CHAPTER 3

What happens to the body?
Physiology of fasting during Ramadan

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WHAT IS KNOWN?

- Fasting during Ramadan can alter meal schedules, fluid intake, and the circadian rhythm.
- A reduction in body weight may also occur as a result of fasting during Ramadan.
- The glucose profiles of people without diabetes are remarkably stable and within the normal ranges, and aside from some small excursions around Iftar, the profiles are not too different from the non-Ramadan period.
- People with diabetes may be at risk as fasting during Ramadan can increase glucose variability and the risks of hyperglycaemia and hypoglycaemia; there is a significant and rapid rise in glucose at Iftar in people with diabetes.

WHAT IS NEW?

- Fasting during Ramadan is associated with a reduction in total sleeping time of about one hour and is linked to an increase in day time sleepiness.
- Changes to indicators of body clock mechanisms have been demonstrated which can affect many hormonal rhythms.
- Despite there being changes to activity patterns and reductions in energy expenditure, there is no significant change in the total energy expenditure. Likewise, resting energy expenditure does not change significantly during Ramadan fasting.
- An overall reduction in energy intake of around 240 kcal/day during Ramadan fasting has been shown in one study.
- There is a gradual shift in the proportion of fuel utilisation from carbohydrates to fat as the fasting day progresses.
- Several studies have shown up to a twofold reduction in insulin sensitivity during Ramadan fasting.
- Low density lipoprotein (LDL) and triglyceride (TG) levels have been seen to decrease during the Ramadan fast (RF).
- Hormonal changes during Ramadan fasting include a reduction in morning adiponectin levels, large increases in morning leptin levels and reductions to morning and evening growth hormone levels. A modest reduction in testosterone in men has also been reported.
- Gut microbiota changes and genetic changes can occur when fasting during Ramadan.
- People with other medical conditions can be at risk of changes unrelated to glucose homeostasis and face practical issues when conducting the Ramadan Fast. Important conditions to consider are previous bariatric surgery, chronic kidney disease and hypothyroidism.

WHAT IS MISSING?

- Further research is needed into the direct short-term and long-term effects of the changes that occur during the RF.
- Further research needs to be conducted in people with diabetes to assess whether the changes seen in healthy individuals are exacerbated.
- These changes need to be separated by diabetes type and people with accompanying comorbidities.
- More comprehensive studies of hormonal changes with Ramadan fasting are needed.
1. INTRODUCTION

The Ramadan fast (RF) entails a major shift from the normal ways of eating to an exclusive nocturnal eating pattern. In this form of intermittent fasting, multiple modulations of the human body physiology may occur [1]. These changes can induce or alter pathophysiological states depending on the pre-existing state of the disease and the individual’s compliance to diet, lifestyle, and therapeutic regimens [2].

During Ramadan, individuals that fast tend to avoid consulting their doctors [3]. 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 the RF. Obtaining evidence for guidelines can be problematic; it is very difficult to ask individuals to volunteer for Ramadan related research studies at a time of spiritual focus and when there is an anticipation of breaking the fast in family union and obligations to attend religious practices in the feeding hours. Studies can also take longer to complete as Ramadan occurs only once a year, so there is a small window of opportunity to collect information.

Much of the insight gained to date has been extrapolated from studies involving subjects who have fasted for more than 48 hours. However, recently, many more studies of the RF have been conducted, with new and updated evidence emerging on different aspects of physiology during Ramadan and these will be discussed in this chapter. The chapter will be presented in four sections: Physiology, Pathophysiology in Diabetes, and Pathophysiology of the RF in other conditions, particularly those commonly encountered in people with diabetes.

2. RAMADAN PHYSIOLOGY

FASTING IN HEALTHY INDIVIDUALS

The RF affects several fundamental aspects of human physiology including sleeping patterns and circadian rhythmicity, fluid balance, energy balance, and glucose homeostasis. It represents a major shift from normal ways of eating as well as in sleep and wakefulness patterns. The RF differs from other common forms of fasting (Figure 1); as no food or drink is consumed 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 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. For instance, the Ramadan fasting day in the summer of Scandinavian countries can last more than 17 hours.
SLEEP AND CIRCADIAN RHYTHM

3.1 Changes in sleeping patterns during Ramadan

Sleeping patterns are invariably altered during the RF (Figure 2) [1, 5]. Typically, sleep is broken before dawn to enable Muslims to eat before fasting begins (Suhoor). Most will return to sleep afterward 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, and increased sleep latency [5, 6].
Comparison of sleeping and activity patterns between Ramadan and non-Ramadan periods.

During non-Ramadan days there is breakfast, lunch, and dinner at specific times. During Ramadan, breakfast (Suhoor) is much earlier and is taken just before dawn; there is no lunch and the Iftar meal is taken just after sunset. Also, during non-Ramadan days, the sleeping pattern is continuous from night through to the early morning hours, while in Ramadan, the sleeping pattern is more fragmented between the early morning hours, the afternoon, and midnight. Adapted from Saadane et al. [7].

A recent meta-analysis found total sleep time (TST) during Ramadan to be reduced by around 1 hour [8]. This resulted in increased daytime sleepiness indicated through a 1-point increase in the Epworth sleepiness scale (ESS). Another review that examined the impact of Ramadan fasting on sleep-wake patterns among physically active individuals and found similar reductions in TST [9].

Sleep deprivation has been associated with decreased glucose tolerance [10], and the correlation between sleeping duration and insulin resistance has been a subject of renewed medical interest [11, 12]. Short sleep duration is also independently associated with weight gain, particularly in younger individuals [1].

3.2 Effects on Circadian Rhythm

It cannot be over-emphasised that the shift from routine and “normal” mealtimes and sleep/wakefulness patterns during Ramadan are sudden and truly drastic. Eating times change from daylight to the darker hours between sunset and dawn. This can profoundly impact the circadian pattern of the body with consequential cardiometabolic changes [13]. Indicators of the body clock mechanisms have been found to alter; one study reported changes in the acrophase of proximal skin temperature (an indicator of core body temperature) indicating a shift-delay in the circadian clock [14]. Many hormone rhythms have been shown to alter with Ramadan fasting. These include serum leptin, ghrelin, cortisol, and melatonin levels [1, 5, 6, 15, 16]. Some of these will be discussed further in other sections of this chapter.
4. FLUID BALANCE AND RAMADAN

Absolute restriction of fluid intake between dawn and sunset is an integral aspect and of Ramadan. This can have potentially important consequences, particularly in individuals with poorly controlled diabetes. Some effects that need addressing, in otherwise healthy individuals, are the extent of fluid and electrolyte loss during the fasting day, and potential adverse effects or beneficial benefits this may have on the person. The effects of total fluid restriction in experimental settings, in manners somewhat akin to the Ramadan fast, have been investigated by Danielsson and colleagues [17] (Figure 3). Twenty young healthy female volunteers were subjected to a prolonged fast (from 10 pm–4 pm next day) and had their weight and fluid output recorded. The study showed that the rate of fluid loss for the initial overnight period (10 pm to 8 am the next day) was 1.26 g/kg body weight/hour and that for the next day’s time period was 0.99 g/kg body weight/hour. The corresponding total fluid deficit was 1.47 kg for the full 18-hour period of fasting. Although this study was not performed to address the Ramadan fast, the measurements can be a useful guide when thinking about fluid fluxes during the RF.

Reported changes to the fluid balance with the RF include a higher fluid and total water intake and a marked rise in urine osmolality in the afternoon, indicating a compensatory water conservation and a reduction in obligatory urine output [18]. Currently, the available evidence in the literature do not support concerns about the association of Ramadan fasting with pathological dehydration in normal circumstances [19]. However, dehydration may be a more relevant issue 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 [20].
5. ENERGY BALANCE

THE CONCEPT: ENERGY INTAKE (EI) AND ENERGY EXPENDITURE (EE)

Ramadan fasting affects meal patterns. As such it is expected that food and energy intake will alter. Furthermore, activity patterns also change with potential changes in energy expenditure. The concept of energy balance during Ramadan fasting merits further exploration and will be discussed here.

5.1 Energy intake when fasting during Ramadan

An obvious change during the RF is the omission of lunch and the prolonged gap between the two main meals of the day. This has direct effects on appetite and hunger scores during the daylight hours which rises steadily, reaching a peak by *Iftar* time. This, potentially, can lead to a disproportionate volume of food being eaten at sunset. Interestingly, the pattern of increasing hunger during a Ramadan fasting day has been reported to show some adaptation and attenuation in female participants towards the end of Ramadan [21, 22].

There are few studies of energy and food intake during the RF. El Ati *et al.* investigated a group of 16 healthy female volunteers fasting during Ramadan and reported 84% of total daily energy intake was taken at the evening meal, and the remaining 16% was taken between 8 p.m. and midnight [23]. This is in contrast to periods before Ramadan where breakfast, lunch and dinner constituted 9.4%, 41.6% and 21.8% of the total daily energy intake. Although the findings of this small study cannot be generalised to the larger population of fasting Muslims, the observation of a disproportionately large meal at *Iftar* time is a common finding [24, 25]; often reflected in feeding patterns ([Figure 2](#)) and in glycaemic profiles.

A study of 160 healthy fasting men by Nachvak *et al.* found an overall reduction in energy intake of around 1 MJ/day (239 Kcal/day) during the Ramadan fast. This would be equivalent to an energy deficit of 7170 Kcal over 30 days. Assuming that the energy intake records were accurate, there were no changes in the 24-hour energy expenditure and the generally accepted formula of 7000 Kcal being equivalent to a 1 kg body fat loss, a deficit of 7170 Kcal by the end of Ramadan would be equivalent to 1 kg weight loss by the end of Ramadan. However, in the same study a 2 kg weight loss was reported, suggesting some inaccuracies in the food intake records, or differences in the overall energy expenditure accompanying the RF [26].

The apparent daily energy deficit incurred by the RF is much less than the energy deficit of skipping lunch (350 Kcals vs approximately 800 Kcals) which suggests some degree of compensation, mostly through an increase in energy intake during the non-fasting hours.

5.2 Energy Expenditure and its components when fasting during Ramadan

The resting metabolic rate (RMR), activity energy expenditure (AEE) and thermic effect of food (TEF) are three components of a 24 hour total energy expenditure (TEE) [27]. RMR is the energy expended when an individual is in a fully rested position, but not sleeping. Typically, it is the largest component of energy expenditure. The RMR is affected by weight, gender, age and muscle mass; of these, muscle mass is the best determinant of RMR. In addition, the RMR is also affected by hormonal changes and is particularly sensitive to changes in thyroid hormones. The AEE is the energy expended due to activity. In sedentary individuals, the AEE
makes up a smaller component of the TEE. The AEE is also the most variable component of the TEE and can be several times higher than the RMR in professional athletes. TEF is the energy cost of digesting food, or the increase in measured metabolic rate in response to a meal. This rise in the TEF actually starts even before the ingestion of food and typically continues for several hours thereafter. Proteins have a higher cost of energy in terms of TEF compared to fat and carbohydrate rich food. TEE is the sum of the three components (RMR+AEE+TEF); direct measurements of TEE in free-living conditions is challenging but can be done using the doubly labelled water as the gold standard.

As the RF has been associated with changes in sleep, weight, activity patterns and mealtimes and content, it is feasible that some or all components of energy expenditure may alter fasting during Ramadan. Lessan *et al.* investigated different aspects of energy expenditure [28]; see Figure 4. TEE during and after Ramadan fasting was measured using the doubly labelled water method; RMR was measured using indirect calorimetry. The study found no significant difference in TEE (2125 Kcal/day vs 2299 Kcal/day) or the RMR (1365 v 1362 Kcal/day) with Ramadan fasting compared to the non-Ramadan period. It is also important to consider that there were major differences in activity patterns between the two periods, with a significantly lower step count during Ramadan (9950 steps/day) compared to post-Ramadan (11363 steps/day). Participants were noted to be more active at night-time during Ramadan with less activity during the day. It has been postulated that the reduction in activity energy expenditure was offset by the reduced time spent during sleep in Ramadan.

**FIGURE 4**

Resting energy expenditure (TEE) and total energy expenditure (TEE) during Ramadan and post-Ramadan.

There is no significant difference in TEE, or RMR between Ramadan and post-Ramadan periods (2224 Kcal/d compared with 2121 kcal/d, respectively). Adapted from Nader Lessan *et al.* [28].
5.3 Effects of Ramadan fasting on body weight and composition, in healthy individuals

Hunger-satiety cycles and food utilisation during Ramadan change in accordance to the shift in the timing of the main meal [21]. The gap between the main meals can intensify feelings of hunger, particularly towards the end of daylight hours. Resisting the temptation to have a particularly large meal at iftar can be difficult and studies have reported a large proportion of total daily calorie intake occurs at this time [29]. In general, studies have reported the effect of Ramadan on weight change to be varied, with a reduction in weight, or no change at all being the most common findings. However, in some individuals a net energy excess can lead to overall weight gains.

This inter-individual variability in weight trends with Ramadan fasting is determined by personal, cultural and social factors; but genetic, epigenetic and other factors such as gut microbiome may also play a role. The question of weight change with the RF has been explored in several, albeit small, studies. The reported net change has been modest with an average weight loss of 1-2 kg by the end of Ramadan. A meta-analysis of earlier studies by Kul et al. showed a small weight loss of around 0.7 kg in fasting men, but not women [22]. The largest study by Hajek et al., conducted on 202 participants recruited at mosques in East London, showed a net weight loss of around 0.8 kg by the end of Ramadan with the lost weight being regained 4-5 weeks after Ramadan [30].

Two other meta-analyses have explored the RF and changes in weight. Fernando et al. showed that the mean weight loss associated with Ramadan fasting was 1.34 kg and that most of the weight was regained a few weeks after Ramadan [31]. A positive correlation between starting body mass index (BMI) and weight lost during the fasting period was also identified. Furthermore, there was a significant reduction in fat percentage between pre-Ramadan and post-Ramadan in people that were overweight or obese, but not in those of normal weight. Loss of fat-free mass was also significant between pre-Ramadan and post-Ramadan but was about 30% less than loss of absolute fat mass. At 2–5 weeks after the end of Ramadan, there was a return towards, or to, pre-Ramadan measurements in weight and body composition. The study concluded that even with no advice on lifestyle changes, there are consistent, albeit transient reductions in weight and fat mass with the Ramadan fast, especially in people with overweight or obesity [31]. Another meta-analysis found the pooled weight reduction with Ramadan fasting to be around 1 kg (95% confidence interval: −1.164 kg to −0.880 kg) [32]. Sub-group analyses found fasting time (measured in hours/day) to be the best correlate of weight change at the end of Ramadan, while age and sex not being as influential. Expectedly, the season of the fasting month and geographical location also impacted the effect of Ramadan fasting on body weight [32]. However, this reported weight loss is not universal, some other studies have reported weight gain [33]. Additionally, some studies have found possible gender differences in weight change, with net weight losses observed in males and no weight changes observed in females [22]. Another study found that weight loss was greater in Asian populations compared to Africans and Europeans and that there does not appear to be a gender difference in the absolute magnitude of weight loss with Ramadan fasting [34]. These results highlight the variability in outcomes and may be because of the different contexts of individuals that fast during Ramadan.
6. GLYCAEMIC CHANGES DURING RAMADAN

FASTING IN HEALTHY INDIVIDUALS

Depending on the duration, fasting can be divided into three distinct phases: the post-absorptive phase lasting from 6-24 hours; the gluconeogenic phase lasting from 1-10 days, and the protein conservation phase which occurs if fasting lasts greater than 10 days. The RF is an intermittent form of fasting and, as such, it is a post-absorptive state with a partial overlap into the gluconeogenic phase. The fast is interrupted by the feasting period at sunset. During the fast, the central nervous system and many other tissues preferentially use glucose produced by glycogen breakdown \[ \text{Figure 5A and 5B}. \]

6.1 Glucose homeostasis

In healthy individuals, increases in glucose levels in the blood after eating stimulates insulin secretion, which in turn triggers the liver and muscles to store glucose as glycogen \[ \text{Figure 5A} \] \[35\]. During fasting, circulating glucose levels fall and insulin secretion is suppressed \[35\]. Glucagon and catecholamine secretion is increased, stimulating glycogenolysis and gluconeogenesis, which then leads to an increase in blood glucose levels \[35\]. Liver glycogen can provide enough glucose for the brain and peripheral tissues for around 12 hours \[20\]. Each fasting period is often longer than 12 hours and may therefore be considered to be a state of intermittent glycogen depletion and repletion \[ \text{Figure 5B}. \]\n
In the earlier (morning) part of the fasting day, there is a marked dominance of carbohydrate usage as the main source of fuel, whereas lipids become more important towards the afternoon and the time for breaking the fast at sunset (\textit{Iftar}) draws closer \[4, 36\]. In practice, most people who take their first meal at dawn are in a state of glycogen depletion by the late afternoon, at which point ketogenesis occurs. Omission of \textit{Suhoor} leads to a depletion of glycogen stores and results in a ketotic state much earlier in the fasting day.

6.2 Insulin sensitivity

Insulin sensitivity has been investigated in several studies. Many of these studies identified an association between fasting during Ramadan and with evening hypercortisolism and insulin resistance \[16, 37, 38\]. Ajabnoor \textit{et al.} reported a Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) of 1.98 in the morning measured before Ramadan increasing to 4.51 in morning during Ramadan. The corresponding evening values for pre-Ramadan and Ramadan were 4.94 and 12.01 respectively \[37\]. As such, the RF should be considered a state of insulin resistance.
Physiology of **feeding** in non-diabetic healthy individuals.

**Panel A:** In individuals without diabetes, after eating, increased glucose levels in the blood stimulate insulin secretion, which in turn triggers the liver and muscles to store glucose as glycogen.

**Panel B:** During fasting, circulating glucose levels fall and insulin secretion is suppressed. Glucagon and catecholamine secretions are increased, stimulating glycogenolysis and gluconeogenesis leading to an increase in blood glucose levels [39].

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6.3 Glucose profile

Studies utilising continuous glucose monitoring (CGM), that have been performed over the last few years have shed some light on other important changes to glucose homeostasis in the context of the RF. Several parameters have been examined including indicators of overall glycaemic control, hyperglycaemia and hypoglycaemia risk and glucose variability. The number of participants in these studies are typically quite small, and as such, the results should be interpreted with caution. Several studies report a reduction in fasting glucose levels during Ramadan [22, 40, 41]. However, most CGM studies, remarkably, showed stable blood glucose levels in healthy individuals (without diabetes) during fasting hours, with no significant differences in the markers of glucose exposure and average, highest or lowest glucose sensor readings [42]. At iftar, a modest rise in interstitial glucose (and therefore blood glucose) is seen, but with this increase it remains within normal ranges [43].
Interestingly, glucose homeostasis does not appear to revert back to that of pre-Ramadan in the early post-Ramadan period. Pallayova et al. reported a statistically significant increase in the hyperglycaemic (> 140 mg/dL) area under the curve (AUC) after Ramadan compared to both before and during Ramadan, along with an increased glucose variability after Ramadan (p=0.01). Both the area under the interstitial glucose concentration curve for the entire day and the average glucose were positively associated with BMI during (p=0.004 and p=0.005, respectively) and after Ramadan (p=0.01 and p=0.01, respectively) indicating that overweight and obese, but otherwise healthy subjects might be more prone to higher glucose excursions during Ramadan which could continue for days after the Ramadan fasting period has ended. The study also indicated atypical CGM patterns in a small group of subjects, distinguished by a prolonged increased glucose exposure, particularly in response to a meal [42].

7. LIPID CHANGES DURING RAMADAN IN HEALTHY INDIVIDUALS
Several studies have demonstrated that Ramadan fasting is associated with favourable effects on the lipid profile of healthy individuals [29, 44-46]. 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 [22]. There were however some differences in the effects of fasting on lipid profile between genders, with a statistically
significant increase in HDL in females, and a small statistically significant decrease in TG levels in males after Ramadan [22].

8. HORMONAL CHANGES DURING RAMADAN FASTING IN HEALTHY INDIVIDUALS

Changes in sleeping patterns during the Ramadan fast occur to accommodate for an early morning meal and also for the time spent in prayers, particularly in the evenings and early mornings. It is therefore expected that circadian and hormonal rhythms may alter. Several hormones have been investigated in the last few years and their changes with Ramadan fasting have been described. In reviewing the literature on hormones and hormone changes during Ramadan fasting, it is important to consider the effects on different factors including pulsatile secretion, circadian rhythmicity, stress response, and also the effect of eating and timing of meals. Other important factors to consider are gender and weight. As such, the effect of Ramadan on hormones may be different between men and women, and also in individuals of different ages or weight. Changes in hunger and hormones are described below; Figure 7A.

8.1 Cortisol

Cortisol is the chief glucocorticoid hormone under hypothalamic and pituitary control and secreted by the adrenal cortex. Cortisol secretion normally follows a circadian rhythm with a peak in the morning and a trough in the evening. It is also a stress hormone, with levels rising in response to physical and psychological stress. All of these factors may be of relevance in the context of the RF. Cortisol has important effects on blood glucose, through its effects on insulin sensitivity. A high level of cortisol is associated with a rise in blood glucose. Studies on the changes in cortisol with Ramadan with considerations to circadian changes have been very few. Bahijri et al. investigated various metabolic and hormonal parameters in 23 participants before and during Ramadan fasting [16]. Samples were taken at 9 AM and 9 PM. The study found lower morning cortisol levels and higher evening cortisol levels during Ramadan compared to the pre-Ramadan period (Figure 7B). The morning to evening cortisol ratio changed from 2.55 to 1.22. This reduction in the morning to evening cortisol ratio seems to be consistent in the few studies that have looked at cortisol circadian rhythmicity during Ramadan fasting.

8.2 Adiponectin

Adiponectin, hormone and adipokine, which is involved in regulating glucose levels as well as fatty acid breakdown, impacting metabolic activity and insulin sensitivity via actions on fat tissue, liver and skeletal muscle by regulating glucose metabolism and mitochondrial biogenesis [47]. Adiponectin modulates glucose metabolism and high levels are associated with increased insulin sensitivity [48]. Adiponectin is also indirectly involved with the inhibition of gluconeogenesis [48]. Plasma adiponectin levels can rise in response to caloric restriction; see Figure 7C. One study exploring the role of adiponectin during the RF observed a significant reduction in healthy males after 4 weeks of Ramadan [37] and another reported decreased levels of adiponectin in the mornings during Ramadan, compared to Sha’ban, whereas evening adiponectin levels showed no significant difference between these two periods [41]. Conversely, a study involving healthy males with risk factors for type 2 diabetes mellitus (T2DM) reported a significant increase in adiponectin at the end of Ramadan [49].
8.3 Leptin

Leptin is a satiety hormone secreted by the white adipose tissue. It has negative effects on feeding through its effects on the hypothalamus. Leptin also has important roles in bone metabolism and immunity. There are different patterns of leptin secretion between Ramadan and non-Ramadan times; see Figure 7C. In healthy individuals, leptin level rise in response to food. Its secretion follows a circadian rhythm, with a peak between 10 PM to 3 AM [50]. Leptin levels are positively related to weight and body fat. The effects of Ramadan on serum leptin seems to be directly related to the changes in the time of eating. Ajabnoor et al., in 2014, showed that compared to the pre-Ramadan period, Ramadan fasting leptin levels were much higher in the morning, but evening levels were similar to that of pre-Ramadan [37]. Alzoghaibi et al. found similar effects, but also reported reduction in night-time levels of leptin when compared with the period before and after Ramadan [51].

8.4 Ghrelin

Ghrelin is also an appetite stimulating peptide hormone. Circulating Ghrelin levels are high pre-prandially and drop after eating. As such, Ghrelin levels and its fluctuations might be expected to alter during RF. However, Alzoghaibi et al. found no significant differences in Ghrelin in individuals of a healthy weight during the RF [51]. Another more recent study in overweight and obese individuals reported a marked reduction in ghrelin in the last week of Ramadan [15].

8.5 Other hormones

Growth hormone is also an important hormone that can alter during Ramadan. It is known to affect insulin sensitivity, and acts as an important regulator of protein and fat metabolism as well as bone health. In children, it has a vital role in healthy growth and development. Growth hormone is normally secreted in a pulsatile manner. Its secretion also follows a circadian pattern, with the highest peaks in the early hours of the morning. As such, any study of growth hormone changes in the setting of Ramadan will need to take these into consideration with multiple samples taken during the 24-hour period. No such comprehensive study has been conducted as of yet. However, in the study by Ajabnoor et al., 9 AM and 9 PM growth hormone levels were taken in 23 healthy individuals, and lower levels were found during Ramadan in both the morning and the evening [37].

Other hormonal changes reported in RF include a modestly reduced reduction in testosterone in single men, towards the end of Ramadan period [52].
Physiology of feeding and fasting in healthy individuals.

Panel A: Changes in hunger–satiety cycles during Ramadan. During fasting hours, there is a progressive rise in hunger rating which peaks just before iftar time. Hunger–satiety cycles during Ramadan change in line with the shift in the timing of main meals, with wider gaps between meals intensifying feelings of hunger. This increase in the hunger during fasting hours is seen in both sexes and is intense by iftar. 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. Adapted from Finch et al., [21].

Panel B: Changes in cortisol circadian rhythm during Ramadan. Changes to sleep and food intake impact on circadian rhythms; compared with non-Ramadan periods, lower morning cortisol levels and higher evening cortisol levels have been observed during Ramadan. Adapted from Diabetes and Ramadan: Practical Guidelines International Diabetes Federation (IDF) [39].
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FIGURE 7
Physiology of feeding and fasting in healthy individuals.
Panel C: Circulating day and night levels of leptin, adiponectin, hsCRP and HOMA-IR during Sha‘ban – (a) and 2 weeks into the Ramadan – (b) in 23 healthy young Saudi Arabians. **p<0.01, ***p<0.005, ****p<0.0001. Adapted from Ajabnoor et al. [37].

9. NEW EVIDENCE OF CHANGES THAT CAN OCCUR WHEN FASTING DURING RAMADAN
9.1 Ramadan fasting and gut microbiota

Gut microbiota have emerged recently as an integral player in the progression of chronic diseases of obesity, and diabetes, alongside a range of other environmental and genetic factors [53, 54].

Recent studies indicate that dietary modifications, including intermittent fasting, have a substantial role in changing the gut microbiota in a way that improves the immune system and body metabolism. Furthermore, this positive change in gut microbiota has been found to affect body fat composition by changing the white adipose tissue into more mitochondria-dense browned tissue through a process known as “browning or beiging”, which in turn help to increase energy expenditure and reduce the chances of developing obesity [55].

The specific effect of Ramadan fasting on the gut microbiome has not been extensively studied. A pilot study (N=9) from Turkey revealed that microbial richness was significantly increased at the end of the Ramadan fasting period; no significant differences were found in terms of phylogenetic diversity metrics [56]. Studies in model organisms, such as mice, support the findings in humans and highlight the important changes that can occur to gut microbiota when fasting is conducted. Most recently, intermittent fasting has been found to reshape gut microbiota in healthy mice, with the length of the daily fasting interval being an important influencing factor [57].

The human salivary microbiota has been looked at as an important non-invasive approach to explore the bacteria shed from oral surfaces. This type of microbiota might also mirror oral
and general health [58]. Recent work using next-generation sequencing (NGS) techniques, on salivary microbiota and 16S ribosomal deoxyribonucleic acid (rDNA) from 64 obese individuals who were fasting during Ramadan, showed a statistically significant change in the phylum Candidatus Saccharibacteria/TM7 at the end of Ramadan when compared to the pre-Ramadan. The significance of this change is not currently known.

9.2 Ramadan fasting and gene expression

Although genes are inherently fixed and cannot be changed throughout the human life, it is well established that dietary and lifestyle behaviours affect human gene expressions [59], in a way that may modulate the risk of developing chronic diseases such as diabetes [60]. This effect of dietary and lifestyle behaviours is expressed by virtue of the epigenetic mechanisms such as histone acetylation and DNA methylation that affect the degree of gene expression [61].

The epigenetic effect of Ramadan fasting has been an area of recent interest. Some studies have indicated an impact of observing fasting during Ramadan on CLOCK circadian rhythm-controlling genes, a central component of the circadian molecular clock [62], antioxidant enzyme-controlling genes (TFAM, SOD2, and Nrf2) [63], and metabolism and aging-controlling genes (SIRT1 and SIRT3) [63]. In the study of Ajabnoor et al., CLOCK gene expression was significantly higher in the morning than in the evening during the pre-fasting month (Sha’ban) than during Ramadan fasting month, a matter that is explained by the changes in the sleep pattern encountered during Ramadan fasting days [62]. This significant change in the CLOCK gene expression has an adverse effect on glucose homeostasis and may contribute to the reported changes in insulin secretion patterns and increases in insulin resistance during Ramadan [16, 37]. These results highlight the potential adverse effect of staying up for long time during the night hours of the Ramadan month, a widely observed practice in many Islamic communities during Ramadan.

Madkour et al., investigated 56 overweight and obese participants and showed that the relative gene expressions, compared to normal healthy controls, for the antioxidant genes (TFAM, SOD2, and Nrf2) were significantly upregulated by variable degrees at the end of Ramadan (90.5%, 54.1%, and 411.5%, respectively). For the metabolism-controlling gene (SIRT3), genetic testing showed strong evidence (p<0.001) of downregulation, concomitant with a non-statistically significant reduction in SIRT1 gene expression at the end of Ramadan [64]. These results suggest that Ramadan fasting ameliorates gene expressions of anti-inflammatory and antioxidant regulatory genes, implying that Ramadan fasting may entail a protective effect against oxidative stress and its adverse metabolic-related derangements in non-diabetic obese individuals.

10. PATHOPHYSIOLOGY OF FASTING IN INDIVIDUALS WITH DIABETES

When fasting, insulin resistance/deficiency can lead to excessive glycogen breakdown and increased gluconeogenesis in people with type 1 diabetes mellitus (T1DM) and T2DM. In addition, in T1DM, augmented ketogenesis can occur. As a result, the risks facing people with diabetes are heightened during Ramadan. These include hypoglycaemia, hyperglycaemia, diabetic ketoacidosis, dehydration and thrombosis [20]. As well as fasting, the act of feasting during Ramadan also carries risks for those with diabetes (Figure 8).
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 people with T1DM and T2DM, respectively, compared to non-Ramadan periods \[65\]. During the fast, people with T1DM may fail to secrete adequate levels of glucagon in response to hypoglycaemia, leading to further decreases in blood glucose levels \[20\].

**FIGURE 8**
Pathophysiology of fasting in people with diabetes.

Panel A: Substrate oxidation as a function of daytime fasting. (Left). In individuals with diabetes, the underlying pathophysiology and the medications used to treat the condition both disturb glucose homeostasis. When fasting, insulin resistance/deficiency can lead to excessive glycogen breakdown and increased gluconeogenesis in people with T1DM and T2DM; in addition, in T1DM, augmented ketogenesis can occur.

Panel B: (Right) Recorded measurements of lipid and carbohydrate oxidation during Ramadan fasting. Substrate oxidation was measured by indirect calorimetry. Statistically significant time effects were observed \((p<0.05)\). Left: Adapted from Diabetes and Ramadan: Practical Guidelines International Diabetes Federation (IDF) \[39\]. Right: Adapted from Alsubheen et al.\[36\].

In addition, as a result of autonomic neuropathy, some people with T1DM may have a defective adrenaline response and therefore an inadequate response to hypoglycaemia \[66\]. The incidence of severe hyperglycaemia was also found to be increased during Ramadan (3-fold and 5-fold in people with T1DM and T2DM, respectively) \[65\].

**10.1 Glycaemic control and glucose variability**
Over the last few years, continuous glucose monitoring (CGM) studies have been performed in people with diabetes before and during Ramadan \[43, 67-69\]. As well as CGM, flash glucose monitoring (FGM) has also been available, and has been used to explore changes in glucose profiles during the RF. FGM is less invasive and more user friendly, and as such has been more...
readily accepted by the fasting individual. Both FGM and CGM have limitations that have to be considered when interpreting results of studies using these techniques.

One such CGM study investigated glucose variability in Ramadan in 33 individuals. An increase in the mean amplitude of glycaemic excursions (MAGE), was seen in the early stages of Ramadan compared to that of before Ramadan (p=0.006) but not in late-Ramadan and post-Ramadan. The higher MAGE in early Ramadan was only seen in individuals on multiple (>2) anti-diabetic drugs and those on sulphonylureas. No significant changes were seen in coefficient of variation, time in range, time in hyperglycaemia, or time in hypoglycaemia. Aside from an initial increase in glucose variability, fasting during Ramadan for people with non-insulin treated T2DM was found not to cause any significant changes in glucose variability or time in hypoglycaemia during CGM recording days compared to non-fasting pre-Ramadan period [70].

A larger study involving 50 people with T2DM, and six people with T1DM reported no significant differences in markers of glycaemic control between Ramadan and non-Ramadan periods [43]. There were no significant differences in the number of high or low glucose excursions, time spent in euglycaemia, hypoglycaemia, and hyperglycaemia [43]. However, major intra- and inter-individual variability in CGM profiles were observed. A rapid rise in glucose levels after Iftar was seen (Figure 9). Possible contributing factors to changes in glucose profiles have been postulated and include changes in dietary behaviour and a shift to carbohydrate-rich meals at Iftar.

FIGURE 9
Mean continuous glucose monitoring (CGM) profiles from people with diabetes before and during Ramadan.

A rapid increase in blood glucose is observed at Iftar time; the intake of the carbohydrate-rich meals at Iftar, and the involvement of hormonal changes are possible contributing factors that may explain this pattern. Inappropriate timing and inadequate dosing of anti-diabetic medication may also be important contributors to this rise. Figure adapted from Lessan et al. [43].
10.2 Effect of Medication type

In the study by Lessan et al., subgroup analyses by medication grouping (whether insulin, or sulfonylurea were part of the anti-diabetic regimen) showed a clear hierarchy in glycaemic profile outcomes with RF. Insulin-treated individuals showed the least favourable glucose profile with the highest AUC during Ramadan fasting, followed by those treated with sulfonylureas. Those treated with Metformin or not treated at all had the most favourable CGM profile. The risk of hyperglycaemia (high blood glucose index-HBGI) during Ramadan increased after Iftar in most groups and was highest in the insulin treated group. The risk of hypoglycaemia (low blood glucose index-LBGI) and MAGE were also higher in the insulin-treated group compared to other medication groups. A comparison of Ramadan glycaemic outcomes in different medication categories found the RF resulted in no deterioration in glycaemic profiles (mean glucose and glucose variability) among most individuals, although in a few people a deterioration or an improvement was seen, (Figure 10) [43].
**FIGURE 10**

Pathophysiology of fasting in people with diabetes.

**Panel A:** Mean continuous glucose monitoring (CGM) recordings for people with diabetes and controls when not fasting (Top) and fasting (Bottom) by type of treatment: Group 1 diet with/without metformin; Group 2 gliptin with/without metformin; Group 3 sulphonylurea with/without other oral agent(s); Group 4 insulin with/without other oral antidiabetic agents (OADs). The difference between groups when compared to controls was statistically significant (p<0.05, Wilcoxon’s signed-ranked test) for mean interstitial glucose during Iftar and the predawn meal Suhoor (shaded areas in the bottom graph).
**CHAPTER 3**

What happens to the body? Physiology of fasting during Ramadan

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**11. RAMADAN FASTING AND OTHER MEDICAL CONDITIONS: RELEVANCE TO DIABETES**

Several other common conditions can be affected by RF and many can be present in patients with diabetes. These include conditions such as hyperlipidaemias, hypertension, chronic kidney disease (CKD), ischaemic heart disease (IHD) and vitamin D deficiency. For some of these, only an adjustment of timing of medication during RF is needed. For others, such as CKD and IHD, advice from a specialist and if available multi-disciplinary management is recommended (see chapter 5: Risk stratification of people with diabetes before Ramadan and chapter 13: Risks of fasting during Ramadan Cardiovascular, Cerebrovascular and Renal complications).

**11.1 Hypothyroidism**

Hypothyroidism is a common endocrine condition and frequently seen in people with diabetes. There is no evidence of any significant changes occurring as a result of the RF in people with hypothyroidism as an underlying condition. However, changes to the timing of thyroxine ingestion are inevitable during the RF and in some individuals, this can lead to interference in

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*Size of bubble indicates glucose SD

FIGURE 10

Pathophysiology of fasting in people with diabetes.

**Panel B:** Mean interstitial glucose (IG) levels during non-Ramadan (blue circles) and Ramadan fasting derived from continuous glucose monitoring (CGM) data from the same individuals (concentric circles). Circle size corresponds to standard deviation (SD). Red circles: insulin-treated; orange circles: sulphonylurea-treated; purple circles: gliptins with/without metformin; green circles: no medication/metformin; and black circles: controls (no diabetes). Different trends were identified: A: good initial control with no significant change on fasting; B: poor initial control with no significant change on fasting; C: poor initial control with improvement on fasting; and D: good initial control with further improvement on fasting. In general, no significant SD changes were seen between non-Ramadan and Ramadan, indicating similar trends in overall glucose excursions during the two periods. The main outliers (D) were individuals taking insulin and sulphonylureas. Adapted from Lessan et al. [43].
thyroxine absorption and therefore suboptimal control of hypothyroidism. Thyroxine should be taken at least half an hour before breakfast. Its absorption can also be delayed if taken on a full stomach. In particular, absorption can be slowed by the concurrent use of iron supplements and antacids. The RF presents a challenge for individuals with hypothyroidism since the usual breakfast time is changed to a time earlier (pre-dawn Suhoor) [71]. Importantly, Suhoor is often a period of rush and taking thyroxine half an hour before the meal can have practical issues. Likewise, taking thyroxine at Iftar and waiting half an hour before eating takes the positive social impact and satisfaction of eating with the rest of the family away. The optimal time to take thyroxine and possible dose adjustments during the RF is a matter of debate [72], with one advocated solution being to take thyroxine later at night with the proviso that no heavy food is taken between Iftar and late night.

11.2 Bariatric surgery

Bariatric surgery (BS) is the most efficacious treatment for obesity. It is frequently performed in people with T2DM — many of whom are also obese. Many Muslim individuals choose to continue with their normal practice of fasting after bariatric surgery and this is an issue that might be of concern to doctors and healthcare professionals. Specific concerns include the inability to consume large meals and, in theory, absorb certain macronutrients. Few studies have explored these issues. Al-Ozairi et al., conducted a telephone survey of 207 participants with a history of previous sleeve gastrectomy and reported a reduced calorie intake of around 20% and 17% in men and women, respectively, during Ramadan. Of these reduction in caloric intake, the corresponding protein reductions were around 45% in men and 32.5% in women. No changes in fluid intake with the RF were reported. Participants reported feeling less hungry during while fasting during Ramadan [73].
SUMMARY

- Fasting during the month of Ramadan can precipitate dramatic changes in meal schedules, fluid intake, sleep patterns and circadian rhythms.
- These changes can have an impact on hormone levels and their normal rhythms. In people with diabetes, these include:
  - Insulin resistance and increased glucagon levels.
  - A shift in cortisol circadian rhythm with a blunting of the morning to evening ratio.
  - Reduction in morning adiponectin levels.
  - Large increases to morning leptin levels.
  - Reductions to morning and evening growth hormone levels.
  - Modest reductions in testosterone in men have also been reported.
- Fasting during Ramadan can have a direct impact on the gut microbiota which could lead changes in health.
- Fasting during Ramadan can induce epigenetic changes to genes such as those controlling circadian rhythm.
- Ramadan fasting can be associated with favourable physiological changes among healthy individuals such as decreased body weight and favourable changes in lipid profile.
- In people with diabetes however, Ramadan fasting can be associated with certain risks due to the pathophysiology that disrupts normal glucose homeostatic mechanisms.
- People with hypothyroidism as a comorbidity to diabetes may require specialised advice in taking thyroxine during Ramadan.
- People with diabetes, and in particular those with T1DM, should seek medical advice before deciding to proceed with Ramadan fasting.

ACKNOWLEDGEMENTS

Authors wish to thank Miss Ilham Saadane and Miss Ryan Khaled for their help with some of the illustrations used in this chapter.
REFERENCES

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