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Research Article

Ramadan 2020 and Beyond in the Midst of the COVID-19 Pandemic: Challenges and Scientific Evidence For Action

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This review is dedicated to the memory of the corresponding author's father, Professor Ahmed Khalifa Abu-Median, and father-in-law, Engineer Salih Mohammed Ahmed Mohammed Osman, who both passed away during the preparation of the manuscript.

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Abstract

Background: Ramadan is a sacred month in Islam, which involves 29–30 days of dawn-till-dusk dry-fasting. Millions of Muslims observed Ramadan fasting (RF) this year in the midst of the COVID-19 pandemic. Certain ethnic groups worldwide, including Muslims, have been disproportionately affected by COVID-19, raising fears that fasting could bring additional health risks. This directly impacted on the current challenges faced by health professionals. The COVID-19 virus is expected to become seasonal. Therefore, the evidence presented in this review is valid beyond Ramadan as intermittent fasting is practiced more widely, irrespective of religion, throughout the year as a therapeutic and prophylactic means for several conditions.

Methods: A wide range of literature databases were searched for the effects of RF and intermittent fasting on human health and then linked to COVID-19 impact to generate the evidence.

Results: This review presents a body of evidence proving RF is safe and beneficial for healthy people who adopt a balanced diet, drink plenty of fluids, and engage in regular physical activity. Fasting reduces levels of pro-inflammatory cytokines (IL-1β and IL-6), which are associated with severe COVID-19. Furthermore, increased handwashing and hygiene during Ramadan may reduce infection risks. For some, social isolation, physical inactivity, reduced access to food and stress – linked to the pandemic – may minimize the benefits that may have been achieved during a "normal" Ramadan.

Conclusions: RF during the COVID-19 pandemic is not a cause of concern for healthy people. Ill people are exempt from fasting and should seek medical advice if they wish to fast. RF during the COVID-19 pandemic is a unique experience and future research will reveal its impact on human health.

Keywords: COVID-19; Ramadan; fasting; health; mental; exercise; isolation; lockdown; diabetes; biomarkers

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1. Introduction

Fasting can be defined as abstinence from food, either completely or partially, for a certain period of time [1, 2]. For thousands of years, people following various religions have believed that fasting for a period of time is the key to spiritual healing [3]. In recent years, there has been a surge in research on fasting, not as a religious practice, but as a means to improve health and fight disease. The type of fasting that has been most investigated is called intermittent fasting (IF), which involves time-restricted feeding [4–6]. This kind of fasting is characterized by limiting daily consumed food over a specific period of time during the day with no calorie restriction, and such time limit can vary from 4 to 12 hr [4]. The vast majority of these studies reported beneficial effects of fasting on human health including protection against cancer, cardiovascular disease, diabetes, neurodegenerative disease, extending life span, cognitive function, intellectual performance, and metabolic regulation among healthy adults and patients with different disorders [7–9]. As a consequence of these research studies, IF has become popular across the world for those wishing to improve their health. Moreover, Ramadan fasting (RF) is also a type of IF [10, 11]. It is sometimes referred to as Ramadan intermittent fasting in the scientific literature. IF in various contexts and patterns is currently one of the most common health and fitness approaches throughout the globe.

Worldwide, RF is practiced once a year on the ninth month of the lunar calendar by millions of Muslims from various ethnic backgrounds [3, 12]. During RF, Muslims abstain from food and drink from dawn to sunset every day for a continuous period of 29–30 days. The period of daily fasting varies from 12–19 hr, as the Islamic year is based on a lunar cycle, thus each year, the month of Ramadan starts 11 days earlier than the Gregorian calendar, and it can fall during any season throughout the year [12, 13]. In Islam, RF is obligatory for all healthy Muslims, both males and females who have reached the age of puberty. People with chronic or acute illnesses, travelling, menstruating and pregnant women, breastfeeding mothers, children who are below the age of puberty, and the elderly who cannot afford fasting are exempt from fasting [13]. During the month of Ramadan, Muslims usually have two to three meals after dusk till dawn, and there are no restrictions on the amount of food/drinks that can be consumed, as this is mainly driven by cultural habits [14].

Spiritually, Muslims take the month of Ramadan as an opportunity to make meaningful alterations to their lifestyle in general that could have long-lasting effects and enable them to live a healthier and happier life with their families. Additionally, it enhances an individual's self-control and self-discipline [15]. As a result of these implications, some Muslims who are exempt from fasting for medical reasons insist to fast during Ramadan. However, while the vast majority of studies on RF show a positive impact on human health and physiology, it may also have some adverse effects such as dehydration and hypoglycemia [16, 17]. Moreover, fasting during the current major global outbreak could lead to serious complications among high-risk patients. Therefore, it is essential for these people to seek the best advice from physicians and religious scholars.

The purpose of this review is to provide recent scientific evidence on the following issues by taking into consideration the current COVID-19 crisis and its impact on the lives of people:

- The safety of RF and its effects on human health among healthy individuals and people who have medical conditions.
- The effects of RF on immunity and mental health.
- The benefits and drawbacks of observing fasting during COVID-19 pandemic.
- Recommendations that may support Muslims who are concerned that fasting during the current circumstances could impact their health.

2. Methods

A wide range of literature databases such as Google Scholar, PubMed, Science Direct, Scopus, MEDLINE (EBSCO), Cochrane Library, and Web of Science were searched for the effects of RF and IF on human health and linked to COVID-19 impact to generate the evidence. The most used terms in the search were RF and human health, RF and diabetes, Islamic fasting and blood biomarkers, diurnal intermittent fasting (DIF), COVID-19 and/or mental health, COVID-19 and exercise, COVID-19 and fasting.

3. Results and Discussion

3.1. The novel coronavirus (SARS-CoV-2) and the disease (COVID-19)

During the last two months in 2019, cases of a fatal disease presenting with respiratory distress were reported in Wuhan City in China [18]. The outbreak started in a seafood market, and the molecular investigation (PCR and Next-generation Sequencing) of samples from first patients identified the causative agent as a novel coronavirus with a high sequence identity at 79.6% and 96% to that of SARS CoV, which caused the outbreak of severe acute respiratory syndrome in 2002 and a bat coronavirus, respectively [18, 19]. Coronaviruses that normally infect humans predominantly cause common cold-like symptoms, however, the newly emerging coronaviruses such as SARS-CoV in 2002 and MERS-CoV (Middle East Respiratory System Coronavirus) in 2012 caused epidemics with mortality rates of 10% and 37%, respectively [20, 21]. The novel coronavirus was referred to as 2019-nCoV and later named as SARS-CoV-2 [22]. The disease was recognized as COVID-19 in January 2020 by the WHO and was declared as a pandemic in March 2020 [23, 24]. In addition to the four common human coronaviruses (HCoV-229E, HCoV-OC43, HCoV-NL63, and HKU1), SARS-CoV, and MERS-CoV, SARS-CoV-2 is the seventh coronavirus to infect humans.

Clinically, the first COVID-19 patients presented with dry cough, difficulty in breathing, pneumonia, fever and headache, with ICU admission and mechanical ventilation due to respiratory failure [19, 25]. Chest radiological evidence revealed multifocal opacities

[26]. Evidence of venous thromboembolism is now emerging [27, 28]. By late January 2020, 80 patients died among 2,794 others infected [19]. The virus is transmitted via virus-laden droplets in the air and through human-to-human contact [19, 26, 29]. This resulted in the WHO's recommendations for handwashing and social isolation. Similar to the SARS-CoV and MERS-CoV, zoonotic origin has been postulated for SARS-CoV-2 based on genetic evidence, with control of primary host been suggested to stop the spread of COVID-19 [19, 21, 30, 31].

The pandemic is evolving progressively in many parts of the world and at different patterns, with over seven million confirmed cases and over 400,000 deaths. By the time the number of cases dropped dramatically in China in March 2020, confirmed cases increased around the world reaching a peak in May 2020. For up-to-date information, real-time interactive reports are available from several sources such as the WHO (https://covid19.who.int/) and Johns Hopkins University (https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6) [32].

As reported previously for SARS-CoV, SARS-CoV-2 has been found to bind the same receptor, the angiotensin-converting enzyme 2 (ACE-2) receptor, for cell entry, leading to subsequent inflammation in the respiratory tract [19, 33]. It has been suggested that COVID-19 infection is associated with dysregulation of the immune system [34]. This includes damage to lymphocytes, and in patients with severe disease, an increase in proinflammatory cytokines and chemokines are seen [34]. Current research suggests that those severely affected by the disease are people with weaker immune system and having underlying conditions such as diabetes, hypertension, and chronic obstructive pulmonary disease (COPD). Furthermore, elderly men are more affected compared to women [35].

While there is no current research regarding the prevention or alleviation of COVID-19 disease by boosting the immune system through IF, it is interesting to note that a recent study reported that a low-carbohydrate, high-fat ketogenic diet protected mice from Influenza A virus [36]. Ketones can also be produced through IF, including RF. For example, one study reported that RF results in an increase in circulating ketone levels, which remained elevated during nine months after the end of the fasting period [37]. A recent study on mice reported that ketone production itself may not be sufficient to improve memory function and the gut microbiome [38]. They reported that a ketogenic diet impaired memory and led to a relative increase in harmful gut bacteria. In contrast, IF, which also produces ketones, improved the memory function and gut microbiome. The authors suggested that microbiome-available carbohydrates, such as resistant starch, improve the gut microbiome composition. The findings of this research suggested that consumption of some carbohydrate-rich foods, especially resistant starch, during RF could be beneficial. It is difficult to state if changes induced by RF, such as increase in ketones, will be beneficial for the protection against COVID-19, but it is certainly an area for further research.

3.2. Effects of Ramadan fasting on human health and risks

3.2.1. Effects of RF on stress

Investigating the effects of RF on human health is a continuing concern among Muslim communities all over the world. It has been shown that RF has a favorable effect by helping to overcome stress; this was investigated on around 100 medical students using a specific scale in a questionnaire before and after Ramadan [39]. In addition, a study carried out in Saudi Arabia among healthy volunteers (young adults) found that the level of the wake-promoting neurotransmitter, Orexin-A, was significantly higher during the fasting hours in Ramadan, indicating that RF has a positive impact on alertness [40]. Likewise, IF has been reported to decrease stress levels in humans, and this effect could be mediated by regulating the stress hormone (corticosterone) and inflammatory markers (IL-6 and TNF-α) [41, 42]. Therefore, these impacts could help some Muslims who have experienced mild stress during the COVID-19 outbreak, such as anxiety due to social isolation. On the other hand, some Muslims complain of headaches during RF, and this perhaps results from lack of sugar, water, caffeine, and from some other restrictions [43]. Moreover, it has been suggested that alteration of sleep pattern and circadian rhythm could have a role in changing the individual's feelings/mood [43, 44] . One previous study reported that total sleep time is reduced by about 1 hr in Ramadan and the Epworth sleepiness scale increased by nearly 1 point [45]. Thus, although these factors gradually disappear during the month of Ramadan as the body gradually adapts, this could have negative effects on people who are already suffering from depression or severe anxiety. Therefore, this highlights the importance of seeking medical advice before the month of Ramadan, particularly for people with pre-existing medical conditions.

3.2.2. RF – the role of diet and nutrition

To date, there is no clear conclusion about dietary patterns during the month of Ramadan. There is great variability in the factors that could have an effect on diet composition, including cultural habits, geographical factors and duration of fasting [1]. The consumption of food during Ramadan is generally reduced to two meals; the *Iftar* meal (breaking of fast), which is the largest meal and consists of three-quarters of the daily calories, and the *Suhoor* meal (before dawn), where a small amount of food is consumed around 25% of the total calories per day [46]. It has been reported that even though the number of meals is restricted to two meals in major Muslims areas, most people consume the same calories they would consume before Ramadan [14]. In other words, people do not tend to decrease the amount of food they eat during Ramadan, instead in some areas such as Middle Eastern countries, they prepare recipes that contain high fat, such as fried chicken and meat [14]. In addition, they consume plenty of dairy products such as whole milk, yoghurt, and cheese. In contrast, a recent study with 160 healthy men revealed that food intake decreased with the exception of carbohydrates [47]. The finding regarding increased consumption of carbohydrate-rich foods during Ramadan is consistent with the findings of other studies [48]. A significant

reduction in the body mass index (BMI) and body weight have been reported in some studies among healthy individuals [14, 49]. Additionally, a recent two-arm randomized, controlled, single-blinded study conducted in Ramadan revealed that consuming high-fiber cereal had a positive effect on health and well-being, including improvement in blood lipids and bowel functions [50]. Therefore, greater dietary advice and guidance to the public are needed while controlling the advertisement of unhealthy foods when nearing and during Ramadan [51]. These observations indicated that fasting during COVID-19 pandemic could have both positive and negative impacts. Some people, who enjoy cooking, will be pleased to spend time in the kitchen preparing their Iftar. However, this could be stressful and a concern for others, particularly those who have concerns about their finances and their inability to go out and buy the right types of foods. In addition, shortage of certain foods in some areas in the world is another concern. Consequently, this would have the potential to adversely influence their health, as they might be unable to provide a balanced diet, which is required for good health.

Importantly, a well-balanced diet could have an important role in modulating the immune biomarkers. Increased calorie intake (as in obesity for instance) has been shown to be associated with disturbance in the immune system and a risk of significant rise of infection [52]. Moreover, inadequate nutrition (macronutrients and micronutrients) is significantly associated with an increased risk of immune deficiency, particularly in developing countries [53, 54]. Consequently, this would lead to increased risk of recurrent infections and increased mortality and morbidity rates. In this context, although it is believed that consuming additional micronutrients such as vitamin A, vitamin D, and iron could boost immunity and support the body against the challenges of getting infections, this fact would only be effective in the case of a deficiency state, meaning that if these micronutrients are within normal levels, it will not be necessary to take these supplements [55]. However, a systematic review and meta-analysis concluded that vitamin D supplementation protected people against acute respiratory tract infection [56]. This is important in light of the fact that COVID-19 is associated with respiratory tract infection. Although there is no evidence regarding the prevention and treatment of COVID-19 using vitamin D, a clinical trial is currently underway [57]. In the UK, Public Health England has been recommending people to take vitamin D supplements. In their coronavirus update, the UK National Health Service (NHS) states:

> *Consider taking 10 micrograms of vitamin D a day to keep your bones and muscles healthy. This is because you may not be getting enough vitamin D from sunlight if you're indoors most of the day. There have been some news reports about vitamin D reducing the risk of coronavirus. However, there is no evidence that this is the case* [58].

Findings of the clinical trial that is underway may shed more light on the potential of vitamin D in the prevention or treatment of COVID-19 [57]. Meanwhile, individuals who are performing any type of IF, under lockdown, should try and safely take advantage of any daily exercise permitted by the authorities to boost their vitamin D levels through sunlight exposure. Furthermore, it is advisable to eat foods that are known to be rich in vitamin D including oily fish such as sardines, mackerel, and salmon. Excessive intake of certain foods that have been linked to develop diabetes, such as rice and sugary drinks,

should be avoided. There is no specific dietary guideline available for those in COVID-19 quarantine, however, a balanced diet that is rich in immuno-supportive nutrients has been recommended by some researchers [59]. A combination of physical activities and balanced diet is the key aspect of a healthy lifestyle, as maintaining this synergistic action is essential to boost the immune system and protect against infections.

3.2.3. RF and lipid biomarkers

Many studies in the literature have investigated the effects of RF on lipid biomarkers. Khattak *et al.* [60] found that fasting during Ramadan improves the lipid profile, including the total cholesterol (TC), triglycerides (TGs), and low-density lipoproteins (LDL) with a remarkable reduction in all biomarkers in 25 volunteers, obese and non-obese, including young adults and adults. Moreover, a recent systematic review and meta-analysis reported that IF is beneficial for enhancing the lipid profile in humans [61]. Conversely, another study reported that the levels of LDL, TC, and TGs were the same and did not change among healthy adults, whereas there were significant reductions in other values including lipoproteins (Lp), apoprotein B, ratio of LDL/HDL, factor VII and fibrinogen level [62]. Additionally, a recent systematic review and meta-analysis reported small improvements in TGs and HDL-cholesterol [63]. Another systematic analysis highlighted that RF leads to improvements in lipid parameters, in particular HDL-C levels [64]. However, according to this study, men and athletic subjects benefited more.

Overall, like with other forms of IF, RF helps in reducing the risk factors of atherothrombosis and atherosclerosis and in compensating for any metabolic alteration that might have occurred throughout the year before Ramadan. Social isolation and lockdown are likely to make it more difficult for people to be physically active, and therefore improvements in lipid markers seen during a previous Ramadan may not be seen this year. Therefore, people should make extra effort to be physically active at home and take opportunities to exercise outdoor as much as possible and as permitted under the lockdown rules.

3.2.4. RF and exercise

A growing body of literature recognizes the importance of a healthy lifestyle and its beneficial effects on humans, including mental health, decreased risk of obesity, and chronic illnesses [55]. Over the last few decades, the role of physical activities on activating the immune system to fight infections has been heavily examined [65, 66]. It has been established that moderate exercise/training is associated with a low incidence of upper respiratory tract infections (URTI) in comparison to a sedentary lifestyle [67, 68]. Therefore, regular exercise is recommended during the current COVID-19 pandemic, as it could be an effective strategy to avoid the risk of infection with the virus [69]. For instance, people could be encouraged to practice home exercise, such as stretching, walking, and strengthening. A recent study reported that type 2 diabetics from Saudi Arabia displayed low physical activity and poor sleep behaviors during Ramadan [70].

During COVID-19 lockdown, the type 2 diabetics who are fasting, need to take extra care to ensure that they are physically active and have sufficient sleep to better manage their diabetes. No study has investigated the impact of exercise on COVID-19 yet, although carefully carrying out moderate exercise has been suggested in the literature [71,72]. The inability to carry out physical activity due to COVID-19 quarantine has been identified as a serious health issue and some have suggested the types of physical activity that people can perform at home [71, 73]. The recommendations for doing exercise are based on studies that have reported a positive impact of exercise on the immune system, decrease in mortality from influenza and pneumonia, and reduction in severity and duration of acute respiratory infections [74, 75].

The effects of RF among athletes has been examined widely, and it has been reported that RF in combination with regular physical activity has had a positive impact on biochemical parameters and improved metabolic syndrome risk factors such as hyperglycemia, dyslipidemia, obesity, and hypertension [76, 77]. However, a recent systematic review and meta-analysis, that included all the studies up to July 2018, investigated the effects of RF on sleep patterns among athletes and concluded that the heterogeneity was very high among the studies in the literature, and that this was predominantly affected by the study design and location [78]. This suggested that more consistent studies are needed with focus on educational programs (healthy diet and exercise) on large samples of the population during RF. This will help to provide people and healthcare providers with scientific evidence on the beneficial and/or adverse effects of RF and physical activities.

Of great significance is a recent study that explored the effects of fasting on the expression of the muscular secreted proteins (Myokines) in mice [79]. They have shown that the expression of myostatin gene (*Mstn*) and IL-6 were increased significantly with a reduction in the expression of irisin gene (*Fndc5*) and the insulin-like growth factor-1 (IGF-1) gene (*Ifg1*) [79]. Similarly, another study concluded that fasting for 6 hr in mice was associated with a significant rise in IL-6 gene expression and in the circulation, suggesting that this myokine could have an important role in providing the required energy for the metabolic adaption during fasting [80]. Moreover, fasting for around seven days in walking catfish was associated with a noticeable rise in the expression of myostatin [81]. It has been noticed that the contraction of skeletal muscle fibers during exercise stimulates the secretion of these molecules, suggesting that they might play a key role in mediating the beneficial effects of exercise on human health and could protect the human body from inflammation and any metabolic disturbance [82, 83]. Despite the limited studies among humans, these observations indicated that it might be the combination of exercise with fasting that is essential to increase the expression of these molecules or the patterns of fasting had a key role in the secretion of these molecules. So far, one study has explored the effects of RF on the myokines circulating levels including adiponectin and irisin in young adults (male and female), with an average age of 20 years in Jordan [84]. The blood samples were taken before and at the end of Ramadan, and ELISA was used to measure the serum level of these molecules [84]. It was established that there was a direct relationship between the physical activities and irisin level during RF and the levels of irisin and adiponectin were remarkably decreased

during Ramadan. In this context, novel studies among humans are essential to examine the effects of different types of fasting on the myokines expression levels including RF in healthy individuals and in patients with medical conditions.

The available data suggest that exercise in a fasting state decreases body weight and fat mass, although more controlled studies are needed for definitive recommendations to be made [85]. A moderate intensity exercise during fasting is recommended for the prevention of hypoglycemia. Training in the evening compared to training in the morning while fasting may be more effective in enhancing aerobic performance. Athletes may wish to train in the fasting state in the preseason as fasting increases the activity of fat-burning enzymes [85]. However, fasting can elicit negative effects on performance in some events, and hence modifications to the training schedules, for example, fasting during the preseason, may minimize such effects [85].

3.2.5. RF and weight loss

RF has been reported to be associated with a significant weight loss among healthy males and females [13, 86]. Ali and Abizari [87] have shown that RF was associated with a significant weight loss among 360 healthy teenagers from high schools, aged 16 years on average. Furthermore, a meta-analysis and systematic review reported that RF resulted in minor improvements in five different metabolic syndrome components including waist circumference [63]. The authors also revealed a small reduction in body weight that was attributed to RF [88]. In addition, a meta-analysis of data derived from 70 publications concluded that RF resulted in a transient weight loss and a reduction in fat mass [89]. Furthermore, Sadeghirad et al. [86] have noticed that the percentage of weight loss was completely reversed within two weeks after the month of Ramadan. On the other hand, weight gain among some Muslims during RF has been reported as well [43, 90].

Although weight loss after Ramadan was stated by the majority of the studies, modulation of lifestyle is essential to maintain the beneficial effects of fasting. This could be achieved by eating healthy food and maintaining physical activities during the month of Ramadan and the rest of the year. Particularly in the current pandemic involving quarantine and lockdown, it could be argued that observing the month of Ramadan is an opportunity to prevent the risk of gaining weight and obesity among people. Moreover, it could be used as a means to lose weight for people with obesity or at risk of obesity. In this context, it has been shown that IF was beneficial for weight loss and could be used as an effective therapeutic approach for obesity [91]. A study on obese mice revealed that IF is effective in preventing weight gain despite consumption of foods that are rich in fat and sugar [92]. This may explain why most studies reported a slight decrease in weight after Ramadan [63]. However, a combination of diet and exercise are most effective in improving lipids levels and body weight [92]. Preventing the risk of obesity is essential in this pandemic. It is important to note that NHS audit has recently indicated that around 66% of seriously ill patients with COVID-19 are obese [93]. This could be related to the fact that being overweight may significantly decrease one's immunity and negatively impact on the function of the respiratory system [93, 94].

3.2.6. RF and medical conditions

One of the most significant current arguments is how RF may affect people who have chronic medical conditions such as diabetes (T1D & T2D), acute cardiovascular disease (CVD), asthma, and chronic kidney disease. Data from several studies suggested that fasting during Ramadan has no impact on the incidence of CVD disorders such as myocardial infarction, ischemic stroke, and heart failure [95]. This was the conclusion of a systematic review and meta-analysis study, including all the studies in the literature with no restriction to a certain period. However, it has been noticed that the number of studies was limited, and more comprehensive international studies were needed to evaluate how RF could influence cardiac health, taking all the confounding factors such as diet and sleep pattern into consideration [95].

Most of the research that has been conducted in relation to the effects of RF on the metabolic and glucose biomarkers in T2D were among adults and young adults (≥ 18 years old who are included in few studies) [96, 97]. The findings were highly controversial with massive variation in the study design and methods that were used to measure and assess the metabolic parameters [98]. It has been reported that RF is safe and that it has a significant impact on weight reduction among adult patients with T2D and no significant increase in the frequency of hypoglycemic/hyperglycemic attacks in comparison to the control population [99–102]. Furthermore, it is associated with a remarkable improvement in glucose lipid biomarkers including hemoglobin A1c (HbA1c), fasting blood glucose (FBG), fructosamine, TG, and LDL [97, 103]. On the other hand, the Epidemiology of Diabetes and Ramadan 1422/2001(EPIDIAR) study reported that RF was associated with a significantly increased frequency of hypoglycemic attacks among patients with T1D and T2D [104]. Norouzy et al. [16] have established that RF was associated with a substantial disturbance in blood glucose control in T2D patients who are on diet control and antidiabetic pills, but it was also associated with a significant reduction in insulin level one month after Ramadan, suggesting that RF could have a long-term positive effect. Therefore, these observations suggest that RF could be safe among high-risk people as long as they receive close supervision from their physicians.

The effects of RF on diabetes among children and adolescents have been examined mainly in T1D [105, 106]. Evidence supported the fact that around 60% of children and teenagers with T1D are able to fast more than half of the month of Ramadan and that they can fast safely in association with proper focused education before Ramadan and close follow-up during Ramadan, where patients are advised to break their fasting during hypo/hyperglycemia [107–109]. Furthermore, most of the recent studies reported that RF was not associated with an increased risk of diabetic ketoacidosis (DKA) [110]. However, other studies considered this group as a high-risk group who should not fast during the month of Ramadan as it may increase the incidence of DKA, dehydration, and hypoglycemia among T1D in these age groups [105]. The role of RF in glucose biomarkers among children and adolescents with T2D has not been examined yet. All these findings suggested that seeking medical advice is essential before the month of Ramadan. Under the COVID-19 lockdown, children and adolescents may have benefited the most from Ramadan 2020 by getting sufficient rest and sleep since they did not

need to travel to school, colleges, or take exams. Parents who took their children to school and also had to go to work might have also got some relief from their daily routine. However, as a consequence, both parents and children may be less physically active, leading to weight gain. Therefore, it is important to engage in physical activity of some form, even within the home environment during the lockdown.

It has been reported that a 30-day IF, such as RF, showed a significant increase in the levels of some gene products that correlated with immune system regulation, neuropsychiatric disorders, DNA repair and carcinogenesis, that is, RF developed a serum proteome protecting against cancer, obesity, metabolic syndrome, inflammation, as well as numerous neuropsychiatric disorders [111]. Also, Ben Fraj et al. [112] have concluded that RF has no impact on the lung function, and this was evaluated by using spirometry test and comparing spirometric data between the fasting and non-fasting healthy adolescents aged 12-15 years. The same observation has been reported among adults [113]. Moreover, another piece of research has shown that the pulmonary function parameters did not alter in healthy young adults who were observing RF [114]. However, the effects of RF on asthma and COPD patients have not been investigated widely. A pilot study among adult males (67-74 years old) with stable COPD showed that hematological indices were markedly decreased by the end of Ramadan [115]. However, authors have noticed that there was no significant effect on the inflammatory markers (Erythrocyte Sedimentation Rate and C-reactive protein (CRP)) [115]. In addition, it has been noticed that over a period of three years, the flow rate of patients in the emergency department decreased during the month of Ramadan [116]. The vast majority of patients were complaining of gastrointestinal symptoms. This indicated that the incidence of developing serious medical conditions may reduce during RF.

There is no scientific evidence that supports the effect of fasting during COVID-19 infection, while the benefits of fasting during several illnesses have been reported [117]. This has been examined among 1,422 individuals who were admitted to a clinic due to various reasons. They were asked to follow a specific fasting program based on a low-calorie intake (200-250 Kcal/day) for a period between 4 and 21 days [117]. Researchers have shown that practicing this kind of fasting during illness was associated with positive impacts on the patient's well-being and reduced the risk of developing any serious complications. However, a study on a mice model reported that fasting might be beneficial in bacterial infections, but could have negative impacts on viral infections [118]. Therefore, all Muslims observing the month of Ramadan should seek medical advice in case they have COVID-19 infection as continuing to fast during the illness could affect their health.

Not many studies have been conducted to explore the impact of Ramadan on infectious diseases. One study reported that individuals were less likely to be infected with a pathogenic species, *Shigella* spp., during Ramadan compared to the non-Ramadan period [119]. Other than this, the authors reported that the proportion of infecting pathogens were largely the same for both periods. Reasons suggested for the decrease in *Shigella* spp. included better hygiene associated with an increase in the frequency of hand and foot washing for special prayers during Ramadan. In this context, one could

argue that an increase in handwashing during Ramadan may reduce COVID-19 infection. Future research will reveal if Ramadan increased or decreased the rate of infection.

3.2.7. RF and risk of dehydration

Several attempts have been made to evaluate the impacts of RF on water homeostasis (the total body fluid balance between fluid intake and fluid output per day) and the risk of dehydration. A study among Malaysian Muslims proved that RF has no effect on urine osmolality and urine volume overnight indicating that fasting is not associated with serious water deprivation [120]. On the other hand, studies in different countries found that urine volume was significantly reduced and this was associated with asignificant increase in osmolality, serum albumin, creatinine, sodium, and chloride during the day of RF with a tendency of osmolality to increase at the end of the month of Ramadan [121, 122]. This suggested that fasting could result in a hypohydration state due to lack of fluid and this might lead to deterioration in water homeostasis.

The risks of adverse effects are greater in those with medical conditions such as kidney disease who choose to fast during the month of Ramadan. Moreover, most of the existing bodies of research on hydration levels during RF suggested that healthy people who are observing the month of Ramadan have to ensure that they have an adequate fluid intake during the non-fasting period [17, 43, 123, 124]. Furthermore, it has previously been observed that if dehydration took place during the fasting hours in Ramadan, there is an association with an increased incidence of migraine headache, dizziness, and fatigues, particularly among employees who are working for long hours and in hot weather [125]. However, this may not be applicable during the current lockdown where most people are not working or working at home at their convenience. Therefore, this could have a positive outcome on Muslims during Ramadan.

3.2.8. Effect of RF on gut microbiota

Gut microbiota is a term that refers to all bacteria, archaea, and eukarya that colonize the human gastrointestinal tract and have co-evolved with the host over thousands of years to form a sophisticated and mutually beneficial relationship [126]. These microorganisms bring many benefits to the host through a range of physiological functions. Not only are changes in microbes present in the human gut linked with infectious diseases, but they are also associated with the pathogenesis of many other conditions including cancer, diabetes, obesity, asthma, autism, as well as neurodegenerative diseases [127, 128].

Recent studies have reported the beneficial changes in the gut microbiome as a result of IF, including RF. For example, one study with nine participants reported a significant increase in microbial richness after Ramadan [129]. An increase in bacteria (*Akkermansia muciniphila* and *Bacteroides fragilis* groups) that are present in healthy individuals was observed [129]. Studies on the impact of RF on the microbiome are still at their infancy, and the number of study participants investigated tends to be rather small. However, some of the findings reported thus far indicated changes that are considered to be beneficial. One of these studies revealed that after Ramadan there is an increase

in *Akkermansia* spp. and a decrease in *Alistipes* spp. These changes are suggested to be beneficial for reducing inflammation [130]. Modifying the microbiome through IF is being explored on animal models as a strategy for treating diabetes [131–133]. Further research on the link between IF, the gut microbiome, and diabetes is needed.

As yet, there are no data available regarding the impact of COVID-19 infection on the gut microbiome. There are some discussions regarding the potential of modulating the gut microbiome as a therapeutic approach for COVID-19 and its comorbidities [134]. This approach is most recently suggested as a potential therapeutic role of dietary probiotics to treat the dysbiosis that may occur in COVID-19 patients. It follows the "National Health Commission of the People's Republic of China" recommendation to use the modulators of gut microbiome such as polysaccharides from a traditional Chinese medicine Lung Cleansing and Detoxifying Decoction to preserve the intestinal microbial stability in severe and critical COVID-19 cases [135]. It is interesting that research carried out so far suggested that RF brings about beneficial microbial changes that are useful for reducing inflammation. More research is required to investigate if IF can be useful against viral infections.

3.2.9. Effects of RF on immune system

Several studies have reported that RF attenuates proinflammatory cytokines and immune cells in healthy individuals [136, 137]. This included lymphocytes, monocytes, granulocytes, interleukin 6 (IL-6), interleukin 1 beta (IL-1β), and tumor necrosis factor α (TNF α). These proinflammatory markers were assessed over three stages; before, during, and one month after Ramadan among a group of 50 self-controlled healthy volunteers in Jordan [137]. This study indicated that RF had the potential effect to inhibit the expression of circulating cytokines. Moreover, it provided good evidence that RF has the potential to be used as a preventive and therapeutic approach for autoimmune diseases such as inflammatory bowel disease, rheumatoid arthritis, and psoriasis [137]. A more recent study also stated the beneficial effects of RF in patients with rheumatic diseases such as rheumatoid arthritis and spondylarthritis [138].

Many studies investigated the effects of RF on different immune biomarkers and the results were controversial (Table 1). This could be related to the study design and the confounding factors of a Ramadan diet, physical activities, season, and hydration level. Furthermore, a recent systematic review and meta-analysis found that RF had possible anti-inflammatory and antioxidative implications on healthy Muslims [11]. This was examined by assessing the inflammatory markers (IL-1, IL-6, CRP, and TNF-α) and the oxidative stress marker malondialdehyde (MDA) by systematically reviewing and analyzing the available literature up until 2018, including 12 observational studies among different countries [11]. Similarly, another research group have supported these findings based on a systematic review [139]. Additionally, it has been shown that RF was associated with noticeable reductions in high-sensitivity CRP and the gene expression of IL-1 [140].

In patients suffering from COVID-19, it has been reported that an uncontrolled immune response, including the release of proinflammatory cytokines and chemokines, causes a

"cytokine storm" that attacks different organs of the body, including the lung (reviewed by Soy et al. [141]). This causes severe respiratory distress syndrome and eventually death. Therefore, reducing the levels of cytokines and chemokines can be beneficial against severe COVID-19 infection. In this context, a study by BaHammam and co-workers revealed that DIF, during and outside the month of Ramadan, significantly decreased plasma levels of cytokines (IL-1β, IL-6, and IL-8) [142]. This study suggests that people can fast even outside Ramadan as a strategy for boosting the immune system and preventing disease.

Table 1: A summary of studies that have investigated the effects of RF on immune biomarkers.

References	Country	Study design	Participants	Age range (mean)	Examined markers	Effects of RF
[142]	Saudi Arabia	Prospective study	12 males	25.1 ± 2.5	IL-1β, IL-6, and IL-8	↓↓
[136]	Turkey	Observational study	20 males	27.4 ± 5.2	IL–2, IL–8, TNF-α, CRP.	↓↓
[143]	India	Observational study	34 males	16–64	IGF-1, IL-2	↓↓
[137]	Jordan	Observational study	50 (21 males and 29 females)	18-51	IL-1, IL-6, TNF-α	↓↓
[144]	Indonesia	Observational study	27 males	18-22	TNF-α	↓
[10]	Denmark	Nonrandomized, crossover, intervention study	10 males	18-35	IL-6, TNF-α, IL-10	↔
[145]	Iran	Prospective observational study	30 males	20–35	IL-6, hs-CRP	↔
[146]	Turkey	Observational study	35 males	20–59	IgG, IgM, Salivary IgA	↓, ↔, ↓

↓ Decreased; ↔ Unchanged

Interestingly, a cross-sectional study among young adult athletes conducted by Khazaei et al. [147] showed that RF was associated with increased level of IgA and C4 at the end of the fasting month. Authors have indicated that this positive impact on the immune system may have an important role in decreasing the risk of respiratory infections in sports people. It is well-known that IgA is predominantly present in the secretions of the upper respiratory tract and in saliva [148]. IgA is also considered as the front-line defense mechanism against pathogens, particularly viral infections [148, 149]. However, another study showed that the levels of IgG and IgA are slightly decreased during RF, but still within the normal range [146]. It seems that the effects were varied and could be related to the fasting hours and physical activities. Further, this might be related to immune modulations as the level of immune biomarkers could be increased after the period of fasting. Therefore, the long-term effects of RF on the level of these molecules need to be explored.

3.2.10. RF and autophagy

Autophagy is an intracellular fundamental process, characterized by the ability of cells to eliminate and recycle the intracellular pathogen and organelles in the lysosome [150, 151]. It has been reported that RF stimulates autophagy, where all the cellular debris and aggregated proteins are removed, and this could occur in the first week of Ramadan as a consequence of severe depletion in the glycogen storage and massive amounts of free fatty acids (FFA) production [14, 151]. Therefore, the liver starts to convert these molecules (Acetyl CoA and FFA) to form ketone bodies in a metabolic process called ketogenesis, which is stimulated by glucagon hormone [14].

Ketone bodies are used as a source of energy for the cellular function in the brain cells, heart, and kidney. Numerous studies have highlighted the key protective role of ketosis against pathological processes, such as reducing heart disease risk factors, decreasing the risk of diabetes, weight loss, and profound antioxidants defense [151–154]. Furthermore, it has been reported that autophagy mediates and regulates various inflammatory processes [155]. Nosaka et al. [156] have recently reported that stimulating autophagy as a result of fasting in mice was associated with a substantial impact on regulating the inflammatory reactions due to acute lung injury, which is commonly caused by mechanical ventilation and acute respiratory distress syndrome. Authors noticed that this effect was mediated by the role of autophagy in decreased production of IL-1β from macrophage, an inflammatory marker that increases lung permeability and hypoxemia. The stimulation of autophagy and mitophagy through IF allows cells to eliminate oxidatively damaged proteins and mitochondria, reduce protein synthesis, and enable recycling of undamaged molecules [157]. Furthermore, the temporary reduction in global protein synthesis acts to conserve molecular resources and energy [157]. Recently, targeting the autophagy process has been suggested as a therapeutic strategy against COVID-19 [158].

3.3. Adverse effects of the COVID-19 pandemic on mental health

It is well-known that humans have an amazing power to overcome extreme conditions, such as lack of money, worries for ill family members, domestic conflicts/abuse. This ability to resist does vary between people. Recently, Brooks et al. [159] have discussed the psychological effects of quarantine by evaluating several factors involving frustration, quarantine duration, inadequate information, and infection fears. They suggested that the period of quarantine is one of the most important strategies in reducing the spread of infection, and this period is also often associated with substantial drawbacks. The study highlighted that officials should handle this period carefully for instance by providing full information to people regarding what is happening and ensuring that there are adequate supplies such as food and medicines [159]. Moreover, the negative impacts of quarantine on mental health, increase in stress and anger were reported [160, 161]. There are several reports regarding high prevalence of mental health problems linked to COVID-19 crisis in China and some of these were attributed to have impacts on daily life [162, 163]. It has also been reported that the mental health of children and older

people have been affected by the crisis [164, 165]. A significant rise in stress levels could negatively modulate the immune system and increase the risk of susceptibility to infections [166].

It has been shown that loneliness and psychological stress were markedly associated with recurrent influenza infections [167]. There is no current research available that assessed RF under quarantine and pandemic conditions and its relationship to mental health. There are several studies in the literature that report improvements in mental health associated with RF [168-170]. One study reported improvements in people with diabetes who experience depression [171]. A systematic review reported that RF does not cause new mental health problems or disorders and there were no major reasons to advise people not to fast, with the exception of people with major psychiatric disorders [172]. However, there is a report regarding a mental health patient, on medication, who suffered adverse effects that are attributed to fasting during Ramadan [173]. In light of the current literature, fasting during Ramadan may bring positive mental health benefits for healthy people, but those with pre-existing mental health issues should seek medical advice before engaging in fasting.

3.4. Practicing Ramadan fasting during the COVID-19 pandemic

Based on the scientific evidence covered in this review on the effects of RF and several types of IF on human health, it could be concluded that RF among healthy people is safe and has no serious impacts. However, fasting among high-risk individuals could be dangerous for their health, and medical advice is essential. To avoid the risk of spreading the infection between people, religious leaders such as Saudi Arabia's grand mufti have advised that Ramadan prayers to be done at home [174]. Some healthy Muslims are worried that fasting during the COVID-19 pandemic may influence their health and their susceptibility to infections. This can be partially attributed to many rumors spreading in the social media regarding the prevention and cures for COVID-19. One such rumor that has been circulating is that WHO has advised people to drink water frequently, and to keep the throat moist during the COVID-19 pandemic [175]. We could not find evidence for such information from the WHO COVID-19 guidance and indeed various news agencies have cited experts who have refuted the claims that frequent drinking of water, gargling, keeping the throat moist can prevent COVID-19 infection [175, 176]. However, gargling, rinsing the mouth and brushing teeth are all permitted during Ramadan fasting as long as water is not ingested. The main mode of transmission of the virus is by breathing in virus-laden droplets that are present in the air.

RF involves dry-fasting, and drinking water and other fluids is not permitted from dawn till dusk. Therefore, it is generally a common practice to drink plenty of fluids during the non-fasting period and prepare well for the fasting day and avoid dehydration. In any case, those with a medical condition that can be exacerbated by fasting are exempt from fasting.

One of the key public health messages that were promoted during the COVID-19 crisis was the need for regular handwashing. The practice of handwashing is encouraged

in many cultures and religions including Islam, where it is necessary to wash hands before eating foods or performing prayers. In this context, the increase in frequency of handwashing during Ramadan, in order to perform additional prayers has been suggested as a reason for lower infection from one particular pathogenic bacterial species [119]. In social gatherings, in many cultures, it is common for people to share food and consume from the same plates and/or bowls. In order to prevent the spread of COVID-19 from person to person, some have suggested avoiding this practice [177]. Moreover, social gatherings, which are culturally more frequent in Ramadan, must be stopped and guidance for social and physical distancing must be followed as these measures are shown to be effective in reducing transmission of COVID-19 [178, 179]. Self-isolation is recommended for individuals with no or mild symptoms of COVID-19, however, in many parts of the Muslim world, several disadvantaged communities have been disproportionately affected by COVID-19, making it almost impossible to self-isolate in small crowded homes [180].

Healthcare professionals who are fasting are particularly challenged during the pandemic as they are expected to deal with suspected or confirmed cases of COVID-19 on regular basis and work for longer hours. The use of appropriate personal protective equipment (PPE) is essential under these circumstances particularly in isolation/quarantine centers and emergency departments where urgent procedures such as ventilation/intubation and cannulation are carried out. Healthcare staff should follow guidelines and protocols from government on use of PPE [181–184]. More importantly, risk assessment must be carried out among health professionals and supporting staff so that the interaction of high-risk staff with suspected COVID-19 cases is properly managed [185–189]. The disease has claimed the lives of many health workers at different levels despite the standards and quality of healthcare settings [190–192].

4. Conclusion

It is important to stress that Ramadan is more than fasting, the entire life changes during this month including an increase in prayers that requires one to be clean and wash their hands and other parts of the body regularly. Research conducted on RF and other forms of IF highlighted numerous health benefits including positive effects on the immune system, the microbiome, body weight, and body composition. Many of these benefits may not be due to fasting per se, but other changes that occur during Ramadan. In light of the current literature, fasting during the month of Ramadan, in the midst of COVID-19 pandemic, could have a positive impact on healthy Muslims, provided a good diet, lifestyle, and physical activity are maintained. Unfortunately, one or more of these latter activities may not be possible during the COVID-19 lockdown and therefore the full benefits of IF may not be achieved during Ramadan. On the basis of current literature, additional fasting outside of the month of Ramadan may provide beneficial effects that can be protective against diseases including COVID-19.

In the future, research needs to be conducted to assess the impact of COVID-19 pandemic on the health of people who have been fasting during Ramadan. Some people may have benefited, whilst others may have suffered. Public health bodies and

healthcare professionals around the world, who are challenged by changing working practices as a result of the pandemic, should provide support to people whose health may have deteriorated as a result of difficulties arising from fasting under the lockdown, due to poor nutrition, inactivity, social isolation, and anxiety.

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The authors have no conflicts of interest to report.

Author Contributions

Hala Elmajnoun worked on the study concept and design, literature search, drafting the article, interpretation of data, manuscript preparation and editing, accuracy and integrity of all aspects of the work. Mohammed Elhag and Hatem Mohamed contributed in drafting the article and checking the accuracy and integrity of all aspects of the work. Parvez Haris and Abu-Bakr Abu-Median worked on the study concept and design, editing and critical revision, and checking the accuracy and integrity of all aspects of the work, and Abu-Bakr Abu-Median approved the final version of the article to be published.

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