Ramadan intermittent fasting and immunity: An important topic in the era of COVID-19

Mo'ez Al-Islam E. Faris, Mohamed L. Salem, Haitham A. Jahrami, Mohamed I. Madkour, Ahmed S. BaHammam

Abstract:
WITH the growing pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome (SARS)-related coronavirus (SARS-CoV-2) infection, a parallel growing interest arose concerning potential preventive and adjunct therapies, dietary and lifestyle modifications, and remedies that may boost the immunity against SARS-CoV-2 infection. Furthermore, as Ramadan intermittent religious fasting that is practiced by about one and a half billion Muslims throughout the globe is coincide this year with COVID-19 pandemic, a growing debate rose concerning the expected impact of fasting during Ramadan month and the associated dietary and lifestyle behaviors on the body's immunity against the pandemic infection. Published literature was searched to find out how intermittent fasting (IF) and its model of Ramadan affect the various aspects related to the body’s immunity against microbial infections. IF was found to impact immunity by changing different related elements, including oxidative stress and inflammation, metabolism, body weight, and body composition. Dietary and lifestyle modifications during Ramadan month and their impact on immunity, such as water intake and hydration status, sleep duration and timing, caloric intake and mealtime, and social and spiritual activities, were addressed. Further research is warranted to figure out how IF during Ramadan affects immunity against SARS-CoV-2 infection.

Keywords:
Coronavirus, COVID-19, diurnal fasting, infection, inflammation

In December 2019, the new severe acute respiratory syndrome (SARS)-related coronavirus (SARS-CoV-2) firstly emerged in Wuhan, China. It then spread rapidly worldwide to be declared as a pandemic by the World Health Organization (WHO) in March 2020. The disease caused by the new SARS-CoV-2, known as coronavirus disease 2019 (COVID-19), is associated with increased morbidity and mortality, representing substantial global public health concerns. It is not an exaggeration to say that what the world is going through at present represents a pivotal historical moment and a position in the contemporary history of humankind that is similar to the historical viral and bacterial pandemics in the last century.

According to the recent WHO report, respiratory infections can be transmitted through droplets in different ways according to the different droplet sizes. Recent evidence showed that the COVID-19 coronavirus is primarily transmitted through contact routes and respiratory droplets. This droplet transmission occurs when a person is in close contact with another one who is carrying the virus. Therefore, the normal person is at risk of having her/his mouth and nose mucosae or ophthalmic tissue (eye conjunctiva) exposed to potentially infective respiratory droplets. Furthermore, the transmission may occur through fomites...
in the immediate environment around the infected person. Therefore, the transfer of the COVID-19 coronavirus can occur either by indirect contact with surfaces in the immediate environment or with objects used on the infected person or by direct contact with infected people.

Fasting during the Muslims’ holy month of Ramadan represents one of the five pillars of Islam. Ramadan month is the ninth month in the lunar calendar, during which around one and half billion Muslim population abstains from food, drink, and smoking from dawn to sunset for a period ranging from 12 to 20 h based on the season and geographical location.

Further, religious gatherings (such as group prays in the Mosques) and social parties (such as family and friend invitations for iftar, the breakfast meal at sunset) especially for the extended family members, which characterize many Arab and Muslim communities, all are among the most distinguishing community behaviors characterize the holy month of Ramadan.

There is intensive ongoing discussion on the potential negative consequences of fasting-related dehydration. As such, it is not clear whether fasting Ramadan negatively impacts the body’s immunity, and hence causing expansion of the COVID-19 outbreak among the Muslim communities.

Therefore, we intended in this review to revise the available literature pertaining to the impact of intermittent fasting (IF) regimens, and particularly diurnal Ramadan IF (RIF), on the immune response against microbial infections, with particular attention to viral infections and coronavirus.

**Methods**

Google Scholar, ScienceDirect, PubMed/MEDLINE, CINAHL, EBSCOhost, Cochrane EMBASE, ProQuest Medical, Web of Science, and Scopus databases were searched. Keywords used in searching literature included “Ramadan,” “intermittent fasting,” “fasting regimen,” “immune response,” “immunity,” “infection,” “viruses,” “Corona virus,” and “COVID-19.” Original research, systematic reviews, and meta-analyses, along with narrative review articles were collected and reviewed for their significant findings on the impact of fasting regimens and RIF on immunity and immune response against microbial infections. Other related aspects that affect immunity, such as oxidative stress (OS) and inflammation, were collected as well. Both human and in vivo animal studies mimicking RIF and other fasting regimes were reviewed as well. Studies conducted on both healthy and disease patients were considered to highlight the impact of IF and RIF on different sectors of people in any population group.

**Results**

**Intermittent fasting, inflammation, and immunity**

Recent reports indicated that severe COVID-19 patients might exhibit features of systemic hyper-inflammation designated as cytokine storm. This inflammatory storm is characterized by a sharp burst in the inflammatory cytokines interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α and interferon (IFN)-γ. It is well reported that the imbalance in the production of proinflammatory cytokines such as IL-6, TNF-α, IL-1, IFNs type I and II, and IL-10 contributes to immune dysfunction and mediates inflammation of the target tissues. Further, insulin-like growth factor-1 (IGF-1) has been implicated in the etiopathogenesis of the neuroinflammation and associated with age-related neurodegenerative diseases. Several studies have been conducted on the immunomodulatory and proinflammatory effects of RIF on healthy adults. In this regard, our team performed relevant research that started in 2009 and published in 2012. In that study, 50 (29 women and 21 men) healthy volunteers were recruited. Circulating proinflammatory cytokines IL-6, IL-1β, and TNF-α and immune cells (lymphocytes, total leukocytes count, granulocytes, and monocytes) were tested before and at the end of RIF month (after 28 days of daily fasting for about 15 h) and again one month after the end of Ramadan month. The serum levels of the proinflammatory cytokines, IL-6, IL-1β, TNF-α, were significantly lower (P < 0.05) during Ramadan as compared to their levels before Ramadan or after the cessation of RIF. Moreover, the numbers of immune cells significantly reduced during Ramadan, but remained within the normal reference ranges.

We further confirmed these significant reductions in the proinflammatory cytokines in our recent study on the impact of RIF on visceral adiposity and serum adipokines in overweight and obese individuals. In this study, which involved 61 (38 women and 23 men) overweight and obese subjects, we found significant decreases in the serum levels of cytokines IL-6 and TNF-α, as well as the level of IGF-1, coinciding with a significant increase in the anti-inflammatory cytokines IL-10 and IL-10/IL-6 ratio. These findings imply that RIF attenuates the inflammatory status of the body by decreasing the levels of proinflammatory cytokine expression and decreasing circulating levels of leukocytes without adversely impacting the immune response. Another recent study assessed the pure effect of RIF on proinflammatory cytokines while controlling for lifestyle changes that may affect systemic inflammation, such as sleep duration, timing, and quality meal composition.
and caloric intake, and energy expenditure, and multiple samples were collected around the clock to account for circadian changes in the cytokines levels. The study reported that RIF led to significantly decreased plasma levels of cytokines (IL-1β, IL-6, and IL-8), particularly IL-1β and IL-6 across 24 h. In line with our studies, others also highlighted the positive impact of IF on ameliorating the IGF-1 levels. IGF-1 has been shown to augment proinflammatory cytokine levels.

Another study assessed the effect of RIF on circulating levels of immune complex (CIC) and immune indices before and after Ramadan in blood samples of 120 healthy volunteers. The results revealed no significant differences in the CIC level at the end of RIF in comparison with the pre-fasting level, implying that RIF does not harm the immune status of healthy people. The same group found no adverse effect of RIF on the respiratory bursts of neutrophils at the end of RIF month in comparison with the pre-fasting levels. Based on their studies, the investigators speculated that innate immunity response for intracellular infection factors during RIF was not decreased; in fact, it increased, indicating the beneficial effect of fasting to protect against bacterial infection. This speculation was supported by research on an experimental animal model using middle-aged BALB/c mice, which demonstrated the ability of IF to increase the efficiency of the immune system in resisting the pathogenic bacteria Salmonella typhimurium that causes the famous typhoid fever.

This anti-inflammatory and neuroprotective effect of IF against bacterial infection was also shown in another animal model. In one study, rats were subjected to IF (alternate-day fasting diet) for thirty consecutive days after being injected with toxic inflammatory lipopolysaccharides compounds. The study showed that IF induces adaptive responses in the brain and periphery that can suppress inflammation and preserve cognitive function in the animal model of systemic bacterial infection. Further evidence on the neuroprotective and anti-inflammatory effect of IF (alternate-day fasting) was shown on Sprague-Dawley rats exposed to IF for 3 months. IF stimulates IFN-γ mediated neuroprotective signaling in the hippocampus, suggesting a role for this cytokine to protect neurons in animal models against neurodegenerative disorders, severe epileptic seizures, and stroke. IFN-γ is known to be an extremely multipurpose cytokine that can carry out countless biological activities that are essential to other IFNs. Failure in the IFNγ-IFN-γR system severely hampers host immune responses. IFN-γ has been shown to activate macrophages and improve their ability to mount an effective immune response through enhancing antigen processing and presentation, and activating natural killer (NK) cells. The protective effects of IFN-γ can be seen against pathogens, including viral infections, as enhanced survival of neurons infected with Varicella-zoster virus is observed post-IFN-γ treatment. Additionally, IFN-γ have been shown to be effective blocking Ebola virus infectivity. The anti-viral effects of IFN-γ work through the stimulation of RNA-activated protein kinase R and adenosine deaminase RNA specific-1, where the anti-viral actions involve either viral multiplication or genomic stability. However, the effect of IFN-γ on SARS-CoV-2 needs further research.

Adawi et al. systematically reviewed 45 studies that assessed the effect of fasting during the month of Ramadan on immunity. By examining the collected articles, they conclude that fasting during Ramadan was associated with mild transient changes in the immune system, which return to the basal pre-Ramadan status shortly afterward. They also reported, in cardiac patients, that fasting during Ramadan entailed beneficial effects in the alleviation of SO.

In addition to the studies dedicated to the investigation of RIF on human health and immunity, other studies have been conducted on the impact of different forms of fasting, including IF, time-restricted feeding (TRF), alternate-day fasting, and the simulated diet of fasting-mimicking. One study investigated the effect of TRF (a pattern similar to fasting Ramadan) on 40 adult and young adult volunteers. It demonstrated a reduction in the numbers of NK cluster of differentiation (CD) 56 + and CD15+. These data support the ability of TRF to prevent the age-associated perturbations that contribute to immunosenescence.

Apart from the direct effect of RIF on inflammatory and immunomodulatory factors that mediate the immune function, other physiological impacts such as changes in body weight and composition during Ramadan may have an indirect effect on the body’s immunity and ability to fight pathogenic infections. Recent findings highlighted the significant impact that obesity and metabolic syndrome impose on the ability to fight pathogens and on the immune system. These include the alterations in leukocyte development, phenotypes, and activity; disruption of lymphoid tissue integrity; and the coordination of adaptive and innate immune responses. These changes are associated with an overall adverse effect on immunity and the ability to prevent infection. Excessive adipose tissue has been reported to be implicated in the impaired immunity that obese people suffer from. It has been reported that T-cells infiltrating the adipose tissue display activation markers, and regulatory T-cell populations increase within adipose tissue. Beside, adipocytes do not only work as a storage site for lipids, but also they secrete...
a variety of adipocytokines such as adiponectin and leptin.\[26\] These two hormones, in addition to their vital role in body weight regulation, play a significant role in inflammation and immune function.\[26,27\] It is believed that cells of the innate immune system mediate physiological changes present in obesity. Cells from the adaptive immune system play roles in both lean and obese conditions. Researchers believe that obesity has numerous synergistic interactions with viral infections. Also, bacterial infections in the setting of obesity are altered in comparison with healthy-weight subjects.\[28\]

RIF has been shown to reduce weight. Several meta-analyses have documented weight reduction during Ramadan fasting despite being conducted in a free-living unconstrained environment and not giving the participants any advice on lifestyle or dietary modifications.\[28-31\] A recent systematic review and meta-analysis on RIF and body weight (on 4176 participants from 85 studies conducted in 25 countries)\[29\] and metabolic syndrome components (on 4326 participants from 85 studies conducted in 23 countries)\[30\] showed that RIF was associated with a significant reduction in the body weight (about 1 kg), with substantial decreases in the metabolic syndrome components, namely fasting glucose, systolic blood pressure serum triglycerides, and waist circumference, concomitant with a significant increase in the high-density lipoprotein-cholesterol. Further, Another systematic review showed a significant reduction in body fat mass and fat percent at the end of the fasting month of Ramadan.\[29\]

**Intermittent fasting and infection**

A study tested the effect of Ramadan fasting on the ability to fight the pathogenic bacterial infection by *Mycobacterium tuberculosis*, which causes tuberculosis, of thirty fasting volunteers.\[33\] It demonstrated that fasting during Ramadan was associated with a reduction in pathogenicity of the bacteria by increasing the numbers of macrophages. The study also showed the ability of fasting to increase the secretion of IFN-γ, which is known to stimulate the anti-microbial immune mechanisms against multiple bacterial and viral infections, as discussed above.\[33\]

Most interestingly, studies of fasting and immunity were not limited to healthy people. A study that was conducted on Muslim patients infected with the human immunodeficiency virus (HIV) showed the absence of any negative impact of RIF on modifying the frequency of antiretroviral therapy.\[34\] In this study, fasting HIV patients on antiretroviral therapy were shifted from twice-daily dosed to once-daily dosed without significant changes in cluster differentiation of CD4 cell counts, viral load, or hematocrit levels in comparison with the twice-daily dosed therapy in the non-fasting patients.

In another scientific review on the IF and other forms of dietary restrictions, it was shown that such dietary modifications could promote anti-inflammatory effects and to decrease the biological rate of aging. Such changes may alleviate and possibly reverse a variety of autoimmune disorders as well as immunosenescence by killing damaged and old cells and replacing them with functional young ones.\[35\] This protective effect of IF against the autoimmune disease was evident in the animal model of experimental autoimmune encephalomyelitis (EAE). Using female mice (C57BL/6) injected with myelin oligodendrocyte glycoprotein antigen to induce EAE, IF for 35 days after immunization resulted in a significant reduction in the incidence and induction of EAE, and significantly reduced the severity of disease.\[36\] The authors concluded that IF might play a possible role in the treatment of multiple sclerosis patients. This finding was further supported by Cignarella et al.\[37\] who found that IF ameliorates the clinical course and pathology of the multiple sclerosis mouse model (EAE) induced in animals. This was manifested in the ability of IF to to alter the gut ecosystem by increasing the richness and diversity of gut bacteria, enrichment of the Bacteroidaceae, Lactobacillaceae, and Prevotellaceae families and enhanced antioxidative microbial metabolic pathways. Further, they reported that IF altered T cells in the gut with a reduction of IL-17 producing T cells and an increase in regulatory T cells.

**Intermittent fasting and oxidative stress**

It is well established that increased proinflammatory and OS factors participate in weakening the immunity and increase the risk of infection. OS and inflammation are strictly related pathophysiological processes, one of which can be easily induced by another. Thus, both processes are simultaneously found in many pathological conditions and involved in the etiopathogenesis of many acute, chronic,\[38-41\] and infectious\[42-44\] diseases.\[45\] Several mechanisms have been proposed to explain the distinct relationship between OS, inflammation, and infection. One of these mechanisms is that OS plays a dual role in infections.

Free radicals protect against the invading pathogens, which in turn can cause tissue damage during the resulting inflammation. In the process of infection, there is a generation of reactive species by several enzymes, such as nitric oxide synthase, myeloperoxidase, and nicotinamide adenine dinucleotide phosphate oxidase. On the other hand, reactive oxygen species can be generated, by cytochrome P450, xanthine oxidase, and some metals. Some pathological changes arising during infection can be attributed to OS, and the generation of reactive species in infection can even have fatal consequences.\[44\] Further, the two related processes,
inflammation and oxidation, could be the link between anxiety, aging, and immunosenescence.\textsuperscript{[46]}

In a recent systematic review and meta-analysis study on the impact of RIF on inflammatory and OS markers in healthy subjects, Faris et al. reviewed the inflammatory markers IL-1, IL-6, TNF-α, and C-reactive protein (CRP), as well as the OS marker malondialdehyde (MDA). Based on explicit inclusion and exclusion criteria, 12 studies involving 311 participants distributed, over eight countries were solicited. Studies were distributed as follows: 3 studies from Iran, two from Turkey, two from Saudi Arabia, one from Jordan, one from the United Arab Emirates, one from Denmark, one from the Netherlands, and one from Indonesia. The results revealed that RIF was associated with a small to medium reductions in TNF-α (expressed in terms of the effect size measure of Hedge's g value = −0.371) and IL-6 (Hedge's g = −0.407) and minimal reductions in MDA (Hedge's g = −0.219), IL-1 (Hedge's g value = −0.016), and CRP (Hedge's g = −0.119).\textsuperscript{[47]}

A recent study examined the effect of RIF on the genetic expression of three genes that augment the processes of preventing oxidation and inflammation in nearly 60 healthy adults.\textsuperscript{[48]} Results of the study showed that RIF was associated with significantly increased expression of these genes, namely Mitochondrial transcription factor A (TFAM), superoxide dismutase 2, and nuclear factor erythroid 2 related factor 2 genes at high levels of 90.5%, 54.1% 411.5%, respectively, as compared to their levels before Ramadan. These results suggest the ability of RIF to protect against OS and inflammation responsible for weakening the immune system and reducing its defense against infection.\textsuperscript{[48]} This anti OS effect of RIF was further supported by an animal model that mimics the 12 h/day, 30-day of RIF model. Forty male carbon tetrachloride-intoxicated Wistar rats were exposed to RIF mimicking model, and the results showed significant reductions in CRP and MDA parameters for OS.\textsuperscript{[49]} In a similar RIF mimicking model, Shawky et al. showed that IF caused a considerable increase in neutrophil phagocytic activity, phagocytic index, and brain neurotransmitters (norepinephrine and serotonin).\textsuperscript{[50]}

Water intake, dehydration, and immunity against infection

It is well established that immunopathology of airway surface liquid is adversely affected by dehydration status, and that any defects in the functioning of the mucociliary escalator compromise the mucociliary clearance of inhaled pathogens may favor microbial lung infection.\textsuperscript{[51]} Indeed, RIF research denies the harmful effect of fasting on mucociliary clearance. In a study conducted to evaluate the difference in a mucociliary clearance among volunteers who underwent RIF versus Nineveh fasting regimens (refraining from food and drink from morning till sunset for three consecutive days) during the three consecutive days as well as the difference between the fasting period and four weeks following the fasting period in both groups.\textsuperscript{[52]} In this study, RIF (for an average of 15 h for 29 consecutive days, \(n = 40\)) and Nineveh fasting (60 h of nonstop fasting, \(n = 26\)) were compared. No significant difference was found in the mucociliary clearance time between the RIF and control groups (4 weeks after the fasting period).\textsuperscript{[52]}

Insufficient water intake is one of the most compelling and challenging claims that were raised about the possibility that RIF may induce susceptibility to COVID-19 infection. Although RIF dictates refrain from food and fluid, even water intake, no available evidence supports that RIF is associated with dehydration, and no detrimental effects on health have been directly attributed to negative water balance during Ramadan month in healthy subjects.\textsuperscript{[53]} Changes in functional water volume may be more important clinically than gross differences in total body water.\textsuperscript{[54]} In one study, gross total body water statistically decreased,\textsuperscript{[55]} and it was nonsignificant in another study.\textsuperscript{[48]} However, in both studies, gross total body water remained within the normal range of 30–46 kg.\textsuperscript{[56]} Further, total water and fluid intake showed a significant increase during the night hours of Ramadan month in comparison to the pre-fasting period (1131 ± 967 ml/day before vs. 1691 ± 796 ml/day at the end of Ramadan).\textsuperscript{[55]}

Water deprivation is functionally characterized by maximum urine concentration. In 20 Malaysian Muslims, urine was collected before, during, and after RIF in the morning, afternoon, and overnight.\textsuperscript{[57]} The authors found that RIF did not affect the overnight urine volume or osmolality, indicating that the fasting subjects were probably not subjected to severe water deprivation. During Ramadan, the osmolality of the urine samples collected in the afternoon was very high, indicating effective water conservation and a decreased obligatory urine output and maximum urinary concentration.\textsuperscript{[58]}

Among the clinical consequences of dehydration is that dehydration and low fluid intake are associated with increased risk of developing renal calculi.\textsuperscript{[59]} Evidence supporting the lack of adverse effects of RIF on the body’s hydration status comes from a study that was conducted to compare the prevalence of renal colic (RC) in Ramadan with other months of the lunar year. Records of 574 subjects (398 males and 176 females) who were admitted to the two medical centers of a city in a hot region of Iran were reviewed. Twenty-seven males (63%) and 16 females (37%) were admitted in Ramadan, and 37 males (70%), and 160 females (30%) in other months (\(P < 0.4\)) of the year.\textsuperscript{[60]} There was also
no significant difference between the frequency of admissions in Ramadan and mean admission during the other months of the year.\[60\]

A more recent prospective observational study evaluated the effects of RIF on the number of RC visits and laboratory results of patients with RC. Results from 176 patients (89 before Ramadan and 87 in Ramadan) with RC revealed that RIF did not change the number of RC hospital visits. Moreover, although fasting caused some changes in urinary metabolites, there was no enough evidence that these changes increased urinary calculus formation.\[61\]

### Impacts of ritual and social behaviors during Ramadan month

At the sunset breakfast meal (Iftar), social gatherings, many times in buffet style, are frequent in many communities. It is worth noting that talking about fasting the month of Ramadan does not stop with the social and nutritional habits and behaviors that accompany it. This virtuous month of Ramadan is not only a month of fasting, but also a social, devotional month in every sense of the word, and what people gather in prayers and worship and on iftar tables is far from our minds. Perhaps this is one of the biggest challenges facing Muslim societies during Ramadan. The adverse effect of RIF on the immune system that has been refuted is not a challenge. Still, the real problem is those societal behaviors that may be a source of renewed infection in light of talking about the recurrence of the virus outbreaks in the coming seasons. Also, the nature of the food prevailing in the month of Ramadan, which is predominantly sugar and fat, may weaken immunity and reduce the efficiency of RIF system in defending and curbing the virus. It is well established that the typical diet rich with refined sugars, salt, and saturated fat is associated with an increased risk of infection.\[62\]

Several mechanisms have been proposed for the adverse effect of an unhealthy diet on immune function. More attention has been given to the dietary impact on the gut microbiota and the mechanisms by which unhealthy food choices and dietary patterns affect our gut and genes. It has been reported that the overabundance of macronutrients and calories that compose the modern diet may all lead to reduced control of infection, increased inflammation, and increased risk for allergic and auto-inflammatory disease.\[62,63\]

Therefore, fasting performers have to eat balanced food rich in vegetables, fruits, legumes, and nuts rich in micro-nutrients (vitamins and minerals) and polyphenols that boost the immune system and may help in combating COVID-19 coronavirus infection.\[64,65\] A mounting body of evidence indicates that the ingestion of fruits high in polyphenols, carbohydrates, and metabolites effectively supports human body performance, with added benefits including enhancement of anti-viral and oxidative capacity through fruit metabolites, and increased plasma levels of gut-derived polyphenols.\[60,66\]

Further, multivariate logistic regression analysis for data of seventy-eight patients with COVID-19 from China indicated that a history of smoking was a risk factor of disease progression,\[67\] and smoking has been reported to be the most likely factor associated with the negative progression and adverse outcomes of COVID-19.\[68\] This may lead to speculation that RIF may favor a protective environment against SARS-CoV-2 infection and reduce the burden of COVID-19 during Ramadan month, because smoking is not allowed during RIF.\[69\] Furthermore, the spiritual conditions characterizing the month of Ramadan may trigger many smokers to quit smoking, which is looked at as a useful faith-based smoking cessation intervention\[70\], particularly that numerous religious scholars and institutions in North African and Middle Eastern countries have declared smoking to be haram (prohibited)\[71,72\]

It should also be noted that Ramadan month and the accompanying social and religious group activities constitute a risk factor for infection, which compels the fasting persons to stay away and guard against infection points and commitment to social distancing to ward off danger from the other side. Here, a distinction is made between the effect of individual fasting on the one hand, and the social customs and lifestyle changes associated with the blessed month of Ramadan on the other.

Another behavioral risk factor for reduced immunity that may accompany the fasting month is the significant reductions in sleep duration and the disturbances in sleep pattern, as revealed by a recent meta-analysis on RIF and sleep.\[73\] This work showed that total sleep time significantly decreased by about 1 h (from 7.2 h per night before Ramadan to 6.4 h during Ramadan), while daytime sleepiness measured using the Epworth sleepiness scale score increased slightly from 6.1 before Ramadan to 7.0 during Ramadan. These changes in sleep quantity and quality are ascribed to the religious and social activities practiced during the night hours of Ramadan.\[73,74\] It well established that insufficient sleep can increase organism susceptibility to infection through weakening immunity and that sleep deprivation is associated with increased susceptibility to viral infections.\[75,76\] This relationship is explained by the fact that partial sleep deprivation is associated with transiently impaired mitogen proliferation, the decreased human leukocyte antigen-DR isotype, the upregulated CD14, and the variations in CD4 and CD8.\[77\]
Conclusion

This is a summary of the most prominent scientific studies published on the impact of the practice of fasting in all its forms, including fasting the month of Ramadan, on the immune response and efficiency of the immune system. These studies were conducted in humans and animals, and their results showed a combination of the ability to fast to improve the body’s resistance to bacterial infections. At its minimum levels, these studies did not show any adverse effect of intermittent fasting on the immune system, which refutes the claimed adverse impact of RIF on immunity. The claim that there is a possible adverse effect of intermittent fasting on increasing the severity of the impact of the COVID-19 on the immune system is nullified. However, it should be noted from the scientific point of view that none of these scientific studies did test the effect of fasting in the month of Ramadan on the COVID-19 coronavirus infection.

Acknowledgments
Thanks are expressed to Dr. Mohammad G Mohammad and Dr. Mohsen Hegab for their fruitful comments.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Roohan HA, Bryareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020;109:102433.
2. World Health Organization. Modes of Transmission of Virus Causing COVID-19: Implications for IPC Precaution Recommendations. World Health Organization; 2020. https://www.who.int/news-room/cornerstones/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations. [Last accessed on 2020 Mar 30].
3. Ong SWX, Tan YK, Chia PY, Lee TH, Ng OT, Wong MSY, et al. Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient. JAMA 2020;323:1610-2. doi:10.1001/jama.2020.3227.
4. Faris MAE, Jahrami HA, Alsaibai J, Obaiden AA. Impact of ramadan diurnal intermittent fasting on metabolic syndrome components in healthy, non-athletic muslim people aged over 15 years: A systematic review and meta-analysis. Br J Nutr 2020;123:1-22. doi:10.1017/S000711451900254X.
5. Ozalp M. How Coronavirus Challenges Muslims’ Faith and Changes Their Lives? 2 April, 2020. Available from: https://theconversation.com/how-corona-virus-challenges-muslims-faith-and-changes-their-lives-133925. [Last accessed on 2020 Mar 30].
6. McGonagle D, Shardif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev 2020;19:102537.
7. Wang W, He J, Lie p, Huang I, Wu S, lin Y, et al. The Definition and Risks of Cytokine Release Syndrome-Like in 11 COVID-19-Infected Pneumonia Critically ill Patients: Disease Characteristics and Retrospective Analysis. medRxiv; 2020.
8. Umare V, Pradhan V, Nadkar M, Rajadhyaksha A, Patwardhan M, Ghosh KK, et al. Effect of proinflammatory cytokines (IL-6, TNF-α, and IL-1β) on clinical manifestations in Indian SLE patients. Med Inflamm 2014;2014:385297.
9. Labandeira-Garcia JL, Costa-Besada MA, Labandeira CM, Villar-Cheda B, Rodríguez-Perez Al. Insulin-like growth factor-1 and neuroinflammation. Front Aging Neurosci 2017;9:365.
10. Faris MA, Kacimi S, Al-Kurd RA, Fararje MA, Bustanji YK, Mohammad MK, et al. Intermittent fasting during Ramadan attenuates proinflammatory cytokines and immune cells in healthy subjects. Nutr Res 2012;32:947-55.
11. Almeneessier AS, BaHammam AA, Alzoghaibi M, Olaish AH, Nashwan SZ, BaHammam AS. The effects of diurnal intermittent fasting on proinflammatory cytokine levels while controlling for sleep/wake pattern, meal composition and energy expenditure. PLoS One 2019;14:e0226304.
12. Rahmani J, Kord Varkaneh H, Clark C, Zand H, Bawadi H, Ryan PM, et al. The influence of fasting and energy restricting diets on IGF-1 levels in humans: A systematic review and meta-analysis. Ageing Res Rev 2019;53:100910.
13. Che W, Lerner-Marmarosh N, Huang Q, Osawa M, Ohta S, Yoshizumi M, et al. Insulin-like growth factor-1 enhances inflammatory responses in endothelial cells: Role of Gab1 and MEKK3 in TNF-alpha-induced c-Jun and NF-kappaB activation and adhesion molecule expression. Circ Res 2002;90:1222-30.
14. Latifinya A, Vojgani M, Abofazel T, Jafarieh H. Circulating immune complex during Ramadan. J Ayub Med Coll Abbottabad 2007;19:15-8.
15. Latifinya A, Vojgani M, Gharagozlou MJ, Shariﬁan R. Effect of Ramadan on neutrophil’s respiratory burst (innate immunity) and circulating immune complex. J Ayub Med Coll Abbottabad 2008;20:128-31.
16. Campos-Rodríguez R, Godínez-Victoria M, Reyna-Garﬁas H, Arciniega-Martínez IM, Reséndez-Albor AA, Abarca-Rojano E, et al. Intermittent fasting favored the resolution of Salmonella typhimurium infection in middle-aged BALB/c mice. Age (Dordr) 2016;38:13.
17. Vasconcelos AR, Yshii LM, Viel TA, Buck HS, Mattson MP, Scavone C, et al. Intermittent fasting attenuates lipopolysaccharide-induced neuroinflammation and memory impairment. J Neuroinflammation 2014;11:85.
18. Lee J, Kim SJ, Son TG, Chan SL, Mattson MP. Interferon-γ is up-regulated in the hippocampus in response to intermittent fasting and protects hippocampal neurons against excitotoxicity. J Neurosci Res 2006;83:1552-7.
19. Kak G, Raza M, Tiwari BK. Interferon-gamma (IFN-γ): Exploring its implications in infectious diseases. Biomol Concepts 2018;9:64-79.
20. Baird NL, Bowlin JL, Hotz TJ, Cohrs RJ, Gilden D. Interferon gamma prolongs survival of varicella-zoster virus-infected human neurons In vitro. J Virol 2015;89:7425-7.
21. Rhein BA, Powers LS, Rogers K, Anantpadma M, Singh BK, Sakurai Y, et al. Interferon-γ inhibits ebola virus infection. PLoS Pathog 2015;11:e1005263.
22. Adawi M, Watad A, Brown S, Aazza K, Aazza H, Zouhir M, et al. Ramadan fasting exerts immunomodulatory effects: Insights from a systematic review. Front Immunol 2017;8:1144.
23. Gasmì M, Sellami M, Denham J, Padulo J, Kuvacic G, Semlì W, et al. Time-restricted feeding influences immune responses without compromising muscle performance in older men. Nutrition 2018;51:52-37.
24. Andersen CJ, Murphy KE, Fernandez ML. Impact of Obesity and Metabolic Syndrome on Immunity. Adv Nutr 2016;7:66-75.
25. Wang Q, Wu H. T cells in adipose tissue: Critical players in...
immunometabolism. Front Immunol 2018;9:2509.

26. Tilg H, Moschen AR. Adipocytokines: Mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;6:772-83.

27. Stofkova A. Leptin and adiponectin: From energy and metabolic dysbalance to inflammation and autoimmunity. Endocr Regul 2009;43:157-68.

28. Neidich SD, Beck MA. Obesity, immunity, and infection. In: Nutrition, Immunity, and Infection. Florida State, USA: CRC Press; 2017. p. 33-42.

29. Fernando HA, Zibellini J, Harris RA, Seimon RV, Sainsbury A. Effect of Ramadan fasting on weight and body composition in healthy non-athlete adults: A systematic review and meta-analysis. Nutrients 2019;11:478.

30. Kul S, Savaš E, Öztürk ZA, Karadağ G. Does Ramadan fasting alter body weight and blood lipids and fasting blood glucose in a healthy population? A meta-analysis. J Relig Health 2014;53:329-42.

31. Sadeghirad B, Motaghipisheh S, Kolahdooz F, Zahedi MJ, Haghdoot AA. Islamic fasting and weight loss: A systematic review and meta-analysis. Public Health Nutr 2014;17:396-406.

32. Jahrami HA, Alsibai J, Clark CC, Faris MA. A systematic review, meta-analysis, and meta-regression of the impact of diurnal intermittent fasting during Ramadan on body weight in healthy subjects aged 16 years and above. Eur J Nutr 2020;1-26.

33. Lahdimawan A, Hanido K, Indra MR, Prawiro SR. Effect of Ramadan fasting on the ability of serum, PBMC and macrophages from healthy subjects to kill M. tuberculosis. IOSR J Pharm Biol Sci 2014;9:9-24.

34. Yakasai AM, Muhammad H, Babashani M, Jumare J, Abdulmumin M, Habib AG. Once-daily antiretroviral therapy among treatment-experienced Muslim patients fasting for the month of Ramadan. Trop Doct 2011;41:233-5.

35. Choi IY, Lee C, Longo VD. Nutrition and fasting mimicking diets in the prevention and treatment of autoimmune diseases and immunosenescence. Mol Cell Endocrinol 2017;455:4-12.

36. Kafami L, Raza M, Razavi A, Mirshafiey A, Movahedian M. Intermittent feeding attenuates clinical course of experimental autoimmune encephalomyelitis in C57BL/6 mice. Avicenna J Med Biotechnol 2010;2:47-52.

37. Cignarella F, Cantoni C, Ghezzi L, Salter A, Dorsett Y, Chen L, et al. Diet and immune function. Physiol Rev 2014;94:329-54.

38. Biswas SK. Does the interdependence between oxidative stress and inflammation explain the antioxidant paradox? Oxid Med Cell Longev 2016;2016:743297.

39. Bhattacharya A, Chattopadhyay R, Mitra S, Crowe SE. Oxidative stress: An essential factor in the pathogenesis of gastrointestinal mucosal diseases. Physiol Rev 2014;94:329-54.

40. Hussain T, Tan B, Yin Y, Blachier F, Tossou MC, Rahu N. Oxidative stress and inflammation: What polyphenols can do for us? Oxid Med Cell Longev 2016;2016:743297.

41. Barrows IR, Ramezani A, Raj DS. Inflammation, immunity, and oxidative stress in hypertension-partners in crime? Adv Chronic Kidney Dis 2019;26:122-30.

42. Hardbower DM, de Sablet T, Chaturvedi R, Wilson KT. Chronic inflammation and oxidative stress: The smoking gun for Helicobacter pylori-induced gastric cancer? Gut Microbes 2013;4:475-81.

43. Agarwal A, Rana M, Qiu E, AlBunni H, Bui AD, Henkel R. Role of oxidative stress, infection and inflammation in male infertility. Andrology 2018;50:e13126.

44. Pohanka M. Role of oxidative stress in infectious diseases. A review. Folia Microbiol (Praha) 2013;58:503-13.

45. Chatterjee S. Chapter two-oxidative stress, inflammation, and disease. In: Dzubla T, Butterfield DA, editors. Oxidative Stress and Biomaterials. United States: Academic Press; 2016. p. 35-58.

46. De La Fuente M. Oxidation and Inflammation in the Immune and Nervous Systems, a Link Between Aging and Anxiety. Switzerland, United States: Springer International Publishing; 2018. p. 1-31.

47. Faris M, Jahrami HA, Obaideen AA, Madkour MI. Impact of diurnal intermittent fasting during Ramadan on inflammatory and oxidative stress markers in healthy people: Systematic review and meta-analysis. J Nutr Int Metabol 2019;15:18-26.

48. Madkour MI, T El-Serafi A, Jahrami HA, Sherif NM, Hassan RE, Awadallah S, et al. Ramadan diurnal intermittent fasting modulates SOD2, TFAM, Nrf2, and sirtuins (SIRT1, SIRT3) gene expressions in subjects with overweight and obesity. Diabetes Res Clin Pract 2019;155:107801.

49. Sadek K, Saleh E. Fasting ameliorates metabolism, immunity, and oxidative stress in carbon tetrachloride- intoxicated rats. Hum Exp Toxicol 2014;53:1277-83.

50. Shawky S, Zaid A, Orabi S, Shogby K, Hassan W. Effect of intermittent fasting on brain neurotransmitters, neutrophils phagocytic activity, and histopathological finding in some organs in rats. Int J Res Stud Biosci 2015;3:38-45.

51. Lewis BW, Patial S, Saini Y. Immunopathology of airway surface liquid dehydration Disease. J Immunol Res 2019;2019:2180409.

52. Develioglu ON, Sirazi S, Topak M, Purisa S, Kuleki M. Differences in Mucociliary activity of volunteers undergoing Ramadan versus Nineveh fasting. Eur Arch Otorhinolaryngol 2013;270:1655-9.

53. Leiper JB, Molla AM, Molla AM. Effects on health of fluid restriction during fasting in Ramadan. Eur J Clin Nutr 2003;57 Suppl 2:S30-8.

54. Kampmann B, Manz F, Kalkovsky B. Voluntary Dehydration: Loss of Body Mass and Total Body Water But Almost no Change of Functional Water Volume. Quality of Work and Products in Enterprise of the Future; 2003. p. 235-8.

55. Faris MA, Madkour MI, Obaideen AK, Dalah EZ, Hasan HA, Radwan H, et al. Effect of Ramadan diurnal fasting on visceral adiposity and serum adipokines in overweight and obese individuals. Diabetes Res Clin Pract 2019;153:166-75.

56. Chumlea WC, Guo SS, Zeller CM, Reo NV, Siervogel RM. Total body water data for white adults 18 to 64 years of age: The Fels Longitudinal Study. Kidney Int 1999;56:244-52.

57. Cheah SH, Ch'ng SL, Husain R, Duncan MT. Effects of fasting during Ramadan on urinary excretion in Malaysian Muslims. Br J Nutr 1990;63:329-37.

58. Shirreffs SM. Markers of hydration status. Eur J Clin Nutr 2003;57 Suppl 2:S6-9.

59. Bibl G, Meyers A. Recurrent renal stone disease-advances in pathogenesis and clinical management. Lancet 2001;358:651-6.

60. Basiri A, Moghaddam SM, Khoddam R, Nejad AT, Hakimi A. Monthly variations of urinary stone colic in Iran and its relationship to the fasting month of Ramadan. J Pak Med Assoc 2004;54:6-8.

61. Cevik Y, Corbacioglu SK, Cirkirici G, Oncul V, Emekta C. The effects of Ramadan fasting on the number of renal colic visits to the emergency department. Pak J Med Sci 2016;32:18-21.

62. Myles IA. Fast food fever: Reviewing the impacts of the Western diet on immunity. Nutrients 2013;5 Suppl 2:S6-9.

63. Childs CE, Calder PC, Miles EA. Diet and immune function. Nutr J 2014;13:61.

64. Lewis BW, Patial S, Saini Y. Immunopathology of airway surface liquid dehydration Disease. J Immunol Res 2019;2019:2180409.

65. Develioglu ON, Sirazi S, Topak M, Purisa S, Kuleki M. Differences in Mucociliary activity of volunteers undergoing Ramadan versus Nineveh fasting. Eur Arch Otorhinolaryngol 2013;270:1655-9.

66. Nieman DC, Mitmesser SH. Potential impact of nutrition on immune system recovery from heavy exertion: A metabolomics perspective. Nutrients 2017;9:513.
of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl) 2020;133:1032-8. doi:10.1097/CM9.000000000000775.

68. Vardavas CI, Nikitara K. COVID-19 and smoking: A systematic review of the evidence. Tob Induc Dis 2020;18:20.

69. Laway BA, Ashraf H. Basic rules of Ramadan: A medico-religious perspective. J Pak Med Assoc 2015;65:514-7.

70. Ismail S, Abdul Rahman H, Abidin EZ, Isha AS, Abu Bakar S, Zulkifley NA, et al. The effect of faith-based smoking cessation intervention during Ramadan among Malay smokers. Qatar Med J 2016;2016:16.

71. Ghouri N, Atcha M, Sheikh A. Influence of Islam on smoking among Muslims. BMJ 2006;332:291-4.

72. Hameed A, Jalil MA, Noreen R, Mughal I, Rauf S. Role of Islam in prevention of smoking. J Ayub Med Coll Abbottabad 2002;14:23-5.

73. Faris MA, Jahrami HA, Alhayki FA, Alkhawaja NA, Ali AM, Aljeeb SH, et al. Effect of diurnal fasting on sleep during Ramadan: A systematic review and meta-analysis. Sleep Breath 2019;1-12. https://doi.org/10.1007/s11325-019-01986-1.

74. Qasrawi SO, Pandi-Perumal SR, BaHammam AS. The effect of intermittent fasting during Ramadan on sleep, sleepiness, cognitive function, and circadian rhythm. Sleep Breath 2017;21:577-86.

75. Ibarra-Coronado EG, Pantaleón-Martínez AM, Velazquéz-Moctezuma J, Prospéro-García O, Méndez-Díaz M, Pérez-Tapia M, et al. The bidirectional relationship between sleep and immunity against infections. J Immunol Res 2015;2015:678164.

76. Aldabal L, Bahammam AS. Metabolic, endocrine, and immune consequences of sleep deprivation. Open Respir Med J 2011;5:31-43.

77. Wilder-Smith A, Mustafa FB, Earnest A, Gen L, Macary PA. Impact of partial sleep deprivation on immune markers. Sleep Med 2013;14:1031-4.