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Recommended Guidelines for Designing and Interpreting Ramadan Fasting Studies in Medical Research

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ABSTRACT

Ramadan fasting requires significant alterations to routine life, which can affect body homeostasis and metabolism. In spite of several studies conducted on the effects of Ramadan fasting on health and various disorders, there is an absence of comprehensive and reliable results due to heterogeneous methodologies and procedures (which is sometimes inevitable). Based on preliminary studies on this issue, this paper suggests a checklist containing the important factors for designing, interpreting, and comparing the results of Ramadan fasting studies. Circadian rhythm, season/latitude sensitivity, serum osmolality, and lifestyle alterations (e.g., dietary intakes, physical activity, sleep quality and duration, smoking) may be of great importance in Ramadan fasting studies. In addition, the number and pattern of fasting days (consecutive or alternate days) must be considered with regard to gender. Appropriate timepoints for blood/urine sampling might vary depending on cases.

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Introduction

Ramadan is the ninth month of the lunar calendar in which Muslims are obliged to abstain from eating and drinking from dawn to sunset in case of no contraindications. Islamic fasting brings about three main changes in daily routine including sleep pattern, eating, and physical activity (1-3). Thus, Ramadan fasting could be defined as a set of alterations besides fasting, which may affect circadian pattern, biochemical markers, and some physiological functions (2, 4-7).

Despite numerous studies conducted to elucidate the possible effects of this specific fasting pattern on several biological markers of health and disease, some substantial neglected confounders have made the results largely unreliable or inconclusive. This study aimed to elucidate the important factors that should be considered in designing, interpreting, and comparing the results of Ramadan fasting studies. The results of this study would help reach reliable conclusions and prevent faulty interpretations as reported in previous studies.

Circadian Pattern

Most biological functions in the human body follow the 24-hour variations called the circadian rhythm, to help adapt to the daily cycle of light and dark as the earth rotates every 24

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hours. The mechanism of these variations relies on endogenous signals as responses to biological functions.

Hypothalamus suprachiasmatic cells act as a body clock, and are connected to the eyes through nerves; they also receive hormonal signals from the pineal gland. These pathways are potential tools for responses of human body to light. Circadian rhythm is controlled by "clock genes" that code for clock proteins. The level of these proteins rises and falls in rhythmic patterns. These oscillating biochemical signals control various functions including sleep and rest time. Circadian rhythm also controls body temperature, heart activity, hormone secretion, blood pressure, oxygen consumption, metabolism, and many other functions. Furthermore, daily cycles regulate the level of some substances in our blood (e.g., red blood cells, blood glucose, gases, and ions such as potassium and sodium).

The classic phase markers for measuring a mammal's circadian rhythm are melatonin, cortisol, and core body temperature (8). Melatonin is secreted from the pineal gland in the dark and its receptors are located in suprachiasmatic cells, and its secretion is suppressed by natural and artificial light. Melatonin concentration is a strong indicator of the circadian rhythm. Signals of suprachiasmatic nucleus are transferred to the central nervous system, especially the hypothalamus (controlling body temperature, hormone secretion control, and sleep-wake pattern) through raphe nuclei (9).

Typically, serum melatonin concentration is low from 8 a.m. to 8 p.m. and a sudden increase occurs at 8 p.m., which returns to plateau at 0:00 a.m. (5). During Ramadan, a delay in melatonin nighttime peak and daytime slope was reported (10). Moreover, in Ramadan, its concentration is less at 0:00 a.m. and 4 p.m. than the other months (1, 5, 11).

Variation in cortisol circadian rhythm with a significant decrease in 8a.m./8p.m.basal cortisol ratio and higher morning peak followed by a rapid decrease at 12:00 were reported during Ramadan (5, 6). Increased diurnal and decreased nocturnal level of cortisol could be attributed to sleep disruption and late light exposure (5, 12). Cortisol affects metabolism of fat, protein, and carbohydrate, suppresses the immune system, and decreases bone formation. Therefore, variation in cortisol circadian rhythm may influence other biochemical rhythms, as well.

Furthermore, during Ramadan fasting, the normal cycle of body temperature may be disturbed (3) and delay in acrophase of skin temperature and energy expenditure peak were reported (13), which might be associated with hormonal or dietary intake alterations. Indeed, in Ramadan fasting, the routine sleep-wake pattern, exposure to natural or artificial light, food intake, and circadian patterns may be disturbed (14). These disturbances may cause a shift in the biochemical curve or make a different peak time compared to the other months (5, 7).

Therefore, measurement of biochemical variables according to the routine rhythm (before Ramadan) may render inconclusive results. Moreover, during Ramadan, fasting blood sample is usually collected just before sunset, while in the other months it is done early in the morning (at 8:00) (15). Thus, some circadian pattern-dependent variables may not be comparable. Table 1 shows some circadian pattern-dependent biochemical variables, which should be considered while designing and explaining the objectives of studies.

Table 1. Examples of biochemical variables with circadian pattern

Hormones	Neurotransmitters
Thyroid stimulating hormone (5)	Histamine (16)
Cortisol (17)	Metabolic rate (18)
Prolactin (19)	Blood pressure (20)
Insulin (21)	Heart rate (22)
Parathyroid hormone (23)	
Sexual hormones, follicle stimulating hormone, luteinizing hormone (24)	
Growth hormone (25) Adipokines (7)	
Serum biochemistry	
Serum glucose (21, 26)	
Immune cells (27), mast cells and eosinophils (16)	
Fat soluble vitamins (28)	
Lipoproteins (29)	
Fe (30)	

Transient or Permanent Changes

Ramadan-dependent lifestyle modifications may induce biological stress at least for a short while (e.g., the first week of Ramadan) (3, 31). Human body responds to environmental stresses in a variety of biological and cultural ways, i.e., genetic changes, developmental adjustment, acclimatization, cultural practices, and technology.

The body responds to certain stressors through activation of sympathetic nervous system. The sympathetic nervous system is responsible for up- and down-regulation of many homeostatic mechanisms in living organisms. Norepinephrine and epinephrine are two hormones that are released in response to emergencies within the body. However, the human body cannot maintain this state for long periods of time, afterwards, the parasympathetic system returns the body's physiological condition to the normal baseline (32). Indeed, this matter should be taken into consideration while determining the preliminary effects of Ramadan-induced stress and if possibbe investigated the trend of variation.

Reporting stress or adaption phase values require information regarding the trend of variable changes. Regarding variables affected by stress, studying the possible trend of change seems to be necessary for determining the standard and comparable timepoints for assessing a specific variable.

In Ramadan-related studies, specifying the main goal of the study is of utmost importance. In other words, it should be clear whether we are following transient or permanent alterations. Transient variations may sometimes be of great clinical importance. For instance, in a former study, a transient decline in fasting plasma glucose in the first few days of fasting was reported, which returned to baseline in the second half of the month of Ramadan (33). This matter may be of great importance in diabetic patients, due to the increased risk of hypoglycemia and hyperglycemia during Ramadan (34, 35). On the contrary, the aim may be evaluating long-term effects and transient changes (especially within normal range) may not be considered critical or of clinical value.

Definition of Ramadan Fasting

Ramadan fasting is a 29-30 day period of intermittent fasting (a cycle of fasting and non-fasting periods in the 24 hour course of a day). Nevertheless, this period may be interrupted by some events (e.g., travelling or disease) and menstrual bleeding in women. These types of fasting cessation may occur in the early or late Ramadan and can lead to several different models of alternate day fasting. In addition to the possible variations of some metabolites during women's menstrual cycle (36), depending on the variable measured and according to the frequent and special changes of biological stress and circadian pattern, such alternate day fasting may act differently in comparison to the consecutive day fasting, which is originally defined as Ramadan fasting.

Literature review shows no standard inclusion criteria for definition of Ramadan fasting. In most studies, the number of fasting days was not mentioned or considered as an inclusion or exclusion criteria (37, 38) and some others included those who had fasted for at least 10 or more days regardless of fasting pattern (39-41). Ramadan fasting requires a unique lifestyle, which should be continued consecutively during Ramadan. Thus, determining the actual effects of Ramadan fasting requires considering all its aspects.

Season and Latitude

Ramadan is a lunar month and it begins about 11 days earlier each solar year. Therefore, Ramadan travels throughout the months and seasons. Additionally, depending on the time of the year, day length will either increase or decrease as locations progress north or south (across latitudes). There are 90 degrees of latitude and three latitude zones as low, middle, and high. Each latitude zone is 30 degrees wide, and the equator is 0 degrees. 0-30, 30-60 , and 60-90 are low, middle, and high zones.

At 0° latitude (the equator), day length will be approximately 12 hours. Areas on the equator have 12 hours of daylight all year long. As latitude increases to 80° (polar circles: north or south) day length can increase to 24 hours or decrease to zero (depending on the time of year). In general, day length varies throughout the year depending on latitude. Day length varies insignificantly at lower latitudes, whereas the seasonal (winter-to-summer) contrast in length of day increases with increasing latitude.

Locations on similar latitudes have similar day lengths, whereas different latitudes have different day lengths. Depending on the season or latitude, fasting duration can be as long as 8-18 hours and temperature would vary, as well. Differences in the time intervals between dawn and sunset may be associated with variations of lifestyle (e.g., dietary intakes and physical activity), circadian patterns (14), and other environmental conditions that may strongly affect fasting outcomes (42). Therefore, it may not be reasonable to compare the results of studies conducted in different geographical regions, at least in terms of variables influenced by season, latitude, and temperature, unless controlling for those variables.

Many diseases have a seasonal variation. The seasonal variation of the non-communicable diseases revealed a strange seasonal increase in the number of cases of chronic obstructive pulmonary disease in the months of February and December and gastritis in May and June, while falls and injuries showed two peaks in the months of February and June (43). Furthermore, plasma volume usually increases during summer and decreases during winter, which can lead to seasonal variability in serum blood lipid level, especially in women and hyper-cholesterolemic individuals (44). Body basal metabolic rate increases in winter, especially in young adults, and free thyroid hormone level attenuates during winter (45).

Considering the day length variation, comparison of the results should be limited, especially for variables affected by latitude or seasonality (Table 2). Thus, fasting duration should be clearly mentioned in the materials and methods section and the number of daylight hours is suggested to be considered as a continuous measure of seasonality in the multivariate analyses (46).

Serum Osmolality

Various factors may affect hydration status of the body such as activity, diet, and climate. Restricted fluid intake (between Iftar and Sahar) during Ramadan, depending on the amount of sweating and season, can lead to some degrees of hypo-hydration, reduced extracellular fluid (14, 69), and increased serum osmolality even in the normal range (69, 70), especially in the evening (71). In addition to the increased risk of some diseases (e.g., atherothrombosis) (72) and electrolyte imbalances in workers of hot climates (73), such lifestyle-dependent hypo-hydration may lead to, depending on the degree of hypo-hydration, a mis-variation of reported changes in serum or urine concentrations. Therefore, the reported changes in serum or urine concentrations can be misleading if blood samples were obtained just before Iftar.

Table 2. Examples of season/latitude-dependent variables and conditions

Season dependent	
Autoimmune diseases (47)	Serum folate (48)
Gastrointestinal diseases (49)	Serum sodium (50)
Thyroid disease (45)	Serum iron (51)
Chronic obstructive pulmonary disease (COPD) (43)	Serum vitamin D (52)
Coronary heart disease (CHD) (53)	Lipid profile (44)
Asthma (54)	C-reactive protein (CRP) (55)
Dry eye (56)	Thyroid hormones (45)
Emergency general surgery (57)	Basal metabolism rate (BMR) (45)
Suicide (58)	Food intake (59)
Fertility (60)	Latitude dependent
Birth weight (61)	Autoimmune conditions, multiple sclerosis (62)
Glomerular filtration rate (GFR) (63)	Prostate cancer (64)
Neurotransmitter system (65)	Breast cancer (64)
Mood and behavior (66)	Energy metabolism (67)
Blood pressure (68)	Colorectal cancer (64)

There are several methods for determining hydration status such as monitoring body mass changes, measuring sweating and various blood markers, and analysis of urine. The urinary measures of color, specific gravity, and osmolality were reported to be more sensitive at moderate levels of hypo-hydration than blood measurement of hematocrit, serum osmolality, and sodium concentration (74).

Nutritional Intakes and Physical Activity

Ramadan fasting may be associated with inevitable changes in lifestyle including dietary intake (75, 76) and physical activity level (77, 78). The frequency of food intake may decrease during Ramadan with a tendency to take a high proportion of total calorie from Iftar (the sunset meal). In addition, the proportion of macronutrients (carbohydrate, protein, and fat) may change (79-84), and consumption of some special foods (e.g., date, honey, sweets, and soft drinks) increase (80) or decrease (e.g., vegetables and dairy products) (84, 85). Therefore, Ramadan-specific dietary patterns with regard to the study population can be observed (41). Alteration in dietary pattern, consumption of special foods in different communities, and interpersonal differences in dietary intake during Ramadan (41) may lead to heterogeneous and inconclusive results.

Level of physical activity usually diminishes during Ramadan (77, 78); moreover, dietary intake and physical activity play an important role in homeostasis (86, 87); these confounding factors must be controlled while designing and analyzing studies. For the design stage, matching and for the analytical stage, multivariate analysis and adjusting for confounding should be considered.

Smoking

Some people may quit smoking during Ramadan and some others may restrict it only to the time interval between Iftar and Sahar often with reduced number of cigarettes. Since smoking may affect several biological functions in the body (88-90), considering its quitting or restriction during Ramadan would be necessary in the study design and data analysis stages.

Eid al-Fitr

Eid al-Fitr (the first day of the lunar month of Shawwal) is an important religious holiday celebrated by Muslims worldwide. This day marks the end of Ramadan during which Muslims are not permitted to fast. It may be another biological stressful event, accompanied with a change back to usual lifestyle, and may consequently lead to some specific metabolic alterations again.

As with any joyous occasion, food is a big part of the Eid, which is cultural and varies across countries. All these sudden lifestyle alterations may affect dietary-dependent variables. Eid al-Fitr marks returning to the routine lifestyle, which could be as a big stressor and may affect stress-dependent variables at least for a short time.

To overcome the difficulty of choosing the right time for blood or urine sampling, due to disturbance of circadian pattern during Ramadan, researchers design studies based on the comparison of values before and after Ramadan, which may be a sensible decision about more stable variables such as cholesterol. However, some other variables might be immediately affected by lifestyle alterations such as fasting blood glucose and triglyceride level. Thus, appropriate timepoint for sampling should be considered carefully according to the characteristics of the studied variable.

Conclusion

Designing and interpreting Ramadan fasting studies in medical research should be done with caution, considering the circadian pattern of the variables under study, the possible impact of season and latitude, serum osmolality, and lifestyle changes (e.g., dietary intake, physical activity, sleep quality and duration, smoking). The main objective of studies, such as looking for transient/permanent, short/long-term, or rapid/slow changes, should be mentioned, as it can play a role in choosing the appropriate timepoint for sampling.

Moreover, to be able to compare the results of different studies, the number and pattern of fasting days as well as gender of the participants should be mentioned. According to the objectives, adjusting or matching for confounding variables would is also recommended. We developed a checklist, as a guideline, to be applied in designing and interpreting Ramadan fasting studies in medical research (Table 3).

Table 3. Checklist for designing and interpreting Ramadan fasting studies in medical research

Definition of Ramadan fasting	☐ Men ☐ 29-30 consecutive days of intermittent fasting ☐ ≥25 consecutive days of intermittent fasting ☐ ≥20 consecutive days of intermittent fasting ☐ ≥15 consecutive days of intermittent fasting ☐ ≥10 consecutive days of intermittent fasting ☐ ≥25 alternate days of intermittent fasting ☐ ≥20 alternate days of intermittent fasting ☐ ≥15 alternate days of intermittent fasting ☐ ≥10 alternate days of intermittent fasting ☐ Women ☐ 20-24 consecutive days of intermittent fasting (regardless of menstrual cycle) ☐ ≥15 consecutive days of intermittent fasting ☐ ≥10 consecutive days of intermittent fasting ☐ ≥15 alternate days of intermittent fasting ☐ ≥10 alternate days of intermittent fasting
Geographical region, season, and latitude	Hemisphere: ☐ Northern ☐ Southern
	Latitude: ☐ Low ☐ Middle ☐ High
	Year (A.D.) ☐
	Month: ☐ January ☐ February ☐ March ☐ April ☐ May ☐ June ☐ July ☐ August ☐ September ☐ October ☐ November ☐ December
	Season: ☐ Winter ☐ Spring ☐ Summer ☐ Autumn
	Day length ☐ hours, ☐ minutes ☐ Temperature ☐
Objective	☐ Transient/rapid changes during Ramadan ☐ Permanent/slow changes lasting at least for a short time after Ramadan
Circadian pattern	☐ The variables have circadian pattern ☐ The variables have no circadian pattern ☐ Unknown
Set points for assessments or evaluations	☐ Before Ramadan ☐ The first week of Ramadan ☐ The second week of Ramadan ☐ The third week of Ramadan ☐ The fourth week of Ramadan ☐ A few days after Ramadan ☐ One month after Ramadan ☐ Two months after Ramadan ☐ 3-6 months after Ramadan ☐ 6-12 months after Ramadan
The time of blood, urine, etc. sampling	☐ Early in the morning ☐ <7 hours fasting from Sahar (before sunrise meal) ☐ 7-13 hours fasting from Sahar ☐ >13 hours fasting from Sahar ☐ During a hour before Iftar (after sunset meal)
Adjusting or matching for	☐ Dietary intake ☐ Level of physical activity ☐ Sleep duration ☐ Body hydration status (urinary indices) ☐ Body hydration status (blood borne indices)

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