

## Chapter 2

# Ramadan Fasting and Immunity System

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## Abstract

Ramadan fasting represents the ninth month of the Muslim lunar calendar and the fourth of the five pillars of the Islam creed. Even though patients and pregnant women are exempted from observing this religious duty, they may be willing to share this particular moment of the year with their family and peers, by attending the special prayers (such as the *tarawih*), social gatherings and other ceremonies. However, there are no guidelines or standardized protocols that can help clinicians to properly address the issues and concerns of patients and pregnant women eager to fast in Ramadan and correctly advising them. Despite the extensive body of studies conducted on Ramadan fasting, no clear information is available concerning the changes of immunity system during the fasting month. We systematically searched ISI Web of Science (WoS), Scopus, MEDLINE/PubMed, Google Scholar, DOAJ, EbscoHOST, Scirus, Science Direct, the Cochrane Library and ProQuest. We used a proper string made up of a combination of key-words such as “Islam”, “Ramadan”, “Fasting” and “Immunity”. 30 original research articles were included in the current review: 14 studies focusing on immunity changes in healthy subjects, 7 in athletes, 5 in patients with metabolic disorders, 3 in individuals suffering from cardiovascular diseases and hypertension, and only 1 in pregnant women. From the collected evidences, we can conclude that: 1) Ramadan fasting does not result in severe immunological disturbances, being all the changes transient and recovering to normal values and ranges after the fasting month; 2) maternal fasting during the second trimester does not have a significant impact on maternal oxidative stress, fetal development or fetal birth weight; 3) Ramadan fasting can have beneficial effects on patients suffering from metabolic disorders (obesity and diabetes mellitus); 4) Ramadan fasting can have positive effects on patients with stable cardiac diseases and hypertension, improving cardiovascular, lipids profile and oxidative stress; 5) Ramadan can affect and impair the activity of athletes. However, the majority of the studies has

been conducted among healthy volunteers and there is a dearth of data about patients suffering metabolic and cardiovascular diseases. No data are available for patients with autoimmune disorders. Further research in the field is urgently needed.

**Keywords:** Athletes; Biological Pathway and Network; Cardiovascular Diseases; Diabetes Mellitus; Hypertension; Immunity System; Metabolic Disorders; Obesity; Oxidative Stress; Pregnancy; Ramadan Fasting

## Introduction

The Holy month of Ramadan, the ninth month of the Muslim lunar calendar (*Hijra*), is particularly blessed and of great value and significance among Muslims, representing the month of the descent of the *Qu'ran*. Ramadan is not only abstinence from food and drinking, but also from smoking, medication and sexual intercourses (*Surat 2 "Al-Baqarah", ayyat 183 and following verses*).

Ramadan fasting is not, however, a prolonged or continuous fasting, but consists of alternate fasting and feasting (re-feeding) periods [1]. The fast is broken, taking two traditional meals, pre-dawn meal which is termed as *suhoor*, whilst after-sunset meal is called *iftar*. Ramadan duration is variable (29-30 days), mean fasting duration is usually 12-14 hours, but depending on the place and the year it can last also up to 18 hours [1] or even 22 hours, in the extreme latitudes regions [1].

Patients and pregnant women are exempted from this religious duty (*Surat 2 "Al-Baqarah", ayyat 185-186*). However, they could be willing to fast and share the spirituality of this month with their family and peers, by attending the special prayers (such as the *tarawih*, usually prayed in pairs of two in at least 20 *raka'at* according to Hanafis and Shafi'i schools, while some scholars believe that 8, 12 or 20 *raka'at* can be done, with a break after every 4 *rak'ah*), social gatherings and other special ceremonies [3].

The effects of Ramadan fasting on human physiology and pathophysiology is not a mere academic and speculative topic or of limit interest for only the Arabic countries. It has instead clinically relevant and pragmatic implications: in a globalized society, the physicians have to face with issues like the management of diabetes mellitus and Chronic Kidney Diseases (CKDs) in Muslim patients that want to fast during Ramadan [4]. However, information is sparse and no guidelines or standardized protocols exist [4,5].

For these reasons, we carried out an extensive overview on the impact of Ramadan fasting on the immunity system.

## Materials and Method

We systematically searched ISI Web of Science (WoS), Scopus, MEDLINE/PubMed, Google Scholar, DOAJ, EbscoHOST, Scirus, Science Direct, the Cochrane Library and ProQuest. We used a proper string made up of a combination of key-words such as "Islam", "Ramadan", "Fasting" and "Immunity".

Gray literature was also manually searched. Review articles or research manuscripts not pertinent with the aim of this systematic review were excluded, while all the other research articles (including editorials, letters, case reports) were retained. No time and language filters were applied.

Topic	References
Immunity System and Healthy Subjects	Akrami Mohajeri et al., 2013 [11] Chennaoui et al., 2009 [12] Develioglu et al., 2013 [10] Faris et al., 2012a [9] Faris et al., 2012b [18] Ibrahim et al., 2008 [17] Lahdimawan et al., 2013a [13] Lahdimawan et al., 2013b [14] Lahdimawan et al., 2014 [15] Latifynia et al., 2007a [6] Latifynia et al., 2007b [7] Latifynia et al., 2008 [8] Sülü et al., 2010 [19] Zainullah et al., 2005 [16]
Immunity System and Pregnant Women	Ozturk et al., 2011 [20]
Immunity System and Metabolic Disorders	Al-Shafei, 2014a [24] El-Gendy et al., 2012 [25] Radhakishun et al., 2014 [23] Shariatpanahi et al., 2012 [22] Unalacak et al., 2011 [21]
Immunity System and Cardiac Diseases	Al-Shafei, 2014b [28] Khafaji et al., 2012 [26] Nematy et al., 2012 [27]
Immunity Systems and Athletes	Abedelmalek et al., 2011 [31] Aksungar et al., 2007 [30] Chaouachi et al., 2009 [29] Hammouda et al., 2013 [32] Hammouda et al., 2014 [33] Maughan et al., 2008 Trabelsi et al., 2012

**Table 1:** Studies divided according to their main topic.

## Immunity Changes in Healthy Individuals

Latifynia and collaborators [6] studied neutrophil respiratory burst (innate immunity) in a sample of 24 male healthy volunteers (aged 18-35 years, mean age 26.5) using chemiluminescence method. No statistically significant changes in innate immunity were observed before and after Ramadan.

The same authors [7] investigated the impact of Ramadan fasting on Circulating Immune Complexes (CICs) using the polyethylene glycol precipitation method, quantitative chemiluminescence and circulating immune techniques, before and after Ramadan. They assessed a convenience sample of 28 healthy medical students residing in dormitory of Tehran University, out of an initial list of 120 individuals. The mean age of the students was 26.2 years. The mean CIC level was  $2.04 \pm 1.86$  before Ramadan and  $2.63 \pm 2.1$  after Ramadan ( $p$ -value >0.05). The authors found that CIC level was increased in 17 cases and decreased in 11 cases, only 6 cases were out of normal range after Ramadan, and only 1 case of the 6 increased cases had high CIC level before and after Ramadan. Only 3 cases had low CIC level before Ramadan that remained abnormal after Ramadan. 3 cases decreased and set to normal group and one case remained in the abnormal group. The authors concluded that there was no significant difference between the CIC level before and after Ramadan.

The same authors [8] investigated neutrophil respiratory bust in a sample of 21 male students at Tehran University, Tehran, aged 18–35 years (mean 26.5). In 11 cases, the changes of chemiluminescence were in normal range, while 6 cases had CIC changes in normal range. In 9 cases the changes were in normal range which 2 cases had normal level of CIC, before and after Ramadan, the CIC levels in 3 cases was abnormal, however after Ramadan, the values were returned to normal, In spite, in 4 cases CL was normal, that their normal values of CIC changed to abnormal, after Ramadan. Finding that there were

no significant changes in the activity of circulating neutrophils and CIC levels before and after Ramadan, the authors concluded that Ramadan fasting has no effect on neutrophil respiratory burst.

Moreover, a correlation between CIC and neutrophil respiratory burst was found.

Faris and co-workers [9] carried out a cross-sectional study recruiting fifty (21 men and 29 women) healthy volunteers for the investigation of circulating pro-inflammatory cytokines (IL-1 $\beta$ , IL-6, TNF- $\alpha$ ), immune cells (total leukocytes, monocytes, granulocytes, and lymphocytes). The pro-inflammatory cytokines IL-1 $\beta$ , IL-6, and TNF- $\alpha$  were significantly lower ( $p$ -value <0.05). Immune cells significantly decreased during Ramadan, however within the reference ranges. These results indicate that RIF attenuates inflammatory status of the body by suppressing pro-inflammatory cytokine expression and decreasing circulating levels of leukocytes.

Develioglu [10] and collaborators collected blood and saliva samples one week before and during the first week of Ramadan from 35 healthy male volunteers, aged 20-59 years (mean age 35.86 years). Total lymphocyte count and IgG and IgM concentrations were determined in serum, as well as salivary IgA. Serum IgG concentrations decreased significantly during Ramadan compared with before fasting, but were still within the normal range. Salivary IgA concentrations also decreased significantly, whereas serum IgM levels did not change. Lymphocyte numbers increased significantly, but there was no correlation between Ig levels and lymphocyte count.

Akrami Mohajeri [11] and collaborators studied CXCL1, CXCL10 and CXCL12 chemokines, using ELISA assay, in a sample of 58 healthy subjects, aged 20-40 years. The authors found decreased levels of pro-inflammatory CXC chemokines but unaltered levels of homeostatic ones. The scholars concluded that fasting is important in controlling of inflammation via chemokines.

Chennaoui and coauthors [13] recruited 40 healthy volunteers of normal weight, 20 females aged 20-38 years, 20 males aged 23-39 years compared with another 28 healthy age- and BMI-matched volunteers (14 males, 14 females) who did not fast. Serum IL-6, C-Reactive Protein (CRP), homocysteine was measured. IL-6, CRP and homocysteine levels were significantly low during Ramadan in the fasting subjects of both genders when compared to basal values.

Lahdimawan and co-authors [14] studied the effect of Ramadan on the levels of Complement C3, inducible Nitric Oxide Synthase (iNOS), Superoxide Dismutase (SOD) levels in serum and Peripheral Blood Mononuclear Cells (PBMC) in 30 healthy male volunteers. The authors found that Ramadan has a beneficial effect on host defense against *Mycobacterium tuberculosis* and decreases the risk of tuberculosis infection in healthy subjects.

The same authors investigated the functions of macrophage activity in a sample of 27 male healthy volunteers aged 18-22 years (mean age 20.26  $\pm$  1.13 years). Macrophage IFN- $\gamma$ , TNF- $\alpha$ , iNOS increased, while SOD decreased. The authors concluded that Ramadan altered classically activated macrophage regulation and signaling and increased macrophage function, reducing macrophage oxidative stress.

A further study performed by the same authors [15] investigated the impact of Ramadan on endorphin and endocannabinoid and levels. 27 healthy volunteers male aged 18-22 years (mean age 20.26  $\pm$  1.13 years) who fasted during Ramadan participated in the study. Endorphin in the serum, PBMC and macrophage increased, as well as endocannabinoid in the serum, but endocannabinoid in the macrophage decreased. No change for endocannabinoid in the PBMCs. Ramadan has subtle effects on endocannabinoids and endorphins.

Zainullah and co-authors [16] studied the change of psychoneuroimmunological response among 13 individuals, measuring neutrophil, lymphocyte, monocyte, IgG and cortisol. On

the fifth day of the fasting, cortisol, IgG, and monocyte increased, while neutrophil count decreased. On the 16<sup>th</sup> day, cortisol, neutrophil, and monocyte count increased, while IgG level decreased. Towards the end of Ramadan, the level of these parameters returned in the previous range.

Ibrahim and co-workers [17] studied 14 healthy volunteers (9 men and 5 women aged 25-58 years), measuring Malondialdehyde (MDA), glutathione, glutathione peroxidase and catalase. Erythrocyte MDA decreased, while the reduction in lipid peroxidative damage in erythrocytes was slight.

Faris and collaborators [18] investigated the oxidative stress in 50 healthy subjects (23 men and 27 women), measuring the 15-F (2t)-Isoprostane (15FIP). 15FIP increased and correlated with the body weight and total body fat percent.

Sülü and co-workers [19] investigated malondialdehyde and glutathione levels in 45 healthy volunteers (22 females, 23 males, and mean age 28.7 years, range 21-51 years). Malondialdehyde levels increased in both genders; however the increase was statistically significant only in female subjects. Glutathione levels decreased in males, while increased in females. Ramadan could cause oxidative stress in particular subjects depending on some factors such as socio-economic conditions, nutritional habits, and gender.

In conclusion, Ramadan fasting has a modulatory effect on chemokine network, oxidative stress pathway, adaptive and innate immunity.

## **Immunity Changes in Pregnant Women**

Ozturk and collaborators [20] investigated the impact of Ramadan on the immunity system of pregnant women in a prospective controlled matched study of 42 fasting and 30 non-fasting pregnant women. Total Antioxidant Status (TAS), Total Oxidant Status (TOS) and the Oxidative Stress Index (OSI) were measured from maternal serum samples taken on a fasting day during Ramadan. No significant differences were observed between the groups studied in terms of TOS, OSI, maternal age, gestational age, parity, birth weight or weight gain during the pregnancy. The TAS level was evaluated as significantly higher (*p-value* =0.027).

In conclusion, Ramadan fasting has no impact on pregnancy.

## **Immunity Changes in Patients with Metabolic Disorders**

Unalacak and co-workers [21] recruited 10 obese males (7 suffering from a clinically diagnosed metabolic syndrome) and 10 males with a normal Body Mass Index (BMI). Serums White Blood Cells (WBC) count, IL-2, IL-8, TNF- $\alpha$  were significantly lower in both groups compared to pre-Ramadan values.

Shariatpanahi and co-authors [22] studied 65 male with metabolic syndrome, evaluating hs-CRP before and after month of Ramadan. Hs-CRP was decreased significantly, being related to waist circumference and BMI.

Radhakishun and co-workers [23] carried out a prospective cohort study in 25 obese adolescents, measuring hs-CRP levels. A statistically significant increase in hs-CRP concentration was found, recovering to baseline levels after Ramadan.

Al-Shafei [24] carried out a prospective controlled matched study recruiting 40 non diabetic subjects and 40 diabetic patients. Malondialdehyde (MDA) decreased. The scholar concluded that Ramadan fasting improves glycemic control and lipids profile and alleviates oxidative stress in diabetics.

El-Gendy and collaborators [25] studied the oxidative stress in 20 patients with diabetes mellitus. Serum Malondialdehyde (MDA) and Glutathione (GSH) were measured. MDA



decreased, while GSH increased. This study confirmed that Ramadan fasting significantly lowers oxidative stress in the body.

In conclusion, patients with controlled metabolic disorders can safely fast.

## Immunity Changes in Patients with Cardiac Diseases

Khafaji and co-authors [26] investigated immunity changes in a sample of 56 patients (80.4% were male, 67.9% were aged >50 years) of different stable cardiac illnesses were followed, collecting and measuring hs-CRP. 71.4% had no change in their symptoms during fasting while 28.6% felt better. No patient has deteriorated. 91.1% of the patients were compliant with medicine during Ramadan, 73.2% after. 89.3% were compliant with diet during Ramadan with no significant change in body weight in the follow-up period. No cardiac or noncardiac morbidity or mortality was reported. No change was observed in hs-CRP and its level correlated with total cholesterol and serum leptin. Ramadan fasting in stable cardiac patients has no effect on their clinical status, serum leptin, or hs-CRP.

Nematy and co-authors [27] carried out a prospective observational study in a group of 82 patients (38 males 44 females, aged 29-70 years, mean age  $54.0 \pm 10$  years) with at least one cardiovascular risk factor. Homocysteine, hs-CRP and complete blood count were measured. A significant improvement in 10years coronary heart disease risk was found, as well an increased WBC, RBC and platelet count. No other significant changes were observed. Homocysteine and hs-CRP increased during the exercise, suggesting that caloric restriction and exercise seem to ameliorate inflammatory markers of cardiovascular health.

Al-Shafei [28] studied the variation of Pulse Pressure (PP) and oxidative stress in 40 hypertensive subjects and in other 40 healthy individuals. Fasting reduced PP significantly by 17.2%, while Malondialdehyde (MDA) decreased and Glutathione (GSH) increased.

In conclusion, patients with controlled cardiovascular disorders can safely fast.

## Immunity Changes in Athletes

Chaouachi and collaborators [29] studied the impact of the fasting on immunological parameters in 15 elite male judo athletes maintaining their usual high training loads. Small but significant changes in inflammatory variables were found. Serum C-reactive protein increased from  $2.93 \pm 0.26$  mg/L to  $4.60 \pm 0.51$  mg/L, whereas homocysteine remained relatively unchanged. Immunoglobulin A increased from  $1.87 \pm 0.56$  g/L to  $2.49 \pm 0.75$  g/L and persisted high for 3 weeks. There were no changes in the leucocyte cell counts throughout the study. These results suggest that athletes who continue to train intensely during Ramadan are likely to experience a myriad of small fluctuations in immunoglobulins, antioxidants, and inflammatory responses.

Aksungar and collaborators [30] studied 8 middle-distance athletes ( $25.0 \pm 1.3$  years), performing a Maximal Aerobic Velocity (MAV) test 5 days before Ramadan and on days 7 and 21. Plasma levels of IL-6 were determined. IL-6 was increased ( $1.19 \pm 0.25$  vs.  $0.51 \pm 0.13$  pg/mL; *p-value* <0.05), but recovering to normal values after Ramadan. The authors found significant immunity changes that could affect the activity of elite athletes.

Abdelmalek and co-workers [31] studied 9 athletes performing the Wingate test. Plasma concentrations of IL-12 were measured using ELISA assay. The authors found that an acute intense exercise-induced IL-12 response is modified by daytime fasting and modifications in sleep schedule during Ramadan.

Hammouda and collaborators [32] measured the levels of hs-CRP and homocysteine during the Yo-Yo intermittent recovery test in 15 soccer players. Homocysteine and hs-CRP increased during the exercise. During the end of Ramadan, the diurnal pattern of Hcy was inversed. The authors concluded that caloric restriction induced by RF seems to ameliorate

lipid and inflammatory markers of cardiovascular health during intermittent exercise performed in the evening.

The same authors [33] investigated the effects of Ramadan fasting and time-of-day on biochemical responses to an intermittent exercise, Yo-Yo test level 1, in 20 male soccer players (mean age  $17.52 \pm 0.2$  years) measuring Total Antioxidant Status (TAS). TAS was found to increase. Performance was affected by Ramadan fasting only in the evening in young soccer players.

Trabelsi and collaborators [34] investigated immune biomarkers in recreational body-builders, undergoing a hypertrophic training program for 3 times/week. They found that leucocytes, neutrophils, lymphocytes and monocytes remained unchanged.

Maughan and co-workers [35] studied immune markers in 78 Tunisian junior male soccer players aged 16-19 years who continued their usual schedule of daily training and weekly competition. They found that CRP decreased in football players, as well leucocyte count.

In conclusion, Ramadan can affect sports performances.

## Conclusions

From the collected evidences, we can conclude that:

Ramadan fasting do not result in severe immunological disturbances, being all transient changes;

- a. Maternal fasting during Ramadan during the second trimester does not have a significant effect on maternal oxidative stress, fetal development or fetal birth weight.
- b. Ramadan fasting can have beneficial effects on patients suffering from metabolic disorders;
- c. Ramadan fasting can have positive effects on patients with stable cardiac diseases, improves cardiovascular, lipids profile and oxidative stress;
- d. Ramadan can affect and impair the activity of athletes (as also summarized by Trabelsi and collaborators [36]).

However, the majority of the studies have been conducted among healthy volunteers and there is a dearth of data about patients suffering metabolic and cardiovascular diseases. No data are available for patients with autoimmune disorders. Further research in the field is urgently needed.

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