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Ramadan Fasting in Health and Disease in 2021: A Narrative Review

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Abstract

Introduction: The literature on the health aspects of Ramadan fasting (RF) is widely spread in many journals.

Materials and Methods: This is a narrative review of data obtained from the PubMed database (National Library of Medicine, Bethesda, Maryland, United States). We used the search term "Ramadan fasting," and relevant records were examined. The publications are narrated thematically.

Results: The publications spanned fundamental, clinical, professional, cultural, and advocacy facets. The publications crossed conventional disciplinary lines and geographical locations and appeared in journals with different access systems. The contents are presented under the themes that emerged depending on the retrieved literature. This year basic coverage included changes in physiology and nutrition during Ramadan. However, the clinical issues included a wide range of topics. These included the impact of RF on nonalcoholic fatty liver disease and adjustments needed in endocrine replacement therapy for hypothyroidism and adrenal insufficiency. Coverage also included chronic kidney disease. The impact on maternal health, fetal well-being, and long-term effects of RF exposures were addressed in several studies. Studies in cardiovascular medicine focused on blood pressure and cardiovascular risk factors. Sports medicine and athletes' well-being received somewhat prominent coverage. The impact on renal function, particularly in patients with chronic kidney disease, was

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investigated by a few authors. Several groups addressed the eyes' structure and function, neurological conditions, especially headache disorders, and hematological and oncological conditions. Finally, the impact of RF on several aspects of mental health and well-being was addressed by various groups.

Conclusions: Health aspects of RF received a sustained academic interest with a broad spectrum in 2021. This narration provides an overview of the year's scholarly health-related literature on various aspects of health and disease. It should help researchers and clinicians catch up quickly with the health concerns during Ramadan.

Introduction

An increased interest has been expressed regarding possible health-related risks due to Ramadan fasting (RF) practiced by adult Muslims with increasing publications of all types.[1] Patients with acute or chronic medical conditions are exempted from fasting; many still choose to observe the fast. Sometimes, this may indeed be even against medical advice. This may adversely affect their health if high-risk patient groups perform it. Keeping up with developments in Ramadan research may prove difficult. Hence, a narrative overview in a single volume may help present a digest of the research and expert opinion published in a single year, perhaps helping identify the gaps in research and unmet needs in clinical practice.

Materials and Methods

This is a narrative, nonsystematic review of the literature retrieved from one online database over a full calendar year (2021). The search term "Ramadan fasting" was used to identify the relevant records from PubMed (National Library of Medicine, United States). Due to the extensive number, articles on diabetes were published separately elsewhere.[2] The articles were reviewed and narrated thematically to provide reasonably concise reading material. Full texts of original research and systematic reviews and meta-analyses in English were included.

Highlights of the Year's Literature

Several themes were addressed in the year's harvest, excluding diabetes-related work, as listed in ►**Table 1**. These will be discussed concisely below.

General Considerations

The impact of RF on patients with chronic diseases and their experience during fasting was investigated using face-to-face interviews with individuals with at least one chronic disease.[3] Participants were first asked about RF, and those not fasting were asked only the reason(s) and collected sociodemographic data. Fasting participants were enrolled in the research interviews. The survey consisted of 19 questions designed to evaluate the fasting behaviors, current chronic disease, and treatment status of individuals who encountered complications during fasting and their

Table 1 Emerging themes from the literature review on health-related literature in 2021

1	Impact on patients with chronic diseases in general
2	Impact on various aspects of physiology and nutrition in healthy individuals
3	Ramadan's impact on welfare, competitiveness, and safety of athletes
4	Impact on management of hypothyroidism and adrenal insufficiency
5	Impact of COVID-19 on delivery of medical care during Ramadan
6	Cardiovascular outcomes and risk factors during RF
7	RF impact on renal function, physicians' decision-making and patients' perspectives
8	Gastrointestinal and hepatic function during Ramadan
9	Ramadan and maternal and fetal well-being.
10	Ramadan and neurological disorders
11	Changes in the eyes' structure and function
12	Ramadan's effects on rheumatological, hematological, and oncological conditions.
13	Care of post-bariatric and post-transplant patients during RF
14	RF and mental well-being

Abbreviations: COVID-19, coronavirus disease 2019; RF, Ramadan fasting.

sociodemographic data. There were 253 participants with noninfectious diseases. About 63.2% of participants were fasting during Ramadan, 20.6% had consulted a doctor before fasting, and 62.5% never faced any symptoms. Many people with chronic diseases experience symptoms while fasting.

Impact of RF on Physiology and Nutrition

Five original research articles and five systematic reviews addressed the impact of RF on various aspects of physiology and nutrition.

The original studies addressed various RF-related biological and behavioral changes. The effect of RF on the metabolic profile, anthropometry, and serum leptin and adiponectin concentrations was examined in 27 healthy males.[4] Reductions in body weight, fat mass, muscle mass, and waist circumference followed the reductions in energy intake. Insulin sensitivity improved, and serum insulin concentration and homeostatic model assessment of insulin resistance decreased significantly with no significant change in fasting plasma glucose. A significant correlation between the percentage changes in body weight and percentage changes in serum leptin concentration was observed. Also, the effects of RF on resting energy expenditure (REE), body composition, and nutritional status of 27 adults who fasted in 2019 were investigated.[5] REE was measured using indirect calorimetry, and 3-day food records evaluated dietary energy and nutrient intakes before and after Ramadan (BR and AR). Body composition and some metabolic parameters were analyzed simultaneously with REE measurements. Bodyweight, body mass index (BMI), fat-free mass, and hydration status decreased in males and females after the RF. REEs of the participants were decreased by 6.5% post-Ramadan. The decrease in REE was greater in females than that in males. However, no significant difference was found in sleep duration (h), physical activity levels, dietary energy, nutrient intakes, and blood pressures (BP) of both sexes compared to baseline. Thus, RF may lead to a decreased energy expenditure and a change in fat-free mass in healthy individuals. Hydration is important to human health, as water is a critical nutrient in many physiological processes. However, there is currently no clinical gold standard for noninvasively assessing hydration status. A simple time of flight technique for estimating permittivity was used to investigate microwave-based hydration assessment using a population of volunteers.[6] Comparing the estimated changes in permittivity to changes in weight and the times fails to establish a clear relationship between permittivity and hydration. Assessing the subtle changes in hydration found in a population of sedentary, healthy adults proves difficult. More work is required to determine approaches suitable for tracking subtle changes in hydration over time with microwave-based hydration assessment techniques. The food intake among 62 Lebanese adults observant of RF has been compared to their intake for the rest of the year.[7] Participants completed multiple 24-hour dietary recalls, and dietary intake was examined for food groups, energy, macro, and micronutrient consumption. The study highlighted major differences in dietary intake between the fasting month and the rest of the year. With the large number of adults who observe RF, the particularities of dietary intake during Ramadan should be considered in developing context and culture-specific dietary recommendations. The experiences of young adult women observing RF were explored to understand its impact on their body image and eating behaviors.[8] In-depth interviews were conducted with 14 young women at two-time points during and after Ramadan. The questions were related to motivations, experience, eating behaviors, and thoughts related to body image and appearance. Three themes emerged: (1) family and community expectations to fast, (2) exerting control of eating behaviors, and (3) preoccupation with weight and appearance. These results suggest that family and community play a strong role in motivating women to fast during Ramadan, alongside the need to feel a sense of belonging to their community. Furthermore, five systematic reviews and meta-analyses addressed various physiological and nutritional questions on RF. The question of whether intermittent fasting enhances weight loss or muscle gains in humans younger than 60 years old was also addressed.[9] Ten original articles were evaluated. Eight studies were randomized controlled trials, and the other two were cross-sectional studies. These suggested that RF could be beneficial in resistance-trained subjects or overweight people to improve body composition by decreasing fat mass and at least maintaining muscle mass, decreasing glucagon-like peptide-1 levels, and improving health-related biomarkers. However, future studies are needed better to elucidate the effect of intermittent fasting on body composition. Possible effects of RF on the main hormones regulating appetite and satiety, including leptin and adiponectin, were examined.[10] Sixteen eligible studies were included in the systematic review, and 10 of them with complete data on leptin and adiponectin were included in the meta-analysis. A significant decrease in leptin levels was observed after RF. However, RF had no significant effect on adiponectin levels. Subgroup analysis demonstrated a greater decrease in leptin levels among normal-weight subjects than those of overweight/obese subjects. Thus, RF may decrease leptin levels, especially in normal-weight subjects. There was high heterogeneity, which may be explained by the differences between the wide range of study conditions. Studies on the effects of Ramadan versus non-RF on body composition were reviewed.[11] Sixty-six articles met the eligibility criteria. Non-RF was found effective for decreasing body weight, BMI, and absolute fat mass. When contrasting pre- to postintervention data on fat-free mass between treatments and controls, group differences were nonsignificant. Conversely, they observed a significant increase in fat-free mass when comparing pre- to postintervention. Finally, despite being accompanied by dehydration, RF is effective in decreasing body weight and relative fat mass. RF seems to implicate some beneficial adaptations in weight management, although non-RF appears to be more effective in improving overall body composition. Omentin is an adipokine with anti-inflammatory and insulin-sensitizing effects that can play a protective role against cardiovascular disease (CVD) and diabetes. The association between overall dietary intake

and omentin gene expression and circulation was investigated.[12] Twenty relevant studies were included; six were observational and eleven were human clinical trials. In the observational studies, omentin serum concentration was reduced by RF and saturated fatty acid intake. An increase in omentin gene expression was observed with monounsaturated fatty acid intake. There was no association between dietary inflammatory index, macronutrient intake, total calorie intake, and omentin plasma concentrations. In the human interventional studies, omentin plasma concentration increased with a long-term low-calorie, low-fat diet, and no change was seen with an high-fat diet or a short-term low-calorie diet. The authors suggested that a long-term diet with a lower fat content and a balanced distribution of fatty acids may effectively increase omentin plasma concentration, possibly via improved insulin resistance and reduced inflammation. However, more work is needed to confirm or refute this. Finally, the effects of two patterns of time-restricted eating (TRE), traditional TRE and RF, on two markers of circadian rhythm, cortisol, and melatonin, were reviewed.[13] Fourteen studies were included. All RF papers found a significant decrease in melatonin during Ramadan. Two out of the three papers on RF noted abolishing the circadian rhythm of cortisol. However, the non-Ramadan TRE papers did not examine melatonin and mixed cortisol changes. In studies comparing TRE to control diets, increased cortisol levels in the non-TRE fasting group were found in one study, and no difference was found in another. Dinner-skipping resulted in significantly reduced evening cortisol and non-significantly raised morning cortisol. Conversely, breakfast skipping resulted in significantly reduced morning cortisol. This blunting indicates a dysfunctional hypothalamic–pituitary–adrenal axis and may be associated with poor cardiometabolic outcomes.

Impact of RF on Cardiovascular Disease and Risk Factors

The impact of RF on the cardiovascular system included studies on hypertension, cardiac function, and cardiovascular risk factors, including BP variability and endothelial dysfunction. Two independent sets of recommendations were produced in 2021.

The effect of fasting on ambulatory BP and heart rate in treated hypertensive subjects in Tunisia (2019) was examined in 60 hypertensive patients.[14] During Ramadan, the most patient took their treatment once daily. Average 24-hour ambulatory BP, daytime and nighttime mean values of systolic and diastolic BP, and heart rate were not different, regardless of age, sex, medical history, and lifestyle. Also, the prevalence of overweight-obesity, the degree of compliance with dietary recommendations, and the effects of RF on cardiovascular health were examined among 26 women (aged 33.6 years) living in the City of Melilla, North Africa.[15] All participants were overweight or obese; however, more than 60% considered their weight appropriate or low. By the end of Ramadan (ER), the women's BMI and fat component values had fallen significantly, but this loss was recovered later. Dietary records revealed excessive consumption of lipids and sodium and high waist-to-hip ratio. All these factors are related to cardiovascular risk. The authors concluded that promoting nutritional health and encouraging year-round self-care among adult Muslim women is necessary to ensure healthy fasting during Ramadan. The effect of RF on BP, fatigue, sleeping, and physical activity was tested among 1,118 hypertensive patients.[16] There were significant differences between males and females regarding age, educational level, occupational status, income, smoking habits, physical exercise, sports activities, and fatigue. There were significant differences in the biochemistry parameters regarding vitamin D, blood glucose, hemoglobin A1c (HbA1c) level, creatinine, bilirubin, albumin, total cholesterol, triglycerides, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), uric acid, and SBP for both males and females after Ramadan as compared to BR. Also, BMI was significantly lower AR than BR. Thus, the study confirmed that RF does not affect BP, blood glucose, HbA1c level, sleep quality, fatigue, and BMI among hypertensive patients.

The effect of fasting on cardiovascular outcomes in hypertensive patients was reviewed in several major databases.[17] The review included studies assessing Ramadan, intermittent, and water-only fasting. Water-only fasting reduces body weight, BP, and lipolytic activity of fasting hypertensive patients without affecting the average heart rate. RF enhances lipid profile, although it shows conflicting results for body weight, BP, and heart rate variability. The LORANS (London Ramadan Study) is an observational, systematic review, and meta-analysis.[18] In LORANS, the systolic blood pressure (SBP) and diastolic blood pressure (DBP) of 85 participants were measured before and right after Ramadan. In the systematic review, studies were retrieved from several databases. The authors meta-analyzed the effect of these studies and unpublished data from LORANS. They included observational studies that measured SBP and/or DBP BR and during the last 2 weeks of Ramadan or the first 2 weeks of the month after. At least two reviewers conducted data appraisal and extraction in parallel. They pooled SBP and DBP using a random-effects model. In LORANS, 85 participants were recruited; the mean age was 45.6 years, with equal sex distribution. SBP and DBP after RF were lower, even after adjustment for potential confounders. They identified 2,778 studies, of which 33 with 3,213 participants were included. SBP and DBP AR/BR decreased. In subgroup analyses, lower BPs were observed in healthy groups or those with hypertension or diabetes but not in patients with chronic kidney disease (CKD). The authors suggested a beneficial effect of RF on BP independent of changes in weight, total body water, and fat mass. They supported recommendations for professional guidelines that describe RF as a safe religious practice concerning BP. Also, a systematic review and meta-analysis were conducted to measure the effect sizes of changes in cardiometabolic risk factor (CMRF) in healthy adults observing RF.[19] They identified 91 studies (4431 adults; aged 18–85 years) conducted between 1982 and 2020 in 23 countries. Meta-regression revealed that the age of fasting people was a significant moderator of changes in HDL-C and LDL-C. Male sex was the only significant moderator of changes in LDL-C.

The fasting time duration was the only significant moderator of HDL-C at the ER. RF positively impacts CMRF, which may confer short-term transient protection against CVD among healthy people.

The impact of RF on lipid profile and cardiovascular risk factors in patients with stable coronary heart disease was examined in a prospective observational study in Tunisia (2020).[20] Eighty-four patients with stable ischemic heart disease who intended to fast were enrolled. They included 79 males and had a mean age of 57 years. Detailed clinical and biochemical assessments were performed BR and AR. Levels of cholesterol, triglycerides, low-density lipoprotein-cholesterol, and apoprotein A significantly improved AR fasting compared to their BR values. There was a significant decrease in blood fasting glucose, insulin level, homeostasis model assessment of insulin resistance index, and hs-CRP level. In patients with stable ischemic heart disease, RF may be accompanied by improved lipid profile and glycemic parameters without an increase in coronary events.

The impact of fasting on cardiac health and heart rate variability as a measure of cardiac stress was evaluated in 58 patients with controlled hypertension in a prospective cohort during and after RF.[21] Lipid panel and blood glucose were measured at the end of each phase. BP and heart rate variability were monitored on each follow-up day's morning, afternoon, and evening. The mean age was 54 years, and 52% patients were males. Fasting did not affect hypertensive subjects' body composition, lipid panel parameters, and BP; males only presented lower body weight and hip circumference during Ramadan. Blood glucose was significantly higher during Ramadan. Fasting significantly increased heart rate variability during the afternoon period. Ramadan intermittent fasting reduces cardiac stress among hypertensive patients controlled by an adherent to hypertensive medication without affecting their hypertensive state.

Whether RF can improve endothelial dysfunction was documented via the thrombolysis in myocardial infarction (TIMI) frame count method in angiography, including 67 patients diagnosed with slow coronary flow by coronary angiographic BR.[22] All of them were re-evaluated via TIMI frame count within 1 to 3 months after Ramadan. They tested their hypothesis that fasting may improve endothelial dysfunction in the study's TIMI frame count method. TIMI frame counts were measured angiographically from left anterior descending, circumflex artery, and right coronary artery, and they were significantly lower than the counts before fasting. All coronary frame count parameters showed significant improvement after Ramadan compared with the baseline values before the RF period. Their results revealed that fasting and lifestyle changes during Ramadan might be beneficial for improving endothelial dysfunctions in patients with the slow coronary flow. This can be shown easily using the TIMI frame count. This is a practical and easy method for showing coronary functions.

Recommendations for CVD patients during Ramadan were published by two groups in 2021.[23,24] The first group reviewed the literature to help healthcare professionals educate, discuss, and manage CVD patients who are considering fasting. They recognized that studies on the safety of RF in patients with cardiac disease are sparse, observational, have a small sample size, and have short follow-ups.[23] However, they risk-stratified patients into 'low or moderate risk,' for example, stable angina or nonsevere heart failure; "high risk," for example, poorly controlled arrhythmias or recent myocardial infarction; and "very high risk," for example, advanced heart failure. The "low-moderate risk" group may fast, provided their medications and clinical conditions allow. The "high" or "very high-risk" groups should not fast and may consider safe alternatives such as nonconsecutive fasts or shorter days, for example, during winter. All fasting patients should be educated BR on their risk and management (including the risk of dehydration, fluid overload, and terminating the fast if they become unwell) and reviewed after Ramadan to reassess their risk status and condition.[23] They called for further studies to clarify the benefits and risks of fasting on the cardiovascular system in patients with different cardiovascular conditions to help refine these recommendations. The second group convened by the Turkish Society of Cardiology produced another consensus report.[24] They classified the patients as low and high risk according to their diseases and symptom status. Patients with high risk are advised not to fast during Ramadan. They advised that patients with low risk can fast during Ramadan, but their eligibility for fasting should be assessed individually.[24] Also, pre-Ramadan clinical assessment is an essential component of the management of patients with CVD. This should be focused on assessing multiple factors, including age, fragility, functional capacity, symptoms, lifestyle, medications, and other concomitant diseases such as diabetes or CKD. The potential risks and benefits of fasting should be discussed with the patient, and the final decision to fast or not should be clarified individually with a patient-centered approach. It is also essential to follow up with low-risk patients who are determined to fast during Ramadan so that breaking the fast is advised if the clinical situation change.

Impact of RF on Gastrointestinal and Hepatic Function

This year's work has focused on the interplay of RF and two aspects (a) gut microbiome and (b) liver disease. The RF consequence on gut bacterium (Bacteroides and Firmicutes), serum concentration for butyrate, and lipid profile were investigated in thirty healthy subjects BR and ER.[25] Fasting blood samples were obtained to measure fasting blood sugar, lipid profile, and serum butyrate concentration. Anthropometric variables were measured BR and AR for all 30 subjects. Serum levels of butyrate significantly increase during the month. The gut Bacteroides and Firmicutes increased by 21 and 13% after Ramadan. The increment in Bacteroides occurred in both sexes, but Firmicutes significantly increased only in women. Food intake was decreased during Ramadan. RF caused a significant reduction in BMI. Serum levels of LDL, HDL, LDL/HDL ratio, and total cholesterol significantly decreased during Ramadan. The authors concluded that promoting Bacteroides and Firmicutes in the gut might play a crucial role in health promotion. However, more research is needed to achieve a definite conclusion. Also, the effects of RF

on the gut microbiome were examined.[26] Feces, blood samples, and longitudinal physiologic data in two cohorts sampled in two different years were examined. The fecal microbiome was determined by 16S sequencing. Results were contrasted to age- and body-weight-matched controls and correlated to physiologic parameters. RF increased microbiome diversity and was explicitly associated with upregulation of the Clostridiales order-derived Lachnospiraceae and Ruminococcaceae bacterial families. Microbiome composition returned to baseline upon cessation of intermittent feeding. Furthermore, changes in Lachnospiraceae concentrations mirrored RF provoked changes in physiologic parameters. RF provokes substantial remodeling of the gut microbiome. They proposed that RF-provoked upregulation of butyric acid-producing Lachnospiraceae provides an obvious possible mechanistic explanation for health effects associated with RF. Furthermore, whether RF altered the microbiota in Chinese and Pakistani individuals was investigated.[27] Using high-throughput 16S rRNA gene sequencing and self-reported dietary intake surveys, they determined that the microbiota and dietary composition were significantly different with little overlap between ethnic groups (Pakistani and Chinese). Measurement of alpha diversity showed that RF significantly altered the coverage and Albumin, CRP, Endoscopy (ACE) indices among Chinese subjects but incurred no changes among either group. Specifically, Prevotella and Faecalibacterium drove the predominance of Bacteroidetes and Firmicutes in the Pakistani group, while Bacteroides (phylum Bacteroidetes) were the most prevalent among Chinese participants both before and after fasting. They observed significant enrichment of some specific taxa and depletion of others in individuals of both populations, suggesting that fasting could affect beta diversity. Notably, Dorea, Klebsiella, and Faecalibacterium were more abundant in the Chinese group after fasting, while Sutterella, Parabacteroides, and Alistipes were significantly enriched after fasting in the Pakistani group. Evaluation of the combined groups showed that genera Coprococcus, Clostridium_XlV, and Lachnospiracea significantly decreased after fasting. Analysis of food intake and macronutrient energy sources showed that fat-derived energy was positively associated with Oscillibacter and Prevotella but negatively associated with Bacteroides. In addition, the consumption of sweets was significantly positively correlated with the prevalence of Akkermansia. The study indicated that diet was the most significant influence on microbiota and correlated with ethnic groups, while fasting increased specific bacterial taxa in some individuals. Given the dearth of understanding about the impacts of fasting on microbiota, their results provide valuable inroads for future studies aimed at novel, personalized, behavior-based treatments targeting specific gut microbes for the prevention or treatment of digestive disorders. Finally, a systematic review aimed to provide an overview of the existing animal and human literature regarding the gut microbiota alterations in various fasting regimens.[28] The findings suggest that different fasting regimens, including alternate-day fasting, calorie- and time-restricted fasting programs, and RF, could promote health perhaps through the modulation of the gut microbiome. However, further studies are needed to explore correctly the connection between gut microbiota and meal frequency and timing.

Nonalcoholic fatty liver disease (NAFLD) is an important public health condition. Firstly, the impact of RF on nonalcoholic steatohepatitis (NASH) severity scores were examined in a retrospective, case–control study conducted between 2017 and 2019.[29] They included NAFLD patients who had been diagnosed by abdominal ultrasonography. The study population was divided into two matched groups: NASH subjects who fasted all of Ramadan and NAFLD/NASH subjects who did not fast (control). Metabolic/NASH severity scores, homeostatic model assessment of β-cell function and insulin resistance (HOMA-IR), NAFLD fibrosis score (NFS), BARD scores, and fibrosis-4 (FIB4) scores were assessed in both groups BR and AR month. The study included 155 NASH subjects, of whom 74 fasted. Among the fasting group, BMI decreased, NFS declined, BARD scores declined, and FIB4 scores declined. C-reactive protein (CRP) decreased. Moreover, HOMA-IR improved. Therefore, RF improved inflammatory markers, insulin sensitivity, and noninvasive measures for NASH severity assessment. Also, a systematic review and meta-analysis will estimate the effect size for changes in liver function tests (LFT) in healthy people practicing RF and examine the impact of different covariates using subgroup analysis and meta-regression.[30] They concluded that RF induces significant but small (aspartate transaminase, alkaline phosphatase, bilirubin)-to-medium positive changes on LFT. They may confer transient, short-term protection against fatty liver disease in healthy subjects. On the other hand, advice and recommendations based on the available evidence were constructed by an Egyptian.[31] They aimed to answer the research question: Do adult Muslim patients with different liver diseases who fast during Ramadan have a deleterious effect on their health compared to those who did not fast? Relevant publications were retrieved. Although RF was beneficial for patients with NAFLD, it was deleterious to patients with Child B and C cirrhosis and patients with peptic ulcers. Patients with chronic hepatitis, Child A cirrhosis, and those with noncomplicated liver transplants can fast with prefasting assessment and strict follow-up.

RF and Renal Medicine in CKD

Five studies/reviews during 2021 considered various aspects of CKD during Ramadan, covering the impact on CKD, the perspective of physicians and patients with CKD/dialysis, and the impact of RF on renal stones. The effect of RF on some markers of chronic inflammation was evaluated in 20 CKD patients, mean age 61.9 years, with an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 body surface area and not on dialysis.[32] RF was not associated with a significant change in SCr, eGFR, serum albumin, body weight, BMI, body fat, visceral fat, muscle mass, or body water. There was a significant decrease in several markers of chronic inflammation. Therefore, RF was associated with improvement in the state of chronic inflammation with no

significant change in body composition or deterioration of renal function tests in CKD patients. However, the effect of fasting during Ramadan on kidney functions was examined in 130 patients with CKD (stage III–IV CKD) admitted in Ramadan of 2019.[33] The median BUN decreased significantly after Ramadan. There was a significant difference between the nonfasting groups BR and AR concerning creatinine levels. Median creatinine increased significantly after Ramadan. There was a statistically significant difference between the fasting groups BR and AR concerning creatinine levels. In conclusion, RF does not deteriorate kidney functions and leads to a moderate improvement in kidney function. From a different angle, the experiences and perceptions of hemodialysis (HD) patients observing RF from three HD centers in Malaysia were studied using an exploratory qualitative approach.[34] Four major themes emerged from the data (a) "fasting experiences," (b) "perceived side effects of fasting," (c) "health-seeking behavior," and (d) "education and awareness needs." Patients expressed the significance of RF and its perceived impact on their health. A lack of health-seeking behavior among patients raised the need for awareness and education related to RF. These patients' experiences and perceptions regarding RF warrant effective communication between patients and healthcare practitioners through structured-Ramadan-specific education programs.

Finally, a systematic review on the impact of RF on renal stone formation identified 10 observational studies, including 9,906 participants.[35] Nine of the studies were conducted in the context of RF, with the majority finding that renal colic incidence was unaffected by RF. Two other studies noted that urine metabolites and density were altered with fasting but did not translate into clinical outcomes. Since RF is unlikely to significantly increase the risk of renal stones, physicians should counsel higher-risk patients on safe fasting practices accordingly.

Thyroid and Adrenal Replacement Therapy in Ramadan

Endocrine research has focused this year on adrenal and thyroid replacement therapy. First, the best time to instruct patients to take levothyroxine during Ramadan to minimize changes in thyroid function tests (TFTs) during RF was investigated in a prospective design.[36] Hypothyroid patients taking levothyroxine were randomized to receive instructions to take levothyroxine at one of the following three times: at dusk 30 minutes before Iftar meal, 3 or more hours after Iftar meal, or at dawn 30 minutes before suhour meal. TFTs were performed 3 months before and within 6 weeks after Ramadan. Data from patients with at least one blood test BR or AR were analyzed using mixed-effects regression models. Plasma TSH levels were available at one or more time points for 148 patients. The findings suggest that instructing patients to take levothyroxine at the time of breaking the fast 30 minutes before the Iftar meal minimizes unfavorable changes in plasma TSH post-Ramadan. In contrast, instructing patients to take levothyroxine 3 hours post-Iftar or 30 minutes before suhour led to a greater rise in post-Ramadan TSH. Second, cortisol and brain-derived neurotrophic factor (BDNF) have been shown to play a role in mood, body composition parameters, and health-related quality of life (QoL). Therefore, the mechanism of the benefit of RF, particularly on cortisol and BNDF, and their association with mood and QoL were elucidated.[37] Insulin growth factor-1, interleukin-8, matrix metalloproteinase-9, and myoglobin were determined in 34 healthy participants. Serum from peripheral venous blood samples was collected at five time points: 1 week before RF (T1); mid of RF (T2), last days of RF (T3), 1 week after RF (T4), and 1 month after RF (T5). The amounts of biological mediators in the serum samples were determined. BDNF and cortisol significantly decreased significantly at T3 and T4 compared to T1. The benefits of RF for mood-related symptoms seem to be mediated by different biological mediators, notably cortisol and BDNF.[37]

Impact of RF on Neurological Conditions

In 2021, four studies addressed different neurological disorders during Ramadan. They addressed headaches in general (1), migraine (2), and multiple sclerosis (MS) (1). Headaches are a leading complaint during the Holy month of Ramadhan, and several studies in the past have attributed the changing lifestyles and habits as some of the leading triggers. Few recent studies have further elaborated on these findings. A new headache that occurs within 4 hours of breaking the fast during Ramadan was characterized in a cross-sectional study during the last 10 days of Ramadan, based on a random sample of adults.[38] Out of 16,031 participants, 19.6% reported headaches after breaking the RF. In 84.1% of cases, no previous diagnosis of headache or migraine was evident. The characteristics of these postprandial fasting-related headaches were mostly episodic. The nature of the headache was variable, mostly heaviness or tightness. Triggering factors included ingestion of fried food and coffee. Lying down and sleeping was found to be a crucial relieving factor. They concluded that a new headache entity appears to be quite common, occurs less than 2 hours following the first meal, and is mainly of the heaviness and tension-type. More specifically, two studies considered migraine during RF since fasting is a known trigger for migraine. First, a retrospective study included patients diagnosed with migraines to study the impact of RF and changing habits during Ramadan.[39] The frequency, severity of migraine attacks, and the number of analgesic days during Ramadan were compared to those during the month before, the immediately preceding month to Ramadan. The number of breaking fasts due to migraines was reported. The study identified 293 migraineurs. Most of the patients were females (89.1%). Most of their cohort had changed sleep and food habits during Ramadan (93.2%). Most patients completed fasting for the whole month of Ramadan, and 36.5% broke their fasting for some days. Most of their cohort (82.3%) continue on the same management plan for migraines during Ramadan. Patients had a significant increase in migraine days compared with the month before. Also, days of analgesic use and migraine severity increased during Ramadan. In multivariate analysis, change in sleep and feeding habits with nonmodification of the treatment plan BR predicted breaking fasting due to worsening

migraine. Also, migraine interfered with daily activities due to fasting during Ramadan. Second, a prospective observational study performed further analysis of migraines during 2020 Ramadan.[40] Patients fill out a questionnaire using the visual analysis scale with variables such as frequency, duration, and intensity of migraines. Out of 292 known migraineurs with a mean age of 33 years, 75% were males, and half of these had migraines on the first day of Ramadhan. The frequency was reported higher in the first days of Ramadhan compared to the rest of the 20 days. Change in lifestyle habits like sleep and eating patterns, habits alteration, and dehydration were the common triggers. The two migraine studies concluded that (a) changes in sleep, food habits, and dehydration worsen Migraine frequency and severity during Ramadan. (b) Ramadan's potential exacerbating effect on the frequency of migraine attacks should be discussed with patients with migraine. This effect appears to be limited to the first 10 days of Ramadan and then subsides with successive days of fasting. Physicians should educate migraine patients who fast to manage their headaches and habits before starting fasting.

The clinical course of MS during RF and the predictors of relapses and symptoms of exacerbation were explored in a retrospective study of 153 patients.[41] Data were collected from charts and directly from patients. Those who experienced relapses, exacerbation of symptoms, and development of new symptoms during RF had significantly longer disease duration than those who did not experience worsening. Also, the former group had a significantly higher expanded disability status scale than the latter group. Worsening during RF was significantly higher in patients who experienced relapses in the preceding year compared to those who did not.

Although larger studies are needed to confirm these findings, these studies are still open to errors such as small sample size, and the sample was not controlled for age, sex, ethnicity, occupation, and smoking. Despite the available evidence, chance or bias might explain the findings, with recall bias, reporting errors, and selection bias. Confounding factors such as socioeconomic factors, dietary habits, work schedules, infections, inability to take medication appropriately, skipping meals, dehydration, and environmental factors can also affect the results.

Effects of RF on Maternal and Fetal Health

Bernier et al[42] studied the relationship between RF and the risk of stillbirth for Arab women in Canada in a retrospective cohort study using birth certificates between 1981 and 2017. The exposure to RF in the first and second trimester, and the outcome was an early or late stillbirth. They evaluated the association between RF and the risk of stillbirth, adjusted models for maternal characteristics, and assessed associations by cause of death. The study included 78,349 live births and 274 stillbirths. There were 3.5 stillbirths per 1,000 pregnancies for women exposed to Ramadan between weeks 1 and 27 of gestation and 3.4 per 1000 for unexposed women compared those exposed. In adjusted models, maternal RF between weeks 1 and 27 was not associated with the risk of early or late stillbirth. Relative risks for early stillbirth were 1.40 for Ramadan between weeks 15 and 21 and 1.38 for Ramadan between weeks 22 and 27. Relative to no exposure, Ramadan between weeks 15 and 21 was associated with early stillbirth due to congenital anomalies in unadjusted models. The authors concluded that there is no evidence that Ramadan is associated with the overall risk of early or late stillbirth. The effect of prenatal exposure to RF on outcomes, including stunting and underweight for children under 5 years, was examined in those born between 2003 and 2018 in Pakistan.[43] The study uses observational data from four rounds of the UN-supported Multiple Indicator Cluster Survey data collected on 204,186 children. A multivariate logistic regression analysis was conducted on the cross-sectional data of 179,943 children under 5 to assess the risk of stunting or underweight according to the month of gestation coinciding with Ramadan. They observed a significant increase in the risk of stunting and underweight associated with exposure to Ramadan following an inverted-U pattern. The peak impact of Ramadan exposure on an underweight child occurs in the third month of pregnancy. The probability of being underweight is 20% higher compared to children whose gestation did not coincide with Ramadan. The peak impact of RF exposure on stunting occurs in the fourth month of pregnancy, where the probability of stunting is 22% higher compared to children whose gestation did not coincide with Ramadan. The results varied a little by sex. In contrast, exposure to Ramadan in the 9th month of gestation is associated with a reduced risk of stunting for boys and being underweight for both boys and girls. Therefore, this analysis indicates that prenatal exposure to Ramadan during the first two trimesters has negative implications for children's growth, highlighting the critical role of maternal nutritional habits during early pregnancy for the long-term physical development of children. Whether RF-associated nutritional insufficiency could manifest as changes in height during childhood, long before any effects on aging or disease risk at older ages, was evaluated in Iran.[44] Children exposed and those not exposed to RF in utero were compared to identify any systematic difference between their parents' and households' characteristics. The association of child height with prenatal exposure to Ramadan was measured, controlling for seasonality and parent and household. Maternal RF in the second trimester of gestation was associated with a 0.091 age-adjusted SDS decrease in children's height at age 10. The negative association was largest in male children and was approximately 1 cm at age 12 years or older among male children. Maternal RF in the second trimester, the critical period for long bone development, was associated with decreased height.

Fasting practices, beliefs, food group consumption, and minimally adequate dietary diversity were studied in 852 women by RF occurrence and fasting adherence using logistic regression with Hindu women as a seasonal control.[45] During Ramadan in 2018, 78% of pregnant women fasted every day. Over 80% of Muslim women believe that they should fast during pregnancy, and over 50% expect positive health effects on the mother and the unborn child. They

found strong evidence that Muslim women have more diverse diets during Ramadan, with higher odds and increased consumption of pulses, dairy, fruit, and large fish. Dietary diversity increased to a lesser extent on nonfasting days during Ramadan. Ramadan appears to improve dietary quality in both fasting and nonfasting Muslim women in a rural population in Bangladesh. These results may help interpret findings from studies on Ramadan during pregnancy on later-life outcomes and thus contribute to a better understanding of intrauterine influences of maternal nutrition on healthy child development. Furthermore, the perception and knowledge of women about RF and maternal effects of fasting were studied in a prospective, case–control design during Ramadan of 2020.[46] Pregnant women with spontaneous conception and singleton pregnancies who fasted for 7 or more days (92 women) were cases, and those who did not fast (65 women) were taken as controls. The questionnaire was filled out regarding the perception of women about maternal fasting. Only 2.8% of women knew that fasting is *forbidden* in pregnancy. Sixty-five percent of women reported weakness as the main reason for not fasting. He concluded that gestational diabetes, pregnancy-induced hypertension, and preterm delivery were numerically but not significantly higher among women who fasted compared to nonfasting women. There was no difference in anthropometric measurements of newborn children among both groups

Two systematic reviews addressed the impact of RF on maternal and fetal health.[47,48] First, research on any long-term outcome of in utero Ramadan exposure was reviewed, excluding maternal and perinatal outcomes. Sixteen studies were included.[47] Most studies suggest negative consequences from in utero Ramadan exposure on health and economic outcomes later in adulthood. Higher under-five mortality rate, higher mortality under three months and one year, shorter stature, lower BMI, increased incidence of vision, hearing, and learning disabilities, lower mathematics, writing, and reading scores, as well as a lower probability to own a home were associated with Ramadan exposure during conception or the first trimester of pregnancy. Furthermore, age and sex play a pivotal role in the association. Existing studies suggest that in utero Ramadan exposure may adversely impact long-term health and economic well-being. However, evidence is limited. Meanwhile, increasing awareness of the potential risks of RF during pregnancy should be raised among pregnant women, and clinicians and other antenatal care workers should promote better maternal healthcare. Second, the effects of RF on the offspring of mothers, particularly on fetal growth, birth indices, cognitive effects, and long-term effects, were investigated.[48] Studies were evaluated based on a predefined quality score, and 43 articles were included. The study quality had a mean score of 5.4 (range 2-9). Only three studies had a high-quality score (>7), of which one found a lower birth weight among fasting women. Few medium-quality studies found a significant adverse effect on fetal growth or birth indices. The quality of articles that investigated cognitive and long-term effects was poor. The association between RF and health outcomes of offspring is not supported by solid evidence suggesting that larger prospective and retrospective studies with novel designs are needed.

Impact of RF on Rheumatology, Hematology, and Oncology Practices

A miscellaneous group of articles addressed various rheumatology, hematology, and oncology problems. The sustainability of RF effects on rheumatoid arthritis (RA) activity was evaluated in a prospective study including 35 patients with RA who observed RF in 2019.[49] The disease activity was assessed and compared between three-time points: before (T1), during (T2), and after (T3) Ramadan using the disease activity score 28 (DAS28). After significantly decreasing all disease activity parameters between T1 and T2, a gradual increase in clinical and biological outcomes was seen between T2 and T3. Except for CRP, which was significantly higher at T3 ($p = 0.02$), the changes in the other disease activity parameters were not statistically significant. By reference to baseline data (T1), the decrease in ESR, DAS28 CRP, and DAS28 ESR induced after the Ramadan fast was maintained until T3, with statistically significant differences. They can conclude that this study was conducted at the beginning of the fading-out of the effects of RF and that the duration of 3 months may be the recommended interval between fasting periods to maintain the positive effects of intermittent fasting on RA activity. Therefore, RF can induce a rapid improvement in RA activity. The positive effects of this model of fasting can last up to 3 months. The recommended interval between fasting periods may be estimated at 3 months. The same group also reviewed data that assessed the relationship of RF with rheumatic diseases.[50] They found that recent evidence indicates that RF may attenuate the inflammatory state by suppressing proinflammatory cytokine expression and reducing body fat and the circulating levels of leukocytes. Therefore, it may be a promising non-pharmacological approach for managing the course of rheumatic inflammatory diseases. Despite differences between studies on daily fasting duration and dietary norms, there appears to be a consensus that most patients with RA or spondyloarthritis who fasted Ramadan experienced relief from their symptoms. Nevertheless, further clinical trials are required to assess the effect of RIF on other musculoskeletal and bone disorders. Additionally, they evaluated the impact of RIF on chronic medication intake. Even if a few studies on this issue are available, the primary outcomes indicate that RIF does not significantly impair either compliance or tolerance to chronic medications. These findings may reassure patients with a specific fear of drug intake during Ramadan.

Five studies reported the impact of RF on hematological practice. First, three studies addressed the impact of RF on clotting and anticoagulant therapy. The alterations in the anticoagulation response to warfarin and the associated risk factors were examined.[51] One-hundred eighty-three patients receiving warfarin for at least 1 year were included in the study. Warfarin sensitivity index (WSI), prothrombin time international normalized ratio (PT-INR) category, and time spent in therapeutic range (TTR) were assessed.

National Institute of Clinical Health Excellence (NICE) criteria for anticoagulation status were adhered to where TTR (%) less than 65 was considered as poor anticoagulation. No significant differences were observed in warfarin doses between the study participants between pre-Ramadan, Ramadan, and post-Ramadan periods. Significantly more PT-INR tests were carried out during Ramadan than pre- and post-Ramadan. A higher WSI was akin to PT-INR, and lower intraindividual variability was observed in middle-aged and older adults post-Ramadan. Significantly fewer patients had their PT-INR in TTR and more in the subtherapeutic range during Ramadan. A greater proportion of patients had PT-INR in the supratherapeutic range during post-Ramadan, particularly the elderly. Although 38.3% had poor anticoagulation status overall, 92.4% met the NICE criteria for poor anticoagulation during the 3 months (pre-Ramadan, Ramadan, and post-Ramadan periods). RF influences the therapeutic effect of warfarin in terms of lowered TTR (%), reduced proportion of patients achieving therapeutic PT-INR, and increased risk of poor anticoagulation control. Also, Alwhaibi et al[52] evaluated the impact of RF on warfarin efficacy by investigating INR stability in medically stable patients. A retrospective observational study was conducted during Ramadan 2016 on fasting adult patients aged above 18 years and receiving warfarin. The INR values during pre-Ramadan, Ramadan, and post-Ramadan periods were collected after satisfying the inclusion criteria. Time within TTR during the whole period was estimated using the conventional method. One hundred-one patients were 55.8 years old, and 52.4% were females. An upward trend in the proportion of patients with therapeutic INR was noticed during Ramadan (59.4%) as compared to the pre- (56.4%) and post-Ramadan periods (53.5%), respectively. Additionally, the proportions of patients with supratherapeutic and sub-therapeutic INR were the highest and lowest, 23% and 24%, respectively, post-Ramadan compared to other periods. Achieving therapeutic INR during Ramadan was more feasible with the low INR (2–3) compared to the high INR (2.5–3.5) target patients, 63.5 versus 52.6%, respectively. TTR estimation revealed that 62.4 and 37.6% of the patients had excellent and poor anticoagulation status throughout the study period. Therefore, the results confirm that short-term fasting during Ramadan has no significant influence on INR stability and, consequently, therapeutic efficacy in warfarin-treated medically stable patients. Batarfi et al[53] determined the patient-guided modifications of the oral anticoagulant (OAC) medication regimen during Ramadan and evaluated its consequences in a multicenter cross-sectional study (2019). Participants were patients who fasted Ramadan and who were on long-term anticoagulation. Patient-guided medication changes during Ramadan compared to the regular intake schedule BR were recorded. Modification behavior was compared between twice daily (BID) and once daily (QD) treatment regimens. Rates of hospital admission during Ramadan were determined. They included 808 patients. During Ramadan, 53.1% modified their intake schedule (31.1% adjusted intake time, 13.2% skipped intakes, and 2.2% took double dosing). A higher frequency of patient-guided modification was observed in patients on the BID regimen compared to the QD regimen. The authors concluded that patient-guided modification of OAC intake during Ramadan is common, particularly in patients on the BID regimen. It increases the risk of hospital admission during Ramadan. Planning of OAC intake during Ramadan and patient education on the risk of low adherence is advisable.

Two studies were concerned with hematological oncology and radiotherapy. Yassin et al[54] evaluated the effect of RF on patients with chronic myeloid leukemia receiving tyrosine kinase inhibitors (TKIs) by evaluating specific clinical, hematological, and molecular parameters in a 3-year retrospective study. Forty-nine patients were included, aged 46 years, 73.5% males. Imatinib was the most common TKI, used in 25 patients (51%). The mean white blood cells, neutrophils, and BCR-ABL were reduced after fasting compared to before and during with statistical difference. The use of TKIs while fasting did not result in significant changes in hematological nor BCR-ABL levels in their study. Patients who wish to practice intermittent fasting may be reassured in this regard, yet physicians can adopt the safe trial approach, allowing the patients to fast, but with instructions such as when to break fasting.

On the other hand, Lachgar et al[55] studied fasting practices in patients receiving external radiation therapy during Ramadan 2018 in Casablanca. They included all patients who received external radiotherapy, involving a total of 209 patients. Most patients had breast cancer (35.4) and gynecological cancers (18.7%). All patients have fasted Ramadan before the diagnosis of cancer. However, only 39.2% fasted during the treatment by radiotherapy, and 40% of patients discussed the possibility of fasting with their oncologist. The disease stage was the only factor related to the fasting status of patients.

Impact of RF on Athletes' Well-Being

The month of Ramadan may intersect with many sports events. Understanding the effects of RF on physical performance is necessary to guide considerations for athletes. This notion has stimulated an increasing interest in the impact of RF on the general welfare, competitiveness, and safety of athletes, including its impact on sleep physiology. In the past year, several original studies and systematic reviews were published.

The effect of RF on cognitive and physical performance and biochemical responses to specific exercises was studied in elite 12 young female handball players BR, during the first week of Ramadan, and during the last week of Ramadan (LWR) during Ramadan of 2013.[56] A battery of tests was performed as follows: Hooper index, vigilance test, Epworth sleepiness scale (ESS), five jump test (5-JT), modified agility T-test (MAT), maximal standing ball-throw velocity test (MSBVT), and running-based anaerobic sprint (RAST) test. Rating of perceived exertion (RPE) was recorded immediately after the RAST. Blood samples were collected before, after, and during each exercise. The results showed that ESS scores were higher during LWR than BR. Moreover, MSBVT time decreased during LWR. Therefore, performance was

enhanced. The power of three final sprints from the RAST decreased significantly only during LWR compared to BR. RAST fatigue index and RPE scores were higher during LWR than BR. The results also showed that hematological measures, plasma osmolarity, and energetic markers were unaffected by RF. Biomarkers of muscle damage were higher after the RAST only during LWR compared to BR. The authors concluded that RF increased ESS and decreased RAST performances associated with more significant muscle damage and fatigue, especially at LWR. These previous alterations could be attributed to sleep disturbances and circadian rhythms rather than nutritional deficiency or dehydration.

The effects of RF on the morning-evening difference were investigated in team-handball-related short-term maximal physical performance.[57] With a counterbalanced study design, 15 elite female handball players underwent the hand grip (HG), ball throwing velocity (BTV), modified agility T-test (MAT), and repeated shuttle-sprint and jump ability (RSSJA) tests at 07:00 hours and 17:00 h, 1 week BR, and during the second (SWR) and the fourth week of Ramadan (4WR). The oral body temperature (OBT) was monitored prior to exercise, and the RPEs scale was obtained after RSSJA. The results showed that the time of the day affected OBT under all conditions. The HG, BTV, and MAT test performances were higher in the evening than in the morning BR. However, the diurnal variation noted in the HG and MAT tests was reversed during the SWR and 4WR, while the BTV variation was blunted during the SWR and reversed during the 4WR. The best RSSJA performance was observed in the evening BR. However, a reversal of this diurnal variation was observed for the best and mean sprint times, which was blunted by the mean jump height and sprint time decrease during Ramadan. Moreover, RPE was influenced by the time of the day during the month of Ramadan. These findings suggest that the diurnal variation in team-handball-related short-term maximal physical performance may be reversed and/or blunted during RF.

The effects of the 4-week small-sided games (SSGs) training program during RF on changes in psychometric and physiological markers were investigated in professional male and female basketball players.[58] Twenty-four professional basketball players from the first Tunisian division participated in this study. The players were dichotomized by sex, and both groups completed a 4-week SSGs training program with three sessions per week. Psychometric and physiological parameters were measured during the first week and at the end of RIF. Post-hoc tests showed significant stress levels in both groups concerning physiological parameters and significantly lower heart rates in favor of males at posttest. These results showed that SSGs training at the ER negatively impacted the psychometric parameters of male and female basketball players. Researchers and practitioners should consider these sex-mediated effects of training during RF in basketball players when programming training during Ramadan.

Furthermore, the effect of fasting on muscle function and the buffering system was investigated.[59] Twelve male athletes with 8 years of professional sports experience (age 23.2 years, BMI: 24.2 kg/m2) participated in the study. Muscle function, buffering capacity, and RPE was measured during and after RF using the Biodex isokinetic machine, blood gas analyzer, and RPE 6-20 Borg scale, respectively. Venous blood samples for pH and bicarbonate (HCO3-) were measured during and after RF by using the Biodex isokinetic machine, blood gas analyzer, and RPE 6-20 Borg scale, respectively. Samples were taken immediately after 25 repetitions of isokinetic knee flexion and extension. Measures taken during isokinetic knee extension during RF were significantly lower than those after RF in extension peak torque, flexion peak torque, extension total work, extension average power, flexion average power, blood $HCO3^-$, and RPE. No influence of RF was found on the blood pH. Therefore, RF adversely affects muscle function and buffering capacity in athletes. It seems that a low-carbohydrate substrate during RF impairs muscle performance and reduces the buffering capacity of the blood, leading to fatigue in athletes.

The effect of RF on decision-making was evaluated in Kung-Fu athletes.[60] Fourteen male Kung-Fu athletes (mean age = 19 years) completed two test sessions: BR and ER. In the afternoon of each session, participants completed the ESS, Profile of Mood States (POMS), and Pittsburg Sleep Quality Index (PSQI). Participants reported subjective fatigue, alertness, and concentration. Additionally, all participants performed video-based decision-making tasks. Results indicated that reaction time decreased by 30% at ER versus BR. However, decision-making decreased by 9.5% in ER versus BR. PSQI results indicated that quality sleep score, sleep duration, and sleep efficiency were negatively affected at ER compared to BR. ESS was higher at ER compared to BR. In addition, fatigue scores, estimated by the POMS and current subjective feelings (i.e., fatigue, concentration, and alertness), were also negatively affected at ER compared to BR. The authors suggested that RF was associated with an adverse effect on sleep and decision-making, as well as feelings of fatigue, alertness, and concentration.

To test the hypothesis that daily physical activity could be reduced among Muslims due to the inability to refuel and rehydrate in the fasting state, a cohort study was designed among adults registered with the national physical activity community program.[61] Data from a pedometer-based community program was used to extract 3 months of daily step counts before, during, and after Ramadan for 6 years. A survey was conducted among participants to determine fasting practice and other health and environmental factors. A total of 209 participants completed the survey and provided valid data on physical activity. During Ramadan, the average daily steps decreased significantly among fasting participants ($n = 151$) and increased for the nonfasting participants ($n = 58$). Fasting participants preferred before sunset (33.8%) or evening (39.7%) timings of physical activity. In contrast, nonfasting participants preferred the early morning (34.5%). These data suggest that RF impacts daily physical activity behavior, and interventions should focus on creating awareness of the importance of maintenance of adequate physical activity during RF.

The effects of an additional SSGs training program were assessed during RF on technical performance depending on changes in body composition, sleep habits, and RPEs.[62] Twenty-four professional male basketball players from the Tunisian first division participated in this study. The players were randomly assigned to an intervention group ($n = 12$) or an active control group (CG, $n = 12$). Both groups completed a 4-week SSG training program (three weekly sessions). During the first and fourth weeks of the SSGs training, the two groups were evaluated to detect changes in technical performance, dietary intake, body composition, sleep quality index (PSQI) survey outcomes, RPE, heart rate (HR), and blood lactate concentration [La]. During the 4WR period, body composition, dietary intake, sleep latency, sleep duration, and HR significantly decreased only for intervention. However, RPE significantly increased, and technical performances were negatively affected. Analysis adjusted for the percentage of change in sleep duration, body mass, and RPE showed no significant differences in either group. Therefore, the technical performance of professional basketball male players is significantly affected at the ER independently of changes in RPE, sleep habits, and body composition.

Another study involved two groups of soccer players from the Russian Premier League (RPL) of similar age: the exposure group (EG) consisted of 13 Muslims abiding by religious fasting, and the CG included 13 non-Muslim.[63] Using the Instant system, the running performance of each player was controlled in the groups during matches from the RPL before and in the third week of Ramadan (i.e., two matches for every player). None of the measured parameters demonstrated significant changes in any match. Therefore, restrictions on diet and liquid intake during Ramadan negatively influenced the running performance of elite Muslim professional adult soccer players during daytime matches.

The effect of sleep quality on physical performance and the effect of work status on physical performance during RF among athletes were investigated by two groups. In the first study, the effect of RF on the physical performance of male professional medium distance runners was evaluated, considering their sleep quality and work status.[64] Thirty-two athletes participated in this study in the summer of 2019. Data about sociodemographics, training characteristics, sleep quality (PSQI), and physical performance (Cooper Test; Harvard step test) were collected before and during Ramadan. The study suggested that both the quality of sleep and physical performance of the athletes deteriorated during Ramadan, with better quality of sleep having better physical fitness/performance both before and during RF. Athletes who worked beside training achieved worse physical fitness test results and worse sleep quality. The authors suggested that policies aimed to improve physical performance in RF should consider the quality of sleep and the work status of athletes. The second study evaluated the impact of RF on sleep quality and daytime sleepiness in team sports referees.[65] Seventy-eight male amateur team sports referees participated in this study. Participants responded to the Arabic version of the PSQI and the ESS questionnaires before (10-days prior) and during (last 7 days) of the month of Ramadan. PSQI and ESS scores increased significantly during Ramadan, with 83.3% of participants scoring equal to or more than 5 in the PSQI. The percentage of participants suffering from severe excessive daytime sleepiness increased during Ramadan. Sleep duration decreased during Ramadan and was associated with a delay in bedtime and wake-up time. The score for daytime dysfunction and subjective sleep perception, as components of the PSQI, increased, whereas the score for the use of sleep medication decreased during versus BR. The study suggests that RF impaired sleep quality and increased daytime sleepiness in team sports referees. Future studies using objective assessment tools are warranted.

Two systematic reviews of RF and sports were conducted. The first investigated the effects of RF on physical factors in football players and secondarily considered the impact on domestic club football leagues.[66] They conducted a systematic review of studies of football (soccer) players, data collected during and around Ramadan, and injury and/or performance data provided. Twenty-two studies were included. Studies included some iteration of BR, during-Ramadan, and after-Ramadan data. Common measures observed included RPEs, sprinting, sleep, peak heart rate, jumping, Yo-Yo intermittent recovery tests, Wingate anaerobic test, field-specific tests, and injury rates. Decreased physical performance was commonly observed during late afternoon/evening testing (before breaking the fast) and high-intensity exercise. Another group conducted a systematic review on the effect of RF on anthropometric, metabolic, and fitness parameters in normal-weight adults and overweight and obese individuals.[67] The search conducted through several major databases using various combinations of keywords related to nutritional interventions and outcomes of interest. Twenty-three full-text longitudinal randomized and nonrandomized controlled studies were reviewed. The analysis indicated that RF can reduce BM and improve nutrient metabolism in both normal- and overweight individuals. RF does not appear to alter protein synthesis and fat-free mass nor hamper aerobic fitness and muscular performance among physically active individuals, including athletes. The first review concluded that there seems to be a performance deficit related to RF in Muslim football players. The authors suggested further studies to explore the effects of RF on actual match demands and for considerations to be made to accommodate Muslim football players who observe RF. The second review considered RF as a more easily adaptable form of IF is a promising dietary approach to improving body composition and metabolic health while maintaining fitness and muscular function.

Finally, the effect of mental training through imagery on the competitive anxiety of adolescent tennis players fasting during Ramadan was assessed.[68] This study was conducted with male tennis players, randomly allocated to the experimental group (EG; $n = 18$) and age-matched controls (CG; $n = 20$), who watched historical Olympics videos, while EG performed mental training. The competitive anxiety state assessment was recorded four times. The first measurement was carried out 1 week BR, the second measurement during the first week of the month, the third measurement at the

end of the second week, and the fourth measurement during the 4WR. These results revealed a significant interaction (time × groups) for all competitive anxiety subscales. Higher intensity and direction scores for the cognitive and somatic anxiety subscales during Ramadan were compared with BR for both groups. Higher intensity and direction scores for both groups could be found for the cognitive and somatic anxiety subscales during Ramadan compared with pre-Ramadan. This score increase was greater for the CG than for the EG in the middle and at the ER. Finally, the self-confidence subscale score revealed that intensity and direction scores were lower during Ramadan compared with pre-Ramadan for the two groups. The score for self-confidence intensity was higher for the EG compared with the CG at the ER. It was concluded that mental imagery training was effective in reducing anxiety (cognitive and somatic) and increasing self-confidence in the intensity dimension of adolescent tennis players who fast during Ramadan.

The Interplay between COVID-19 and RF

The coronavirus disease 2019 (COVID-19) pandemic raised some special concerns in the context of RF. The questions of whether fasting is safe to practice sport or physical activities during the COVID-19 pandemic health crisis and what healthy lifestyle behaviors while fasting would minimize the risk of infection. First, the dilemma of the COVID-19 pandemic and physical activity during RF was considered, and recommendations to the fasting communities for safely practicing physical activity during the time of the COVID-19 pandemic were provided.[69] They suggested that since COVID-19 lacks a specific therapy. RF and physical activity could help promote human immunity and be part of the holistic preventive strategy against COVID-19. Also, the impact of RF on COVID-19 mortality was evaluated using national data.[70] Seventeen local authorities in England were identified for having Muslims make up at least one-fifth of the population. Indeed, Muslim populations in these areas are among the most deprived. The study found no detrimental effects of RF on COVID-19 deaths. The authors highlighted the previous claims that certain behaviors and cultural practices of minority communities explain the increased exposure to the pandemic. They argued that such claims are not evidence-based. Furthermore, there was debate whether COVID-19 infection and vaccination will hamper Ramadan among the Muslim population worldwide. The proportion of the Bangladeshi population who had adequate knowledge and attitude towards COVID-19 risk of infections and vaccination during RF was evaluated in a cross-sectional study.[71] Five hundred two adults (50.2% males and 49.6% living in urban areas) were assessed by a face-to-face interview. About 72.5 and 76.30% had adequate knowledge and a positive attitude regarding COVID-19 risk of infection and vaccination during RF. No or low formal education was significantly associated with inadequate knowledge and poor attitude. Also, current smokers reported a negative attitude.

The impact of RF on the immune system and COVID-19-related concerns were examined.[72–74] First, RF was proposed to have the potential to optimize the immune system function against the virus during the pandemic as it suppresses chronic inflammation and oxidative stress, improves metabolic profile, and remodels the gut microbiome.[72] On the other hand, maintaining good hygiene and supporting the immune system are effective preventive approaches to dealing with COVID-19. Moderate exercise training and proper nutrition are essential factors to support immune function. Lack of facilities, poor health, and many traditions that lead to public community gatherings may have made many Islamic countries susceptible to this dangerous virus. In such an unprecedented situation, there are many Muslims who doubt whether they can fast or not. Therefore, the proposal of usable exercise programs and effective nutritional strategies is imperative. Second, the proposed effects of RF on the immune system, the effects of RF on resting values, and responses of immunological/antioxidant biomarkers in elite and recreational athletes, together with the critical health, nutrition, and exercise, advise that fasting people need to follow in the event of a COVID-19 pandemic.[73] Finally, vaccine hesitancy has been reported among people and healthcare staff from ethnic minorities. Presumably, Muslims may be more hesitant to receive a COVID-19 vaccination because they do not want to compromise their fast.[74] Hence, it was important for these groups to know that having vaccines intramuscularly during fasting time does not nullify one's fast, and vaccination should not be delayed. Healthcare advocates must work closely with Imam to disseminate this information. Those fasting may also be concerned that potential side effects of vaccination may make it challenging to maintain their fast. Clinicians and COVID-19 vaccinators can advise those fasting to drink more clear fluids and take simple analgesia outside fasting times to mitigate any side effects.

Fasting after Bariatric and Posttransplant Surgery

There are a few reports on RF-related issues in surgical practice. These are considered postbariatric care and posttransplant care. First, the effect of RF on QoL in patients who underwent sleeve gastrectomy.[75] The results suggested that RF caused significant weight loss in sleeve gastrectomy patients. Besides, it did not adversely affect the QoL but increased social functioning. Second, there are no clear recommendations regarding fasting after metabolic/bariatric surgery (MBS). Hence, 61 expert metabolic/bariatric surgeons with experience managing patients who fast after MBS from 24 countries voted on 45 statements regarding recommendations and controversies around fasting after MBS.[76] A modified Delphi method was used, and an agreement/disagreement equal to or more than of 70.0% was regarded as consensus. The experts reached a consensus on 40 out of 45 statements after two rounds of voting; 100% of the experts believed that fasting needs exceptional nutritional support in patients who underwent MBS. The decision regarding fasting must be coordinated among the surgeon, the nutritionist, and the patient. At any time after MBS, 96.7% advised stopping fasting in the presence of persistent symptoms of intolerance. Seventy percent of the experts recommended delaying fasting after MBS for 6 to

12 months after combined and malabsorptive procedures according to the patient's situation and surgeon's experience, and 90.1% felt that proton pump inhibitors should be continued in patients who start fasting less than 6 months after MBS. There was consensus that fasting may help in weight loss and improvement or remission of NAFLD, dyslipidemia, hypertension, and type 2 diabetes mellitus among over 85% of experts. Third, recipients of solid-organ transplants (SOT) often ask healthcare professionals for advice on fasting. Studies on the effect of fasting in transplant patients have all been done in the MENA, where the average fasting duration is between 12 and 14 hours. In comparison, in temperate regions in the summer, fasting duration can be as long as 20 hours. Fasting when patients have to take immunosuppression 12 hours apart with slight time variation poses unique challenges. To this end, a decision-making tool was developed to assist clinicians in discussing the risks of fasting in transplant recipients, considering circumstances such as the COVID-19 pandemic.[77] They highlighted that SOT recipients wishing to fast should undergo a thorough risk assessment 3 months BR. They may require medication changes and a plan for regularly monitoring graft function and electrolytes to fast safely. Recommendations have been based on very high risk, high risk, and low/moderate risk. Patients in the "very high risk" and "high risk" categories should be encouraged to explore alternative options to fastings, such as winter fasting or Fidyah. Those in the "low/moderate" category may be able to cautiously fast with guidance from their clinician. Before the commencement of Ramadan, all patients must receive up-to-date education on sick-day rules and instructions on when to terminate their fast or abstain from fasting.

Eye Structure and Function

Three articles were published on eye structure and function during RF.[78–80] First, the effect of RF and dehydration on intraocular pressure (IOP) and biometric parameters in primary open-angle glaucoma (POAG) patients was evaluated in a prospective study. They included 30 eyes of 30 POAG fasting patients, 40 healthy participants, and 40 nonfasting healthy individuals.[78] POAG patients had a higher IOP at 4 pm during the fasting period than was seen following Ramadan. In addition, the diurnal reduction in IOP and central corneal thickness was more minor in patients with POAG compared with healthy subjects. Second, the effects of RF on diurnal superficial-deep parafoveal vessel density (pfVD) and nerve head (NH)-radial peripapillary capillary (RPC) peripapillary vessel density (ppVD) were measured using optical coherence tomography angiography (OCTA). Related urodynamic and hemodynamic parameters were compared to the nonfasting period in 105 healthy individuals (42 women and 63 men).[79] Their mean age was 34.4 years. OCTA was used to examine the superficial-deep pfVD and NH-RPC ppVD after Ramadan. The parafoveal and peripapillary DVDs (except for NHpp-VD) and IOPs were found to have decreased significantly throughout the day, both in fasting and nonfasting periods. This study confirmed the diurnal changes in the IOPs, mean ocular perfusion pressures, superficial-deep pfVDs, and NH-RPC ppVDs under dehydration and normal terms.[80] The choroidal thickness and superficial and deep vessel density indices of fasting healthy subjects were measured with an OCTA device and compared with nonfasting measurements of 70 eyes of 35 healthy subjects aged 42.9 years. Although a significant increase was noted in central choroidal thickness in the fasting period, no significant change due to fasting was observed in the superficial and deep capillary plexuses. The authors concluded that the choroidal layer might vary in thickness due to fasting-related metabolic factors, while retinal vessels are more stable against such effects.

Impact of RF on Mental Well-Being

Several studies considered RF's impact on general mental well-being and pre-existing mental health issues. The relationship was investigated between RF as a spiritual factor with prolonged hunger and disordered eating behaviors in 238 fastings and 49 nonfasting adolescents in 2016.[81] Between the groups, there was no significant difference between energy intake, Eating Attitudes Test-26 (EAT-26), and the Three Factor Eating Questionnaire-R18 (TFEQ-R18) scores. Figure rating Scale (FRS) revealed that the groups' comparisons of their "ideal" and self were not significantly different. In contrast, the gap between the figures they think was healthy and closest to self was significantly higher among nonfasting adolescents. Most adolescents (97.5%) reported fasting for religious purposes, whereas only 3.4% for losing weight. The EAT-26 total scores were in the pathological range in 16.8% of adolescents who fasted for religious purposes. The study suggests that the motivation of adolescents to fast during Ramadan was due to spiritual decisions rather than weight control or other factors, and RF was not correlated with disordered eating behaviors or body image dissatisfaction. Second, the number of psychiatry hospitalizations during Ramadan was compared to the other months of the lunar year.[82] A cross-sectional and retrospective study was conducted at a psychiatric hospital in Tunisia over five lunar years (1434–1438). A substantial decrease in hospitalizations during Ramadan was observed each year, followed by a constant increase during the following month. Ramadan was the only lunar month with a consistently below-average number of admissions. There has been a significant increase in the mean number of monthly hospitalizations over the years. A general trend toward an increase in the proportion of enforced hospitalizations has been noted. Therefore, Ramadan stands out not only on a religious but also on a social level. Furthermore, 80 individuals completed an ambulatory monitoring period and a laboratory assessment session. Participants who were fasting during Ramadan were matched by sex and khat use status who completed the study while not fasting.[83] Forty participants in each fasting group were included. Results from the ambulatory study indicated that withdrawal symptoms were lower during evening hours in the fasting group than in the no-fasting group. Stress-related changes in positive and negative effects were flattened in the fasting group relative to the no-fasting group. Khat users reported reduced BP responses relative to nonusers. These results demonstrate

that fasting reduces negative affect and withdrawal symptoms in khat users. Khat use was related to blunted BP stress responses independent of fasting. A study of patients with an established diagnosis of depression (100 men aged between 18 and 64 years) was reported from Bahrain during Ramadan.[84] Fifty persons fasted (FG) and 50 personas did not fast (NFG). There were no significant changes in depressive symptoms within the FG versus NFG after controlling for baseline covariates. No adverse effects were reported in either group. The FG experienced significant reductions in body mass, body fat, body surface area, and lean mass. RF did not negatively affect depressive symptoms and improved body composition, suggesting short-term intermittent fasting may be a safe dietary practice for adult males with depression.

During RF, people accept significant disruption in regular activities, including tobacco smoking. Thus, daytime during Ramadan (before sunset) is likely associated with abstinence symptoms emerging among tobacco smokers. The effect of fasting on cigarette smoking and nicotine addiction during Ramadan was examined in a descriptive cross-sectional survey of smokers who fast in Ramadan[85] using a questionnaire delivered through face-to-face interviews at several family medicine clinics in Turkey. There were 354 persons with a mean age of 32.9 years. A significant decrease in cigarette consumption during Ramadan was reported by 80.5% of smokers. The number of smokers who had difficulty resisting the urge to smoke was less in Ramadan than in non-Ramadan. Religious sentiments were reported as the most critical reason for coping with nicotine abstinence (53.7%). In 14.7% of the cases, participants stopped smoking during the whole period of Ramadan. Religious beliefs and willpower were effective in helping people reduce or temporarily stop smoking. Therefore, RF may play a significant role in changing smoking behavior. Also, the hypothesis was tested by measuring tobacco/nicotine abstinence symptoms and cravings among smokers of cigarettes or water pipes during Ramadan.[86] A cross-sectional survey-based study was conducted on a convenience sample of adults. A total of 632 exclusive cigarette smokers and 161 exclusive waterpipe tobacco smokers were included. After fasting and abstaining from tobacco during the day, approximately 75% of cigarette smokers and 20% of waterpipe smokers reported smoking within the first 30 minutes. In addition, 10% of cigarette and 30% of waterpipe smokers reported smoking within the first 60 minutes. No significant difference was found between cigarette and waterpipe smokers in smoking urge. For nicotine craving and withdrawal, significant differences between cigarette and waterpipe smokers were found when comparing mean scores for (i) urge to smoke, (ii) craving for nicotine, (iii) hunger, (iv) desire for sweets, and (v) depression/feeling blue. Therefore, waterpipe smoking is associated with abstinence-induced smoking urge and withdrawal symptoms similar to cigarette smoking. Further research on reducing tobacco smoking should include all forms of smoking. On the other hand, most Muslims who use e-cigarettes fast the month of Ramadan, which results in intermittent fasting. The severity of e-cig withdrawal symptoms among users during RF was evaluated using a self-administered survey developed and validated to solicit anonymous responses from e-cig users in Jordan through a cross-sectional study ($n = 523$; 96.4% males; 86.4% aged between 18 and 40 years).[87] Severity scores of physical and psychological withdrawal symptoms were assessed and calculated. Many participants replaced tobacco smoking with e-cig (53.5%) to help them stop smoking. Over half of the participants experienced relatively weak physical and psychological withdrawal symptoms during the fasting month. Many participants (63.2%) preferred to engage with a busy schedule to tolerate the related withdrawal symptoms they experienced. Ramadan offers an excellent opportunity for smokers to quit, as the reported physical and psychological e-cig withdrawal symptoms were relatively weak.

Finally, the perceptions of fasting exemptions, medication usage behavior, perceptions of relationships with healthcare providers, and factors impacting health management during Ramadan were examined in a qualitative study.[88] Twenty-five adults (men and women) with chronic diseases participated in four focus groups using standard methods. Participants were asked open-ended questions about their fasting ability, medication usage behaviors, healthcare access, and collaboration with providers during RF. Prominent themes/subthemes were fasting exemption, fasting nonexemption, nonoral medication use during Ramadan, healthcare provider involvement during Ramadan, and factors impacting health management during Ramadan. The authors concluded that (a) patients perceive fasting as an essential religious practice, so they tend to self-modify their medication-taking behaviors, and (b) educating healthcare providers about Muslim culture, especially their strong desire to fast, may lead to better management of their medications and viewing pharmacists and other healthcare providers as knowledgeable healthcare providers.

Conclusions

Health-related publications on RF in 2021 covered various fundamental, clinical, professional, cultural, and patient advocacy issues in different disciplines and geographical locations. The prominent coverage included changes in physiology and nutrition during RF. Other clinical aspects discussed include the impact of RF on nonalcoholic fatty liver disease and chronic kidney disease and adjustments required for endocrine replacement therapy in hypothyroidism and adrenal insufficiency. Impact on maternal health, fetal well-being, and long-term effects of RF exposure was addressed in several studies. In cardiovascular medicine, studies focused on BP and cardiovascular risk factors. Sports medicine and athletes' well-being featured prominently. The structure and function of the eyes, neurological conditions, especially headache disorders, and hematological and oncological conditions were addressed by several groups. Finally, the impact of RF on several aspects of mental health and well-being was discussed by various authors. Health aspects of RF received a sustained academic interest with a broad spectrum in 2021. This narration provides an overview of the year's scholarly health-related literature highlighting

essential aspects of health and disease during RF. It should help reduce research gaps and unmet clinical practice needs.

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Erratum: Article has been corrected as per Erratum (DOI: 10.1055/s-0042-1758814).

