consent and despite being safe in most diabetic individuals, their use is not recommended during fasting (Beshyah et al., 2016).

### 9. Advice on Breaking the Fast

All patients should break their fast if blood glucose is <70 mg/dl (3.9 mmol/L) or >300 mg/dl (16.6 mmol/L). All patients should understand that they will need to break the fast if symptoms of hypoglycaemia, hyperglycaemia, dehydration or acute illness occur (IDF-DAR, 2016).

### 10. Conclusion

**Table 1: Management of Muslim diabetic patient during Ramadan**

<b>Patients Education</b>	<ul style="list-style-type: none"> <li>• Quantification of risk</li> <li>• Self monitoring blood glucose</li> <li>• Recognition of symptoms of complications</li> <li>• To break the fast if blood glucose is &lt;70 mg/dl (3,9 mmol/L) or &gt;300 mg/dl (16,6 mmol/L)</li> </ul>
<b>Nutritional Recommendations</b>	<ul style="list-style-type: none"> <li>• Not to exceed the intake of food at the end of day.</li> <li>• To eat high-fibre foods especially during suhur.</li> <li>• It is also necessary to compensate for the lack of water intake</li> </ul>
<b>Adjusting Therapy</b>	<ul style="list-style-type: none"> <li>• To prefer the insulin basal-bolus scheme.</li> <li>• Insulin glargine or detemir should be administered in the evening.</li> <li>• For DM 1 patients, insulin glargine resulted in an excellent glycaemic stabilizer.</li> <li>• The dosage of metformin and pioglitazone should not be modified. It is advisable to distribute the dose of metformin for 2/3 at iftar and the remaining dose at suhur.</li> <li>• The new oral agents are certainly safer than older sulphonylurea, while we must be cautious with the SGLT2 inhibitors.</li> </ul>

Fasting in Ramadan for a diabetic individual should be granted under close medical supervision and after an appropriate educational program focused on controlling glucose levels and medication management (Table 1).

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