



## **Chapter 3.** **Physiology of Ramadan Fasting**

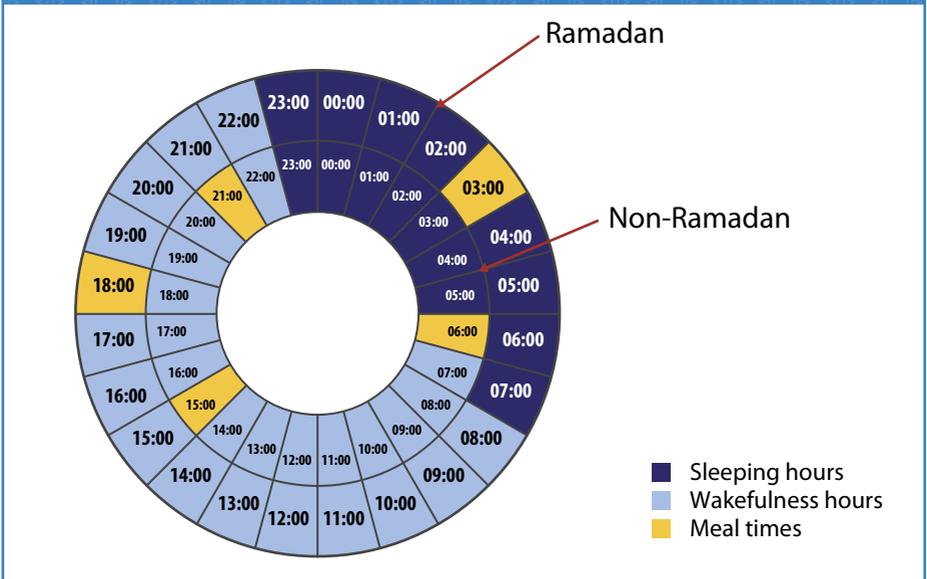
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### 3.1 Introduction

During Ramadan, fasting Muslims tend to avoid consulting their doctors [1]. It is therefore not surprising that potentially invasive studies have been difficult to conduct, leading to a relative paucity of direct evidence regarding the physiological effects of Ramadan fasting. Much of the insight gained to date has been extrapolated from studies involving subjects who have fasted for more than 48 hours. However, over the past few years some studies examining glucose metabolism, lipid profiles, circadian rhythms, sleep, and aspects of hormone physiology during Ramadan have been performed.

In fasting Muslims, the onset of Ramadan heralds a sudden shift in meal times, as well as in sleep and wakefulness patterns. **Figure 1** describes the typical sleeping/eating pattern of Muslims in many countries during Ramadan and in non-Ramadan periods. However, in other countries many Muslims may be awake most of the night and asleep after dawn. As no food or drink is taken during the hours of daylight, the time between meals during Ramadan is much longer than in other months of the year. This has important implications for physiology, with ensuing changes in the rhythm and magnitude of fluctuations in several homeostatic and endocrine processes. The duration of the fast impacts on the physiological changes that occur; this is of particular relevance when Ramadan falls during longer summer days, with higher latitudes experiencing the most hours of daylight.

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



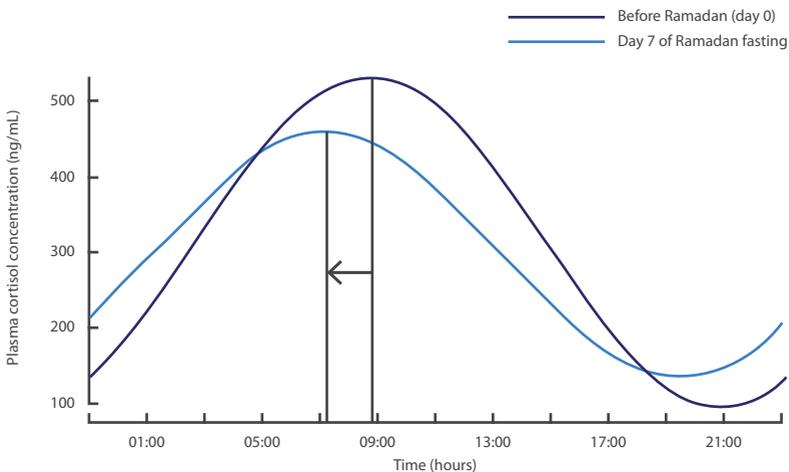
## 3.2 Ramadan physiology – fasting in the healthy individual

### 3.2.1 Changes in sleeping patterns and circadian rhythms during Ramadan

Sleeping patterns are often altered during Ramadan (**Figure 1**) [2, 3]. Typically, sleep is broken before dawn to enable Muslims to eat before fasting begins (suhoor). Many will return to sleep afterwards and wake for a second time to start the day. Some fasting Muslims may sleep in the afternoon. Following the evening meal (iftar), many will stay awake until midnight, or later. The impact of Ramadan on sleep includes decreased total sleep time, delayed sleep, decreased sleep period time, decreased rapid eye movement (REM) sleep duration, decreased proportion of REM sleep, and increased proportion of non-REM sleep [3, 4]. Sleep deprivation has been associated with decreased glucose tolerance [5], and the correlation between sleeping duration and insulin resistance has been a subject of renewed medical interest [6, 7]. However, the relevance of this to fasting during Ramadan is not yet known.

Changes to sleep and food intake impact on circadian rhythms; several changes have been noted, including changes in body temperature and cortisol levels [2-4, 8]. Compared with non-Ramadan periods, lower morning cortisol levels and higher evening cortisol levels have been observed during Ramadan [4, 8]. One study indicated a shift in the cortisol curve on day 7 of Ramadan (**Figure 2**) but on day 21 these changes had almost completely reverted to the pre-Ramadan profile [4]. Alterations in cortisol circadian rhythm may account, in part, for the feeling of lethargy felt by some Muslims during Ramadan.

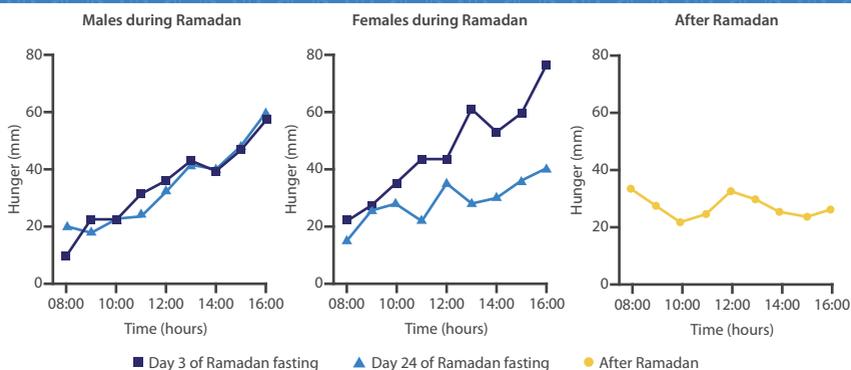
**Figure 2. Changes in cortisol circadian rhythm during Ramadan. A shift in cortisol profile is seen on day 7. This reverts to near-baseline (non-Ramadan) values by day 21 [4]**



### 3.2.2 Effects of Ramadan fasting on body weight in healthy subjects

Hunger–satiety cycles during Ramadan change in line with the shift in the timing of main meals, with the wider gap between meals intensifying feelings of hunger (**Figure 3**) [9]. This increase in hunger rating during fasting hours is seen in both sexes and is intense by iftar time. However, in females, some adaptation seems to occur, and by day 24 of Ramadan fasting, the hunger rating during fasting hours appears to reduce in intensity (**Figure 3**) [9].

**Figure 3. Changes in hunger–satiety cycles during Ramadan. During fasting hours, there is a progressive rise in hunger rating which peaks just before iftar time\***



\*Reprinted from *Appetite*, Vol 31, Finch et al, Appetite changes under free-living conditions during Ramadan fasting, pp159-70, Copyright (1998), with permission from Elsevier [9]

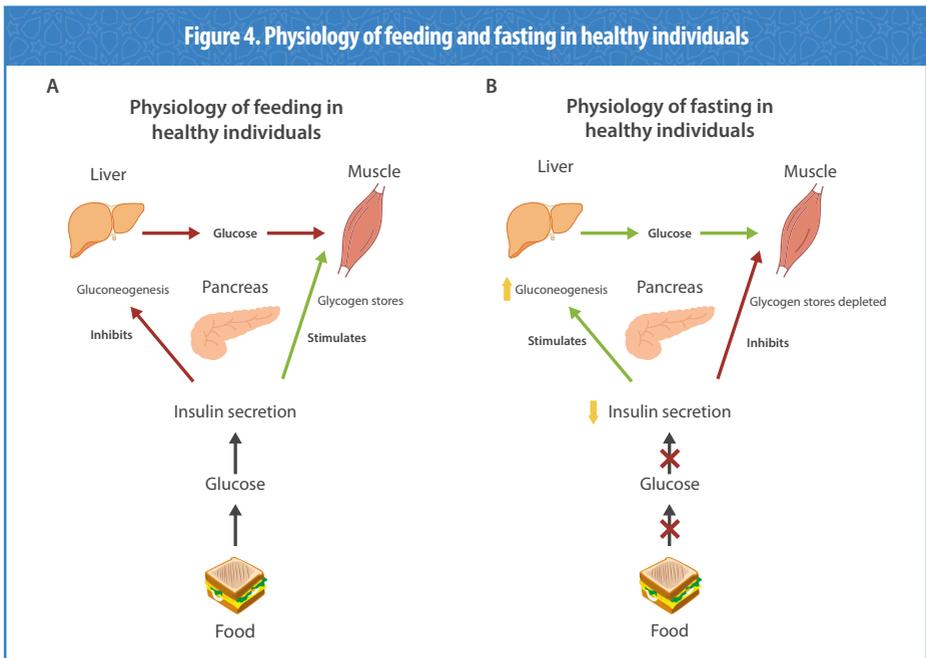
Resisting the temptation to have a particularly large meal at iftar can be difficult and studies have reported that a large proportion of total daily caloric intake occurs at this time [10]. In some individuals a net energy excess can build up, leading to overall weight gain. However, this is not universal and indeed a meta-analysis of studies investigating the effects of Ramadan fasting on body weight reported a net weight loss among healthy fasting individuals [11]. A sub-analysis revealed a gender difference in weight change, with net weight loss observed in males and no weight change observed in females [11].



**Body weight typically decreases or remains stable during Ramadan**

### 3.2.3 Effects of fasting on glucose homeostasis in healthy individuals

In healthy individuals, increased glucose levels in the blood after eating stimulates insulin secretion, which triggers the liver and muscles to store glucose as glycogen (*Figure 4A*) [12].



During fasting, circulating glucose levels fall and insulin secretion is suppressed (*Figure 4B*) [12]. Glucagon and catecholamine secretion is increased, stimulating glycogenolysis and gluconeogenesis, which then leads to an increase in blood glucose level (*Figure 4B*) [12].

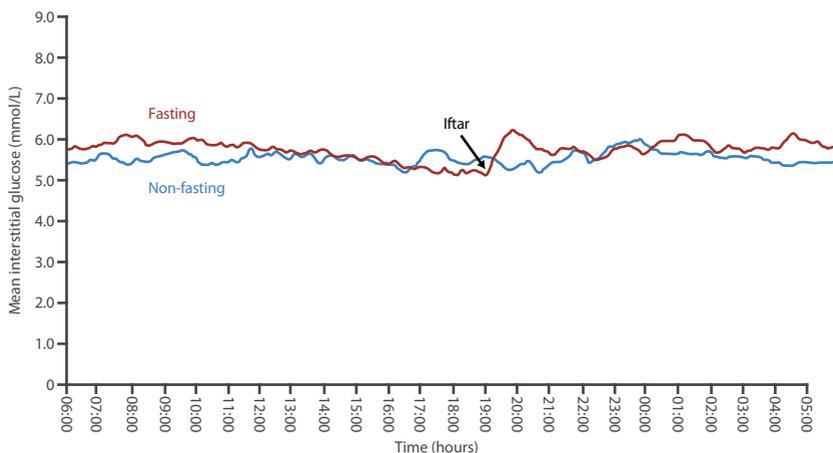
***i* In a healthy individual, fasting causes the release of glucose from glycogen stores (glycogenolysis) and the formation of glucose from non-carbohydrate substrates (gluconeogenesis)**

Liver glycogen can provide enough glucose for the brain and peripheral tissues for around 12 hours [13]. When glycogen stores are depleted and levels of insulin are low, fatty acids are released from adipocytes and oxidised to generate ketones, which can be used as fuel by many organs, preserving glucose for the brain and erythrocytes [13].

During Ramadan, each fasting period is often longer than 12 hours and may therefore be considered to be a state of intermittent glycogen depletion and repletion. In practice, most subjects who take their first meal at dawn are in a state of glycogen depletion by late afternoon, at which point ketogenesis occurs. Omission of suhoor leads to depletion of glycogen stores and ketosis much earlier in the fasting day.

Although fasting blood glucose levels have been shown to decrease during Ramadan [11, 14, 15], a recent continuous glucose monitoring (CGM) study observed a remarkable stability of blood glucose in seven healthy subjects during fasting hours, with no evidence of increased time spent in hypoglycaemia compared with non-Ramadan periods (**Figure 5**) [16]. This is despite reports of increased insulin resistance during Ramadan [8, 17, 18]. At iftar, a modest rise in interstitial glucose (and thus blood glucose) was seen, which remained within normal limits [16].

**Figure 5. Mean continuous glucose monitoring (CGM) profiles from healthy subjects before and during Ramadan; there is a remarkable stability of blood glucose during fasting hours followed by a minimal rise in blood glucose at iftar\***



\*Reprinted from Diabetes Metab, Vol 41, Lessan et al, Glucose excursions and glycaemic control during Ramadan fasting in diabetic patients: Insights from continuous glucose monitoring (CGM), pp28-36, Copyright (2015), with permission from Elsevier [16]

### 3.2.4 Effects of fasting on other metabolic parameters in healthy individuals

Several studies have demonstrated Ramadan fasting to be associated with favourable effects on the lipid profile of healthy individuals [10, 19-21]. A meta-analysis, published in 2014 and involving 30 articles investigating the effect of Ramadan fasting on parameters including blood lipids, found no change overall in high density lipoprotein (HDL) or triglyceride (TG) levels, but large significant decreases in low density lipoprotein (LDL) levels [11]. There were however some differences in the effects of fasting on lipid profile between genders, with a significant increase in HDL in females, and a small significant decrease in TG levels in males after Ramadan [11].



## Ramadan fasting is associated with favourable effects on lipid profile in healthy individuals

Ramadan fasting is also associated with changes in leptin and adiponectin. Leptin and adiponectin are hormones involved in the regulation of appetite, various metabolic pathways and insulin sensitivity [17]. In one study (n=23), morning levels of leptin were shown to increase during Ramadan compared with non-Ramadan periods [17]. In the same study, evening levels of growth hormone, which is known to affect insulin sensitivity, were found to decrease during Ramadan [17]. Leptin levels were also found to be altered during Ramadan in another small study (n=8) [22]. Although the circadian rhythm of leptin was unaffected, night-time levels of leptin were reduced compared with non-Ramadan periods [22].

Adiponectin modulates glucose metabolism and high levels of adiponectin are associated with increased insulin sensitivity [23]. Adiponectin is also indirectly involved with inhibition of gluconeogenesis [23]. The effect of Ramadan fasting on adiponectin levels is unclear. One recent study observed a significant decrease in adiponectin in healthy males after 4 weeks of Ramadan fasting, and another reported decreased levels of adiponectin in the mornings during Ramadan [15, 17]. Conversely, a study involving healthy males with risk factors for type 2 diabetes (T2DM) reported a significant increase in adiponectin at the end of Ramadan [24].

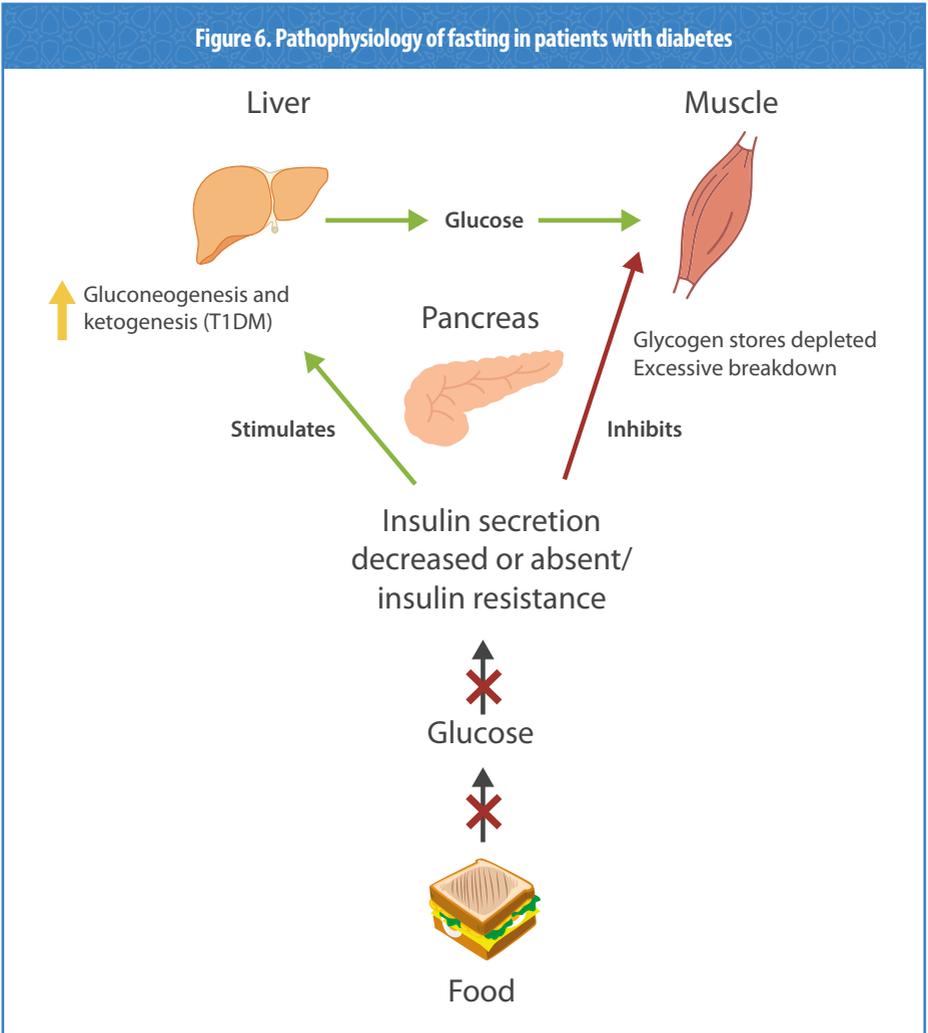
Changes in leptin and adiponectin levels observed during Ramadan may be due to changes in meal and sleeping patterns, or due to the changes in cortisol circadian rhythm that have been reported during Ramadan [8].

### 3.3 Pathophysiology of fasting in patients with diabetes

#### 3.3.1 Glycaemic control and glucose variability

In individuals with diabetes, glucose homeostasis is disturbed by both the underlying pathophysiology and the medications used to treat the condition. When fasting, insulin resistance/deficiency can lead to excessive glycogen breakdown and increased gluconeogenesis in patients with type 1 diabetes (T1DM) and T2DM; in addition, in T1DM, augmented ketogenesis can occur (*Figure 6*). As a result, the risks facing patients with diabetes are heightened during Ramadan. These include hypoglycaemia, hyperglycaemia, diabetic ketoacidosis, dehydration and thrombosis [13]. As well as fasting, feasting during Ramadan carries risks for those with diabetes.

Figure 6. Pathophysiology of fasting in patients with diabetes



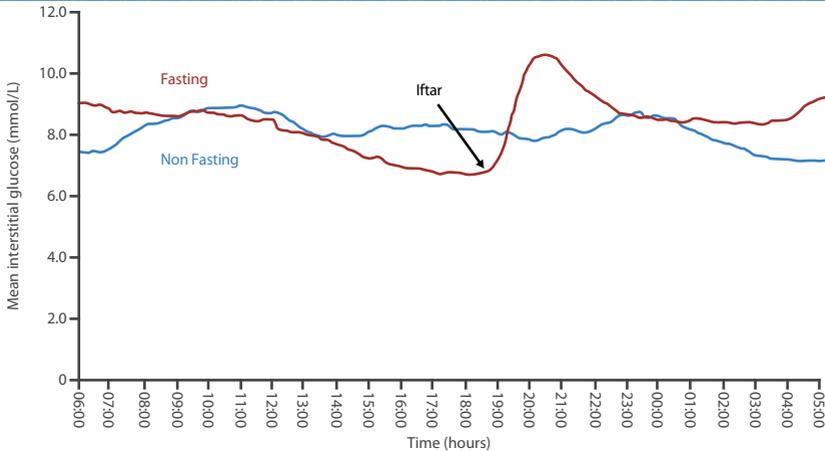
The landmark Epidemiology of Diabetes and Ramadan (EPIDIAR) study found that during Ramadan there was a 4.7-fold and 7.5-fold increase in the incidence of severe hypoglycaemic complications in patients with T1DM and T2DM, respectively, compared with non-Ramadan periods [25]. During the fast, patients with T1DM may fail to secrete adequate levels of glucagon in response to hypoglycaemia, leading to further decreases in blood glucose levels [13]. In addition, as a result of autonomic neuropathy, some patients with T1DM may have a defective adrenaline response and therefore an inadequate response to hypoglycaemia [26]. The incidence of severe hyperglycaemia was also found to be increased during Ramadan (3-fold and 5-fold in patients with T1DM and T2DM, respectively) [25].



**Without suitable management, patients with diabetes are more likely to experience severe hypoglycaemia during Ramadan than in non-fasting periods**

Over the last few years, CGM studies have been performed in patients with diabetes before and during Ramadan [16, 27-29]. One recently published study involving 50 patients with T2DM, and six patients with T1DM reported no significant differences in markers of glycaemic control between Ramadan and non-Ramadan periods [16]. There were also no significant differences in the number of high or low glucose excursions, or time spent in euglycaemia, hypoglycaemia, and hyperglycaemia [16]. However, major intra- and inter-individual variability in CGM profiles were observed. A rapid rise in glucose level after iftar (**Figure 7**) was seen; this is most probably due to the carbohydrate-rich meal at iftar, but other factors such as hormonal changes could also be involved [16]. Inappropriate timing and inadequate dosing of anti-diabetic medication may also be important contributors to this rise [16].

**Figure 7. Mean continuous glucose monitoring (CGM) profiles from patients with diabetes before and during Ramadan. A rapid rise in blood glucose is seen at iftar time\***



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### 3.3.2 Other metabolic effects of Ramadan fasting in patients with diabetes

#### **Effects on body weight**

The EPIDIAR study showed that weight remained unchanged in the majority of patients with T1DM and T2DM (62.5% and 54.1%, respectively) at the end of Ramadan [25]. Other, smaller studies have reported either no effect on weight or weight loss in patients with diabetes during Ramadan [30].

## Effects on lipid metabolism

While favourable changes in lipid profile have been seen in healthy subjects who fast during Ramadan, few studies have investigated changes in lipid profile in fasting patients with diabetes. In those studies that have been performed, both favourable and unfavourable changes have been reported such as reduced cardiovascular risk, slightly decreased total cholesterol and increased total LDL cholesterol [31-33].

## Other effects of Ramadan fasting in patients with diabetes

Two key concerns for patients with diabetes who fast during Ramadan are dehydration and thrombosis. Dehydration may be compounded in hot climates or in individuals who undertake intensive physical labour, as well as by osmotic diuresis caused by hyperglycaemia. Dehydration can lead to hypotension and subsequent falls or other injuries [13]. According to a survey in Saudi Arabia, the incidence of retinal vein occlusion increased during Ramadan when almost 30% of all cases occurred, significantly more than in other months of the year. Dehydration was proposed to be a possible cause [34].

## Summary

- The month of Ramadan can precipitate dramatic changes in meal schedule, sleep patterns and circadian rhythms.
- Ramadan fasting can be associated with favourable physiological changes among healthy individuals, such as decreased body weight and favourable changes in lipid profile.
- In patients with diabetes, however, Ramadan fasting can be associated with certain risks due to the pathophysiology that disrupts normal glucose homeostatic mechanisms.
- Therefore, patients with diabetes, and in particular those with T1DM, should seek medical advice before deciding to proceed with Ramadan fasting.

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