





# Review of the Literature on Ramadan Fasting and Health in 2022

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## Abstract

**Objectives** The literature on health and disease during Ramadan fasting (RF) is widely spread in many journals making it not readily accessible to those interested in the subject. Here, we provide an overview of the research on the interplay of RF with various aspects of well-being published in 2022.

**Materials and Methods** A narrative, nonsystematic review of the international literature from a single major medical online database, PubMed, in one calendar year (2022) was conducted. The search term “Ramadan fasting” was used to retrieve the appropriate records. The relevant literature with substantial data-based content was presented in a concise thematic account, excluding those concerned with diabetes.

**Results** Themes that emerged from the review included the pathophysiology of metabolic changes during RF, nutritional aspects including body composition and energy metabolism, cardiovascular disease and risk factors, renal function and structure, endocrinology (mainly thyroid), neurological disorders, mental health, pregnancy and fetal life, and infections (including COVID). Some miscellaneous clinical themes were identified, such as patients’ and professional perspectives.

**Conclusions** In 2022, the medical interest in RF was again widely spread across specialties. Cardiovascular disease and risk factors attract the most interest in terms of original articles and professional guidelines. We hope with this review to present a concise summary of the scholarly work on the subject in this year.

## Keywords

- ▶ Ramadan fasting
- ▶ patient’s perspectives
- ▶ thyroid
- ▶ cardiovascular disease
- ▶ pregnancy
- ▶ renal function
- ▶ pathophysiology

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## Introduction

Ramadan fasting (RF) is observed by millions of Muslim adults around the world. It lasts for 1 month per the lunar calendar. RF entails abstinence from food, water, all oral substances, intravenous fluid therapy, and smoking between dawn and sunset.<sup>1</sup> Ramadan's impact on health and disease stems from the physiological effects of prolonged fasting during the daytime and possible overfeeding at night and its various social changes, such as changes in exercise and sleep patterns. The last three decades witnessed a rising interest in the research on RF in health and disease. Diabetes is the most extensively studied single medical condition in connection with RF.<sup>2</sup>

The literature on health and disease during RF is widely spread in many journals making it not readily accessible to those interested in the subject. Here, we provide a thematic overview of the global research conducted during 2022 concerning the impact of RF on all aspects of health and disease, excluding the impact on people with diabetes. We aimed to provide a concise bird's eye view of the literature published in a year. This may help busy researchers and clinicians catch up with the year's harvest at a glance. This is the latest thematic series on "Ramadan-Year in Review," 2017–2023, mainly published in this journal. The year's productivity on RF and diabetes is summarized separately.<sup>3</sup>

## Materials and Methods

This is a narrative, nonsystematic review of the literature retrieved from a single major online database over a full calendar year (2022). The PubMed search engine of the National Center for Biotechnology Information (NCBI) at the U.S. National Library of Medicine (NLM) was used. The search term ["Ramadan fasting"], with time filters from January 1, 2022, to December 31, 2022, was employed to identify the relevant records. A total of 163 articles were retrieved and examined for relevance, reviewed, and narrated thematically. Full-text research articles in English were included. No statistical analysis was conducted on the data included in the original articles, and detailed numerical presentations were avoided. Original articles, systematic reviews, and guidelines were included, but letters, cases, short narratives, and statements were excluded. The aim is to provide a concise but adequately representative theme surrounding RF. The literature concerning diabetes during RF was summarized separately and will not be repeated here.<sup>3</sup>

## Results

### Pathophysiology and Nutrition

Several studies investigated the pathophysiological mechanisms of the impact of RF on some aspects of health<sup>4–8</sup> and nutritional changes including body composition and energy metabolism.<sup>9–13</sup>

The effects of RF on nasal mucociliary clearance (MCC) and peak nasal inspiratory flow (PNIF) were evaluated in a prospective study that included 62 healthy subjects

intending to fast.<sup>4</sup> Day 0 (baseline), first day (after 1 day of RF), and 29th (after 29 days of RF) nasal mucociliary clearance time (MCT) with saccharine test and PNIF values were determined. Subject weights (SW) were measured on day 0 and day 29. The mean of SW on day 0 was 78.5 kg, and the mean of SW on day 29 was 78.7 kg. There was no significant difference in SW. However, a significant difference was found between the MCT and PNIF values measured on different study days. The MCT values for day 29 were significantly higher than those for other days. There was no significant difference between the MCT values on the first day and the baseline. The PNIF values for day 29 were significantly higher than those for other days. The PNIF values on the first day were significantly higher than the baseline. On the other hand, a growing body of evidence supports the impact of intermittent fasting (IF) on normalizing body weight and that the interaction between body genes and environmental factors shapes human susceptibility to developing obesity. The *FTO* gene is one of these genes with metabolic effects related to energy metabolism and body fat deposition. Therefore, the changes in *FTO* gene expression upon RF were tested in a group of metabolically healthy subjects with overweight and obesity.<sup>5</sup> Fifty-seven subjects with overweight and obesity were recruited and monitored before and at the end of Ramadan. Six healthy subjects with normal body mass index (BMI) were recruited only to standardize the reference for normal levels of *FTO* gene expression. In the two time points, anthropometric, biochemical, and dietary assessments were undertaken, and *FTO* gene expression tests were performed using RNA extracted from the whole blood sample. In contrast to normal BMI subjects, the relative gene expressions in overweight/obese were significantly decreased at the end of Ramadan compared to the pre-fasting state. Significant reductions were found in body weight, BMI, fat mass, body fat percent, hip circumference, low-density lipoprotein (LDL), interleukin (IL)-6, tumor necrosis factor (TNF- $\alpha$ ), and waist circumference. At the same time, high-density lipoprotein (HDL) and IL-10 significantly increased at the end of Ramadan compared to the pre-fasting levels. Binary logistic regression analysis for genetic expressions showed no significant association between high-energy intake, waist circumference, or obesity and *FTO* gene expression. Along the same lines, the effect of exergaming during RF on body composition, physical performance, and hematological parameters was examined in overweight and adolescents with obesity.<sup>6</sup> Twenty-four adolescents with obesity were divided into two groups (12 in the control group [CG] and 12 in the cooperative sport exergaming group [EG] undertaking 45-minute session during 5 days per week). Participants completed a 6-minute walk test (6MWT), a squat jump test, and 10- and 30-m sprint tests on four different occasions: before Ramadan (T0), the second week of Ramadan (T1), the fourth week of Ramadan (T2), and after Ramadan (T3). Blood pressure (BP), rating of perceived exertion (RPE), body composition, central obesity index, dietary intake, and profile of mood states (POMS) were assessed over the four periods. The results showed that body weight, BMI, and body fat percentage were significantly

lower at T2 compared to T0 and T1 in the EG. After RF, body composition returned to the values recorded before RF. The POMS score was significantly lower during T2 than T0, T1, and T3 in the EG. The vertical jump and the 6MWT distance were significantly higher at T2 compared to T0, T1, and T3 in the EG and in EG compared to CG at T2. RPE was significantly lower at T2 compared to T0, T1, and T3 in the EG and in EG compared to CG at T2. BP was lower during T2 compared to the other periods in EG. The EG experienced significant decreases in total cholesterol and triglycerides during T2. However, no significant changes between groups and periods were reported for all the other parameters. Finally, the influence of IF on serum immunoglobulin A (IgA), salivary IgA (sIgA), IL-17, and IL-22 levels was investigated in 40 healthy men aged 19 to 29 years. Soleimanifar et al<sup>7</sup> were evaluated before and during the fourth week of RF for IgA levels by the nephelometric method as well as salivary IgA (sIgA), IL-17, and IL-22 amounts using enzyme-linked immunosorbent assay (ELISA). Serum IgA levels reduced significantly at the end of RF (226 vs. 196 mg/dL); however, sIgA amounts did not differ between before and the last week of Ramadan. Serum IL-17 reduced significantly, whereas IL-22 levels remained approximately unchanged. **Summary:** 4 weeks of IF during Ramadan reduced the serum levels of IgA and IL-17 but did not affect the production of sIgA and IL-22.

The effects of sex in six disease outcomes of patients who observed RF were evaluated in a systematic review of observational and relevant clinical studies.<sup>8</sup> Eighteen studies reported sex-based differences for variables such as BMI, blood glucose, the frequency of hypoglycemia, renal colic, mortality, thrombosis, and gastrointestinal diseases in patients observing RF. Most differences between men and women were reported in the baseline before and during Ramadan. Indeed, during the period outside Ramadan, the frequency of renal colic, cardiovascular, and gastrointestinal diseases were higher in men, while BMI, thrombosis, and headache were higher in women. In the remaining 21 studies, it was reported that the sex factor was not associated with the effect of RF on the frequency and other outcomes of these diseases. It was suggested that a closer attention to sex differences regarding the frequency and progression of diseases during fasting might help improve patient care and benefit those patients willing to fast.

Nutritional changes are integral to Ramadan, and several authors examined the direct and indirect effects of dietary changes and fluid intake during RF. The changes in dietary intake, chronotype, sleep pattern, and physical activity level before and during Ramadan were examined in healthy adults in Jeddah, Saudi Arabia.<sup>9</sup> Data were collected on 115 adults, mostly females, before and during Ramadan. Significant increases in daily calorie and carbohydrate intakes during Ramadan than before Ramadan were noted. Chronotypes and daytime sleepiness were also associated significantly with RF. A significant slight reduction in body weight during Ramadan was observed. The fasting individuals' healthy eating index (HEI) and diet quality were evaluated during Ramadan in a cross-sectional study of adults aged 18 to 65 years.<sup>10</sup> Food consumption record was

taken with a 24-hour record with food consumption form. Diet quality and adequacy were assessed with the HEI, nutrient adequacy ratio (NAR), and average adequacy ratio (MAR) from food consumption records. HEI and NAR Ca scores were significantly lower in the fasting group (FG) than in the nonfasting group (NFG). In the NFG, HEI scores negatively correlated with BMI and waist-hip ratio. This study suggests that fasting might be associated with low scores of HEI. To address the effects of fluid balance, water and beverage intake and drinking patterns were evaluated to help achieve water requirements during Ramadan in a cross-sectional study employing a self-administered questionnaire (Ramadan of 2021).<sup>11</sup> They utilized a 7-day fluid record (liquid in 7 days) to assess water and beverage intake among participants. A total of 380 participants from five universities across Indonesia completed the questionnaire. The participants' total water and beverage intake during Ramadan was below the recommendation (1,670 mL/day). Water was the highest level of consumption (1,262 mL/day), followed by sugar-sweetened beverages (200 mL/day). They found a significant difference in water and beverage consumption between the time of Iftar, nighttime, and Suhoor.

Time-restricted feeding (TRF) and RF have been recently associated with several health outcomes. Two studies reviewed the literature<sup>12</sup> and summarized the current data on the effects of these regimes on body weight, body composition, and glycemia. Twenty-four records met the inclusion criteria and underwent a risk-of-bias assessment. They suggested the following: (1) TRF may result in moderate weight loss in individuals with overweight/obesity, (2) 14 hours of fasting may be as effective as 16 hours in terms of weight loss, and (3) TRF may lead to improved insulin sensitivity and glycemic responses/variability throughout the day in overweight/obese individuals. Concerning RF, only two studies were available; thus, conclusions were not drawn. An umbrella review summarized the systematic reviews that examined the effects of time-restricted eating (TRE) on weight loss, fasting blood glucose (FBG), and lipids in individuals with overweight and obesity.<sup>13</sup> They compared the effect sizes on these outcomes between conventional TRE and RF. Seven systematic reviews with 30 unique meta-analyses involved 7,231 participants from 184 studies. Meta-analyses at the metadata level suggest that TRE is beneficial for reducing weight and FBG. Meta-analyses at the primary study level suggest that the effect on LGL-C was significant.<sup>13</sup> Subgroup analyses revealed greater effects in lowering FBG, total cholesterol, and LDL-C from RF than conventional TRE.

### Metabolism and Endocrinology

Studies on metabolism and endocrinology included metabolic syndrome (MetS) and obesity,<sup>14–17</sup> thyroid disease,<sup>18–21</sup> and polycystic ovary syndrome (PCOS).<sup>22</sup>

The changes in various components of MetS were examined in healthy adults who observed RF before Ramadan (T1) and at the end of RF (T2).<sup>14</sup> A secondary goal was to assess the impact of RF on MetS severity in various ethnic and sex

groups using the MetS z-score. Seven databases were searched for relevant studies published up to March 2022. The MetS z-score showed improvement at T2 for all ethnic groups and both sexes by  $-0.22$ . RF positively impacts the MetS components and the overall MetS z-score. Also, a prospective study was conducted on subjects with MetS before, during, and after RF.<sup>15</sup> Untargeted proteomics was measured to assess the impact on peripheral blood mononuclear cells (PBMCs) proteome in 14 fasting subjects with MetS. The quantitative proteome analysis showed that apolipoprotein B (APOB) gene protein product (GP) levels were downregulated and had the most statistical significance of the observed difference at the end of 4 weeks of RF: 1 week after 4-week RF compared with the levels before 4 weeks of RF. The comparison between GP levels before and at the end of 4 weeks of RF showed an alteration in the expression of genes associated with lipid and atherosclerosis pathways and C-type lectin receptor signaling pathways. The genes differentially expressed in the lipid and atherosclerosis pathway were APOB, CD36, CALM1, CALM2, CALM3, and HSPA8. One of the differentially expressed genes in the C-type lectin receptor signaling pathway was lymphocyte-specific protein 1 (LSP1), which showed an average of 19-fold increase at the end of 4-week RF compared with the GP levels before fasting. Several GPs associated with the tumor-suppressor effect were upregulated. GPs associated with the tumor-promoter effect were downregulated at the end of 4-week RF or 1 week after 4-week RF compared with the GP levels before 4-week fasting.

Furthermore, the metabolomics changes incurred upon observing RF were investigated.<sup>16</sup> Twenty-five metabolically healthy participants with overweight and obesity were followed before and at the end of RF. Clinical assessments and the metabolomic assay were performed for the two time points. Metabolomics assay revealed a significant reduction in a few metabolites. The analysis revealed that 27 metabolites differed significantly between pre- and post-RF. Among the differentially abundant metabolites, 23 showed a decrease with fasting, including several amino acids such as aspartame, tryptophan, phenylalanine, histidine, and other metabolites, including valeric acid and cortisol. On the other hand, only four metabolites showed increased levels after RF including traumatic acid, 2-pyrrolidinone, PC, and L-sorbose. The MetaboAnalyst platform enriched several metabolic pathways. They concluded that RF entails significant changes in various metabolic pathways that reflect different dietary and lifestyle behaviors practiced during Ramadan. Also, how circulating levels of PCSK9 changed during Ramadan IF in metabolically healthy obese subjects was examined in a cross-sectional study of a convenience sample of 55 overweight and obese participants.<sup>17</sup> The median age was 35 years, and the BMI was 30.2. They found significant increases in serum levels of PCSK9, serum insulin, insulin resistance, and leptin at the end of Ramadan compared with pre-fasting levels. Significant reductions in body weight, waist circumference, systolic and diastolic BP, total cholesterol, triglycerides, HDL cholesterol, and adiponectin were also observed at the end of Ramadan.

Four studies in 2022 investigated the impact of RF on thyroid functions (TF). Alkaf et al<sup>18</sup> retrospectively examined the short- and long-term impact of RF on TF in patients with primary hypothyroidism on levothyroxine. The impact of RF serum thyrotropin (thyroid-stimulating hormone [TSH]), free thyroxine (fT4), and free triiodothyronine (fT3) was investigated in 481 patients within 3 months before Ramadan, 1 to 2 weeks (PR1), and 3 to 6 months (PR2) post-Ramadan. TSH increased significantly from a median of  $2.0 \mu\text{IU/mL}$  at before Ramadan to  $2.9 \mu\text{IU/mL}$  at PR1. This was accompanied by a fall in fT4 and fT3 at PR1. 25.5% of patients with previously controlled TF at before Ramadan had deterioration in TF at PR1. Sixty-one percent of patients with previously uncontrolled TF at before Ramadan remained uncontrolled at PR1. Baseline TSH was significantly associated with loss of thyroid control in Ramadan, with an odds ratio of 1.5. In contrast, other variables, including medications known to affect levothyroxine absorption, were not associated with losing control. TSH, fT4, and fT3 levels returned to normal at PR2. RF can negatively affect the TF of patients on levothyroxine replacement. Although this effect is modest and transitory in most patients, a significant minority exhibit more pronounced and clinically relevant changes. The latter includes those with higher TSH before Ramadan and a smaller group whose thyroid disease appears to be particularly affected by mealtime and lifestyle changes of Ramadan. Elsherbiny<sup>19</sup> reported a prospective study of 292 hypothyroid patients who fasted during Ramadan 2018–2020. Patients choose one of three levothyroxine regimens during Ramadan—regimen 1: 60 minutes before Iftar; regimen 2: 3 to 4 hours after Iftar, 60 minutes before Suhoor; regimen 3: before the start of next fast, 3 to 4 hours after the early Suhoor. Thyroid status was assessed in pre-Ramadan visits and reassessed in the post-Ramadan visit within 6 weeks from the end of Ramadan. Most patients were adherent, but one-sixth were nonadherent. Post-Ramadan TSH was  $2.13 \text{ mIU/L}$  versus  $1.60 \text{ mIU/L}$  pre-Ramadan. Most patients (79.8%) remained euthyroid post-Ramadan, while 20.2% were dysthyroid. Post-Ramadan TSH correlated significantly to pre-Ramadan TSH and it was significantly higher in nonadherent patients than in adherent patients. The same author assessed the effect of twice or thrice weekly versus standard daily L-T4 dosing during Ramadan on adherence, post-Ramadan TSH, and thyroid status. Elsherbiny's<sup>20</sup> study included two groups: group 1 of 11 patients taking L-T4 twice or thrice a week and group 2 of 113 patients taking L-T4 daily. Patients chose between three L-T4 regimens: regimen 1, 60 minutes before Iftar; regimen 2, 60 minutes before Suhoor, on an empty stomach for 3 to 4 hours; regimen 3, before the next fast, on an empty stomach for 3 to 4 hours. Only euthyroid patients were included. There were no significant differences between the groups regarding adherence, post-Ramadan TSH, or post-Ramadan thyroid status. 90.9% in group 1 and 88.5% in group 2 were adherent. Post-Ramadan TSH in group 1 was  $1.9 \text{ mIU/L}$ , and in group 2 it was  $2 \text{ mIU/L}$ . 81.8% in group 1 and 82.3% in group 2 were euthyroid post-Ramadan. Also, Al-Qahtani et al<sup>21</sup> evaluated the impact of L-T4 timing during Ramadan on TSH levels in

post-thyroidectomy patients to determine the best timing for intake and identify the predictors of TSH level changes in a parallel, double-blind, randomized controlled trial. Participants were randomized to the following: group A ( $N=31$ ), 30 minutes pre-Iftar; group B ( $N=34$ ), 3 hours post-Iftar; or group C ( $N=22$ ), 1 hour pre-Suhoor. The TSH levels significantly increased in groups B and C but not in group A. The change in fT4 levels was comparable among the groups: group A, group B, and group C. In a multivariable linear regression analysis, the following variables were significantly independently associated with TSH level change: age, weight gain, and the number of nonadherence days to L-T4. Thus, fasting patients who took L-T4 pre-Iftar did not experience significant changes in TSH, whereas those who took L-T4 post-Iftar or pre-Suhoor did.

Finally, Floyd et al<sup>22</sup> evaluated the effect of TRE on insulin levels and sensitivity in PCOS. They found a single article on RF fulfilling the inclusion criteria. The study showed no firm evidence of a significant effect on insulin levels. As the systematic review retrieved only one study investigating TRE to reduce insulin in women with PCOS, evidence suggests this intervention is impractical. From the narrative review, based on studies in other patient groups, TRE could improve insulin resistance in women with PCOS.

### Cardiovascular Disease and Risk Factors

In 2022, seven original research articles addressed various aspects of cardiovascular disease (CVD)<sup>23–25</sup> and risk factors<sup>26–29</sup> associated with RF: four on cardiac events and three on risk factors. Four other articles provided practical guidelines and management recommendations for people with CVD during RF.<sup>30–33</sup>

Betesh-Abay et al<sup>23</sup> examined the association between RF and acute myocardial infarction (AMI)-related outcomes using retrospectively extracted data from a tertiary hospital database 2002–2017. The study periods for each year were 1 month preceding Ramadan (reference period [RP]), Ramadan, and 2 months after that. A comparison of adjusted incidence rates between the study periods was performed using generalized linear models; 1-month post-AMI mortality data were compared using a generalized estimating equation. Out of 5,848 AMI hospitalizations, 877 of the patients were Muslims. No difference in AMI incidence between Ramadan and RP was found. However, in the 1-month post-Ramadan period, AMI incidence demonstrably increased compared to the RP. Additionally, the highest mortality risk was observed among the patients who underwent AMI in the 1-month post-Ramadan period compared to the RP. The subgroup analyses found Ramadan to differentially correlate with AMI mortality concerning smoking, age, sex, diabetes mellitus, and hypertension, suggesting that RF is a risk factor for adverse AMI-related outcomes among selected Muslim patients. Also, Aydin et al<sup>24</sup> investigated the circadian pattern of ST elevation acute myocardial infarction (STEMI) during Ramadan. They studied consecutive STEMI patients 1 month before and after Ramadan (non-Ramadan group [NRG]) and during Ramadan (Ramadan group [RG]). The RG group was also divided into two groups based on

whether they chose to fast: FG and NFG. The time of STEMI onset was compared. Seven hundred forty-two consecutive STEMI patients were classified into four groups at 6-hour intervals according to symptom-onset time. No consistent circadian variation in the onset of STEMI was observed between the RG and NRG or between the FG and NFG. When analyzed for subgroups of the study sample, neither smoking nor diabetes showed circadian rhythm. There was a trend toward a delay from symptom onset to hospital presentation, particularly at evening hours in the RG. In conclusion, there was no significant difference in STEMI-onset time, but the time from symptom onset to hospital admission was significantly delayed during Ramadan. Finally, Alam et al<sup>25</sup> investigated how RF affects patients with heart failure (HF) with preserved ejection fraction (HFpEF). They enrolled 456 fasting and 482 non-fasting patients in a prospective observational study. The FG showed a decrease in NYHA functional class III and IV and an increase in class I symptoms.

Ben Ahmed et al<sup>26</sup> evaluated the impact of RF on cardiovascular risk factors and lipid profiles in patients with stable coronary heart disease. A prospective observational study was carried out in Tunisia. Eighty-four patients with stable ischemic heart disease who intended to fast were enrolled in May 2020. Detailed clinical and biochemical assessments were performed before and after the holy month. Parameters of glycemic control, lipid profile, ultrasensitive C-reactive protein concentration (us-CRP), and homocysteine were performed before and after Ramadan. Eighty-four patients (79 males), with a mean age of 57 years, completed the study. Levels of cholesterol, triglycerides, LDL cholesterol, and apoprotein A were significantly improved in after Ramadan compared to their before Ramadan values. There was a significant decrease in FBG, insulin level, homeostasis model assessment of insulin resistance index, and us-CRP level. Therefore, in patients with stable ischemic heart disease, RF may be accompanied by improved lipid profile and glycemic parameters without an increase in coronary events. Papa-zoglou et al<sup>27</sup> investigated the impact of religious fasting of Muslims and orthodox Christians on the metabolic and hematological profile of individuals with or without dyslipidemia. Concerning the Muslims, the study included 15 young, non-dyslipidemic Muslim participants abstaining totally from food and liquid from dawn till sunset for 30 days. In Muslim participants, triglyceride, LDL, and total cholesterol levels were increased post-RF. The study adds to the existing literature evidence about the significant impact of RF on the metabolic and hematological profiles of orthodox and Muslim followers. The prevention of dehydration and dysregulation of lipid metabolism during Ramadan's needed. RF should concern both clinicians and dietician nutritionists. Dote-Montero et al<sup>28</sup> summarized the impact of different IF types on human cardiometabolic health, focusing on energy metabolism. First, they discussed the coordinated metabolic adaptations (energy expenditure, hormonal changes, and macronutrient oxidation) occurring during a 72-hour fast. They

then discuss studies investigating the effects of IF on cardiometabolic health, energy expenditure, and substrate oxidation. Finally, they discuss how IF may be optimized by combining it with exercise. Suppose regimens improve body composition, ectopic fat, and classic cardiometabolic risk factors compared to unrestricted eating, especially in metabolically unhealthy participants. However, it is still unclear whether IF provides additional cardiometabolic benefits compared to continuous daily caloric restriction (CR). Most studies found no additional benefits; yet, some preliminary data suggest that IF regimens may provide cardiometabolic benefits without weight loss. Finally, although IF and continuous daily CR appear to induce similar changes in energy expenditure, IF regimens may differentially affect substrate oxidation, increasing protein and fat oxidation. Mengi Çelik et al<sup>29</sup> evaluated the effect of RF on cardiometabolic risk factors (blood glucose, lipid profile, inflammatory cytokines) and sleep quality in healthy Turkish adults. This prospective observational study was conducted with 32 individuals (12 males, 20 females) aged between 19 and 32 years and fasted for 25 or more continuous days in Ankara, Turkey, during Ramadan 1442. Individuals applied fasting for 16 hours in the spring season. Blood samples were taken after at least 8 hours of fasting, anthropometric measurements were taken, and sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) at the beginning and the end of Ramadan. There was a significant decrease in BMI, CRP, and TNF- $\alpha$  levels during RF. There were no changes in lipid profiles and sleep quality. There was a significant increase in FBG levels; however, this change is within normal limits. There was also a significant relationship between BMI and CRP, IL-6, and TNF- $\alpha$  levels.

Four recommendations for patients with CVD during RF were published in 2022. Akhtar et al<sup>30</sup> reviewed the literature to help healthcare professionals educate, discuss, and manage patients with cardiovascular conditions who are considering fasting. Studies on the safety of RF in patients with cardiac disease are sparse, observational, of small sample size, and have a short follow-up. Using expert consensus and a recognized framework, they risk-stratified patients into “low or moderate risk,” for example, stable angina or nonsevere HF; “high risk,” for instance, poorly controlled arrhythmias or recent myocardial infarction; and “very high risk,” for example, advanced HF. 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 fasting shorter days, for example, during winter. Before Ramadan, all fasting patients should be educated 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. The Tunisian Society of Cardiology and Cardiovascular Surgery in consultation with the National Instance of Evaluation and Accreditation in Health has established a consensus after analyzing the literature.<sup>31</sup> They addressed the following questions: (1) What is the impact of fasting on patients with CV patholo-

gies? (2) How to stratify the risk of fasting according to CV pathology and comorbidities? (3) How to plan to fast for patients with CV diseases? (4) What hygienic and dietary measures should be recommended during fasting in patients with CV pathologies? (5) How to manage medication during Ramadan in patients with CV diseases? Naz et al<sup>32</sup> also published CVD patient recommendations. Databases were screened to find relevant studies for an evidence-based consensus regarding the risk stratification and management of CVD. Using practical guidelines of the European Society of Cardiology (ESC), they categorized patients into low-, moderate-, and high-risk categories. They proposed a pre-Ramadan checklist for the assessment of cardiac patients before fasting. Regular moderate-intensity exercise is recommended for most cardiac patients, which has been demonstrated to provide an anti-inflammatory and antioxidant effect that improves immune function. Therefore, in Ramadan, many physiological changes occur during fasting, which brings about a balanced metabolic homeostasis of the body. In addition, RF is a nonpharmacologic means of decreasing CV risk factors. Islam exempts Muslims from fasting if they are unwell; therefore, patients with the acute coronary syndrome (ACS), advanced heart failure (HF), recent percutaneous coronary intervention (PCI), or cardiac surgery should avoid fasting. Hammami et al<sup>33</sup> also reviewed the literature on the safety of fasting in cardiac patients. They examined the changes in BP among hypertensive patients and the incidence of cardiac events during Ramadan in patients with coronary disease and HF. They also assess the modifications of INR levels in cardiac patients who take an oral anticoagulant. They found that RF is safe in stable cardiac patients, even under several drugs. Fasting does not affect BP. There is no difference in cardiac event incidence between Ramadan and the nonfasting months. The level of INR is slightly higher when fasting, and it is thus recommended to monitor patients with high bleeding risk during Ramadan.

### Kidneys

Four studies examined the impact of RF on renal function.<sup>34–37</sup> The first study assessed the relationship between fasting and the risk of acute kidney injury (AKI) to identify patients at high risk in a single-center, retrospective, propensity-score-matched cohort design.<sup>34</sup> Data were collected from adult patients admitted to the emergency room during Ramadan and the following month over two consecutive years (2016 and 2017). A total of 1,199 patients were included; each cohort had 499 patients after matching. In the fasting cohort, the incidence of AKI and the risk of developing AKI were significantly lower (adjusted odds ratio [AOR]: 0.65). The most indicative risk factors for AKI were hypertension (AOR: 2.17), history of AKI (AOR: 5.05), and liver cirrhosis (AOR: 3.01). Secondly, the impact of RF on renal function in 28 adult CKD patients (mean age: 46 years) was examined in a prospective observational study.<sup>35</sup> All 28 patients managed to fast for the whole month, and none displayed any new clinical symptoms or signs. Renal function worsened in four (14.3%), which was significant in those with

CKD stages 4 and 5. Thirdly, the tolerability of RF among 199 prevalent hemodialysis patients (97 males, mean age 45) was evaluated.<sup>36</sup> Patients were divided based on their fasting state into three groups: complete fasting (14%), partial fasting (44%), and nonfasting (42%). Out of 116 fasting patients, only 4 (3.4%) developed complications during dialysis. On the other hand, three patients experienced an improvement in intradialytic hypotension; one also reported an improvement in dyspepsia. Unlike the NFG, they noted a significant reduction in dry weight in the complete and partial fasting groups. Finally, the effects of increased fluid intake during the night on serum creatinine and urea levels were examined in a randomized controlled trial.<sup>37</sup> The participating healthy subjects were randomly divided into two groups of 29 each. The hydrated group drank 2 to 3 L of fluid from sunset to dawn the next day. Kidney function was measured before, during, and after Ramadan. After adjustment for sociodemographic variables, the CG exhibited higher mean serum concentrations of creatinine and urea and lowered estimated glomerular filtration rate (eGFR) than the hydrated group. The RG exhibited the highest mean serum creatinine and urea levels and the lowest eGFR compared to pre- and post-Ramadan periods. All results were statistically significant. RF was not associated with a permanent increase in serum creatinine or urea. For those groups with a high fluid intake, serum creatinine and urea were significantly lower than the controls suggesting a favorable hydration effect during the nonfasting hours.

### Pregnancy

Pregnancy is one of the conditions that have an explicit exemption from fasting. Despite this, many women opt to fast despite having underlying medical conditions during pregnancy. In 2022, three studies examined various aspects of pregnancy.<sup>38-40</sup>

Firstly, whether in utero exposure to the RF period is negatively associated with child nutrition was empirically analyzed. The data for the analyses come from a retrospective assessment of 759,799 children from 103 Demographic and Health Surveys (DHS) across 56 countries during 2003–2020.<sup>38</sup> Considering the month-long Ramadan exposure as a natural experiment, they implemented an intent-to-treat framework, comparing stunting and underweight among children aged 0 to 5 years who were exposed to RF at any time in utero with those who were not exposed. Their findings do not show significant evidence to conclude that in utero exposure to the RF period is negatively associated with child nutrition. On the contrary, except for stunting in Muslim children who had in utero exposure to RF during the first months of pregnancy, they found no significant association between in utero exposure to RF and child stunting and underweight. Their main results are robust to multiple robustness checks. Secondly, a detailed discussion considered the religious rulings on lactation assessment for Muslim breastfeeding women who fast during Ramadan.<sup>39</sup> The authors highlighted that breastfeeding and performing RF are significant religious acts of worship for Muslim women globally. The content and suggestions within this article

should be taken in the general context of millions of mothers and babies who have engaged in RF without known adverse influences or clinical concerns for 1,400 years. While legal dispensations have long since existed within Islamic legal literature, the absence of a framework of harm–benefit analysis to be performed by an individual, a lack of lactation knowledge, cultural expectations, and social norms have overshadowed individual agencies adopting informed decision-making. Finally, the opinions and experiences of Muslim pregnant women about RF in Turkey were documented.<sup>40</sup> This descriptive and phenomenological study included 17 Muslim pregnant women living in Turkey. Content analysis and word cloud analysis were performed. The content analysis revealed two themes. The most frequent words in the word cloud analysis were fasting, pregnancy, Ramadan, fast, religious duty, health, observing a missed fast, relief, concern, baby, thirsty, and hungry. The study showed that religious beliefs, experiences, family, and society pressured pregnant women to keep Ramadan fasts. However, some women did not go on fast due to feeling worried about their physical and psychological health and their infants.

### Surgery

Three studies involving general surgical conditions during Ramadan included stoma care, superior mesenteric artery (SMA) syndrome, and sigmoid volvulus (SV).<sup>41-43</sup> The health-related quality-of-life outcomes and ostomy-related obstacles among patients with an ostomy in Saudi Arabia was examined in a mixed-methods study by collecting quantitative data ( $n = 421$ ) and semistructured interview for collecting qualitative data ( $n = 12$ ).<sup>41</sup> Patients with intestinal stomas demonstrated multiple health-related quality-of-life challenges, including interfering with religious practice, mainly RF and Hajj. Another study examined the clinical records of 416 consecutive cases of SV patients reviewed prospectively from January 1986 to July 2020.<sup>42</sup> The records of 100 consecutive patients with non-volvulus intestinal obstruction were reviewed prospectively in the past 24 months as controls. Premorbid symptoms were evaluated, including acute diarrhea, sudden and excessive body motions, overeating after prolonged starvation, coughing spell, and labor. Among the premorbid symptoms, the 1- to 5-day interval of diarrhea (42 patients), harvesting activation (35 patients), and overeating after RF (31 patients) were found to be significant precipitating factors in SV.<sup>42</sup> A case of a rare SMA syndrome was found in a young man with no medical or psychiatric history during RF. The possible relationship with fasting was discussed.<sup>43</sup>

The American Society for Metabolic and Bariatric Surgery (ASMBS) issued a review document for metabolic and bariatric surgery (MBS) in response to numerous inquiries made to ASMBS regarding the safety and recommendations for fasting for religious purposes after undergoing MBS.<sup>44</sup> The article presents a summary of published, peer-reviewed scientific evidence spanning the years from 2000 to 2020 and a recently published 2021 Delphi consensus and expert opinion. The intent was to provide available objective information about this topic. The majority of the reviewed

literature covers the effects of religious fasting on adults who have not undergone MBS. Guidance was given for religious fasting for spiritual, health, and safety benefits after bariatric surgery but not for using fasting as a weight loss strategy in the adult population. In addition, because of the absence of research on adolescents and children undergoing MBS and fasting, this review focused on summarizing literature regarding adults and making recommendations for adults who underwent MBS and desire to fast. More research on the effects of religious fasting on MBS is needed.

### Sports Medicine

As usual, several studies considered the impact of RF on athletes' well-being and performance when playing during Ramadan.<sup>45-52</sup> Firstly, the efficacy of combining two fasting strategies in men with obesity was assessed<sup>45</sup>: RF strategy versus RF plus concurrent training (RF-CT) program strategy. They explored the possible impact on metabolic and inflammatory biomarkers. Twenty men with obesity, aged 31.8 years, BMI of 33.1 kg/m<sup>2</sup>, performing regular RF, were randomized into two groups: RF-CT ( $n = 10$ ) and RF without training (RF-NCT) ( $n = 10$ ). The RF-CT group participated in high-intensity interval training (HIIT) program combined with resistance exercises for 4 weeks. Body composition, blood glucose, lipid profile, liver biomarkers, and inflammation were assessed before and after the 4-week RF. Both groups showed a significant decrease in weight, fat mass (FM), fat percentage (fat %), and waist circumference and an improvement in blood glucose, lipid profile, and inflammation. Fat-free mass decreased significantly in RF-NCT ( $p < 0.05$ ) while remaining unchanged in RF-CT. However, RF-CT induced greater body composition improvements and decreased lipid biomarkers compared to the RF-NCT group pre-post intervention. The authors concluded that a combination of RF and CT induces greater changes in body composition, lipid profile, inflammation, and liver biomarkers compared to the RF strategy alone. Secondly, the impact of a 30-minute nap (N30) on the Running-Based Anaerobic Sprint Test (RAST) was assessed during and after Ramadan.<sup>46</sup> Ten physically active kick boxers (age: 21.2 years and BMI: 24.0 kg/m<sup>2</sup>) voluntarily performed the RAST test after an N30 and in a no-nap condition (NN) during two experimental periods: the last 10 days of Ramadan and ~3 weeks after Ramadan. During each during Ramadan-NN, during Ramadan-N30, after Ramadan-NN, and after Ramadan-N30 protocol, kick boxers performed RAST performance. A statistically significant difference between Ramadan periods regarding maximum power, minimum power, average power, and fatigue index were found. In addition, the nap factor was statistically significant regarding the maximum power, minimum power, average power, and fatigue index. Taking a daytime nap benefits subsequent performance in RAST. The benefits of napping were greater after an N30 opportunity for during Ramadan and after Ramadan. Thirdly, the effects of home confinement on objective physical activity and physiological and sleep parameters were examined in active individuals.<sup>47</sup> Sixteen male elite fitness coaches (age: 29 years; BMI: 24.7 kg/m<sup>2</sup>) were included in this retrospec-

tive study. One-way analysis of variance was conducted to analyze selected physical activity, physiological, and sleep parameters collected by a smart watch data during four consecutive months (i.e., pre-confinement, first and second months of confinement, and post-confinement, in 2020). RF occurred during the second month of confinement. Compared to pre-confinement, significant changes were registered for almost all parameters during the first and/or the second month of confinements, with (1) higher values for resting heart rate, sleep latency, and total, light, and rapid eye movements sleep times and (2) lower values for physical activity parameters, calories/day spent average and highest respiratory rates, and deep sleep time during the home confinement period (change = 5–36%). During the post-confinement month, all parameters regained pre-confinement values. In conclusion, home confinement-induced detraining negatively influenced the objective measurements of cardio-respiratory and sleep parameters among fitness coaches, with a more substantial effect during the second month of home confinement, possibly due to the effect of RF.

Furthermore, the effect of a walking football (WF) program during RF on heart rate variability (HRV) indices, body composition, and physical fitness was evaluated in middle-aged males.<sup>48</sup> Thirty-one healthy sedentary men were randomized to WF ( $n = 18$ ) and control ( $n = 13$ ) groups. Both groups participated in RF. The WF group was involved in a training program (small-sided games) of three weekly sessions during RF. The time and frequency domains of HRV, body composition, handgrip, lumbar strength, modified agility test (MAT), and 6MWT were measured before Ramadan, during Ramadan, and after Ramadan. They reported that RF has significantly altered some parameters of HRV during Ramadan; the mean HR decreased while the mean RR, LF, and HF increased. WF significantly affected HRV, and mean HR during Ramadan compared with before Ramadan and after Ramadan decreased, while mean RR, HF, and LF increased. During Ramadan, body mass decreased in both groups, while BMI decreased and lean mass increased only in the WF group. Lower body mass and BMI levels were reported after Ramadan only in the WF group. Physical capacity improved after Ramadan, compared with before Ramadan, only in the WF group with longer distance in 6MWT, shorter time(s) in MAT, and higher lumbar strength levels. They conclude that RF increases parasympathetic system activity. WF practice during RF is safe and might improve body composition, physical fitness, autonomic cardiac function, and physical fitness in middle-aged males. Also, the influence of a dietary plan during RF on performance and body composition in a professional soccer player was analyzed.<sup>49</sup> A 20-year-old elite player followed a dietary-nutritional plan with an isocaloric diet and was supplemented with glycerol. The athlete's strength and power in the lower limbs were assessed by performing a countermovement jump (CMJ) and Abalakov vertical jump (ABK) before and after Ramadan. After nutritional planning, the patient's body composition improved in fat loss and muscle mass gain. In addition, this translated into improvements in performance tests, both in the CMJ and ABK. In conclusion, personalized nutritional planning and an



appropriate supplementation and rest protocol can improve soccer players' body composition and performance during fasting.

The effect of RF on sleep duration, sleep quality, daily nap duration, and daytime sleepiness in athletes and physically active individuals was reviewed.<sup>50</sup> Studies that included assessments of sleep quantity and/or quality, and/or daytime sleepiness, and/or daily naps in athletes and physically active individuals were included. Individuals who continued to train during Ramadan experienced a decrease in sleep duration. Additionally, the global score of the PSQI increased from pre-Ramadan to during Ramadan, indicating a decrease in sleep quality. The duration of daytime naps increased compared to pre-Ramadan, whereas Epworth Sleepiness Scale scores remained unchanged versus pre-Ramadan. In conclusion, individuals who continued to train during Ramadan experienced a decrease in sleep duration, impairment of sleep quality, and an increase in daytime nap duration, with no change in daytime sleepiness levels. The effects of RF on physical factors in football players secondarily considered the impact this might have on domestic club football leagues. Also, a systematic review of 22 studies included some iteration of before Ramadan, during Ramadan, and after Ramadan.<sup>51</sup> Common measures observed included RPE, 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 the late afternoon/evening testing (before breaking the fast) and with high-intensity exercise. There appears to be a performance deficit related to RF in Muslim football players. Studies should explore the effects of RF on actual match demands. Due to the month of Ramadan emerging into league calendars, considerations should be made to accommodate Muslim football players who are intermittently fasting. Finally, the effect of Ramadan observance on dietary intake and body composition was examined in adult athletes by a systematic review and meta-analysis.<sup>52</sup> Of the 17 selected studies evaluating body composition, 7 were of strong quality, and the remaining 10 were rated as moderate. Carbohydrate and total water intake decreased with the observance of Ramadan, but fat and protein intake were unchanged. Continued training of athletes during Ramadan was associated with a decreased body mass and body fat percentage, but not lean body mass, toward the end of the fasting month. RF decreases athletes' body mass and body fat percentage but not lean body mass. Longer durations of fasting could provoke more pronounced decrements in body mass. Carbohydrate and total water intake decreased during Ramadan in athletes.

### Gut and Liver

Chen et al<sup>53</sup> used liquid chromatography-mass spectrometry-based metabolomics to investigate the composition of fecal metabolites in Chinese and Pakistani individuals before and after RF. Principal component analysis showed a distinct separation of metabolite profiles among ethnic groups and between pre- and post-fasting samples. After RF, the Chinese and Pakistani groups showed significant differences in their

respective contents of various fecal metabolites. In particular, L-histidine, lycofawcine, and cordycepin concentrations were higher after RF in the Chinese group, while brucine was enriched in the Pakistani group. The Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis suggested that metabolites related to purine metabolism, 2-oxo carboxylic acid metabolism, and lysine degradation were significantly enriched in the total subject population pre-fasting versus post-fasting comparisons. Several bacterial taxa were significantly correlated with specific metabolites unique to each ethnic group, suggesting that associated shifts may influence changes in fecal metabolite profiles related to RF in gut microbiota. The fasting-related differences in fecal metabolite profile and these group-specific correlations between taxa and metabolites support their previous findings that ethnic differences in dietary composition also drive variation in gut microbial composition and diversity. This landscape view of interconnected dietary behaviors, microbiota, and metabolites contributes to the future development of personalized, diet-based therapeutic strategies for gut-related disorders. Mousavi et al<sup>54</sup> summarized the current evidence for the effects of RF and non-Ramadan IF on the gut microbiome. Animal and human studies were screened and reviewed separately by two researchers. Twenty-eight studies were selected after screening. Some of the studies were performed on animal models and some on humans. The results of these studies indicate a significant shift in the gut microbiota, especially an increase in the abundance of *Lactobacillus* and *Bifidobacteria* following fasting diets. Some studies also showed increased bacterial diversity, decreased inflammation, and increased production of metabolites such as short-chain fatty acids in individuals or samples under fasting diets. Moreover, RF, as a kind of IF, improves health parameters through positive effects on some bacterial strains such as *Akkermansia muciniphila* and *Bacteroides*. However, some studies have reported adverse effects of fasting diets on the structure of the microbiome. In general, most studies have seen favorable results following adherence to the fasting diets on the intestinal microbiome. The effects on clinical disease activity, quality of life, and levels of depression were assessed.<sup>55</sup> Patients diagnosed with ulcerative colitis (UC) or Crohn's disease (CD) intending to observe RF were recruited. The following were assessed immediately before and at the end of Ramadan: serum CRP and stool calprotectin, partial Mayo score, Harvey-Bradshaw index (HBI), Simple IBD questionnaire (SIBDQ), and Hamilton depression scale questionnaire. Eighty patients with IBD were recruited (60 UC, 20 CD). Serum CRP and stool calprotectin did not significantly change before versus after fasting. The partial Mayo score significantly rose after fasting. The Harvey-Bradshaw index did not significantly change after fasting. Multiple linear regression revealed that older age and a higher baseline calprotectin were associated with a higher change in Mayo score after fasting. No significant change was detected in SIBDQ or Hamilton depression scale scores. In patients diagnosed with UC, IF during Ramadan was associated with worsening clinical parameters. The effect was pronounced in older patients and those with higher baseline calprotectin

levels. However, IF during Ramadan was not associated with an adverse effect on objective inflammatory markers (CRP and calprotectin). Besbes et al<sup>56</sup> evaluated the impacts of RF on the salivary flow rate (SFR) and metabolic parameters. A thorough literature search was carried out. Six articles met the inclusion criteria. All studies were heterogeneous and had a high bias score and several methodological differences. The following parameters were collected: SFR, melatonin, cortisol, glucose, IgA, uric acid, alkaline phosphatase (ALP), and aspartate aminotransferase (AST). The SFR decreased by 10% during Ramadan in fasting subjects. The circadian pattern of melatonin remained unchanged during Ramadan, but melatonin levels dropped significantly from baseline. The salivary cortisol levels were unchanged or increased during Ramadan. The salivary glucose levels were decreased. ALP increased significantly, while uric acid and AST decreased significantly. Salivary IgA decreased during the last week of Ramadan. To conclude, there is a trend toward a decrease in SFR and the content of most of the biomarkers investigated, except for ALP and uric acid. These changes cannot be easily attributed to any single factor (hydration status, dietary habits, physical activity, or hygiene habits). Badran et al<sup>57</sup> assessed the short-term effects of RF as a sort of IF on NAFLD patients' biochemical, radiological, and anthropometric parameters. Ninety-eight NAFLD patients were recruited and voluntarily subjected to 16 hours of daily fasting for an average of 22 to 29 days without particular dietary recommendations. Anthropometric, laboratory, and radiological parameters were measured before, at 30 days, and 1 month after fasting (fasting and nonfasting phases). Patients were primarily rural residents (76%), hypertensive (34.7%), diabetic (43.9%), and female (76.8%), with overt criteria of MetS (67.3%). Liver transaminases were ameliorated significantly after fasting, which continued the following month, especially in those with elevated ALT before fasting (46%). Eleven patients (24.4%) experienced ALT normalization after 1 month of fasting, further increasing to 33.3% 1 month later. Lipid profiles (cholesterol, triglycerides, HDL, LDL, cholesterol/HDL risk ratio) were significantly corrected following IF and continuing in the next phase. BMI lessened following the fasting, while no remarkable changes were noted regarding waist, hip, and triceps skin fold thickness. Glycemic indices (HbA1c, postprandial, HOMA-IR) and fibrosis markers (FIB-4 and APRI) were significantly ameliorated, while the reduction in inflammatory markers was not long-lasting. IF led to momentous improvements in NAFLD's ultrasonographic, biochemical, and anthropometric parameters, especially in early phases and prediabetics.

### Nervous System

There were three studies of note in 2022 evaluating the effects of RF on various neurological conditions. The first study investigated the effect of RF on cognitive performance, sleep quality, daytime sleepiness, and insomnia of physically active and sedentary elderly individuals.<sup>58</sup> The study involved 58 participants, with an average age of 62.9 years, who were assigned to one of two groups: a sedentary group (CG) who observed Ramadan ( $n = 32$ ) and a physically active

group ( $n = 26$ ) who continued to train while observing Ramadan. The participants completed digital assessments of their cognitive performance and responded to questionnaires assessing sleep parameters 2 weeks before and during the fourth week of Ramadan. The physically active group showed a significant increase in executive function, attention, inhibition, associative memory, and recognition memory during Ramadan compared to before Ramadan. In contrast, the sedentary group's associative learning performance decreased, while their performances in other domains remained unchanged during Ramadan. Both groups experienced poor sleep quality and excessive daytime sleepiness, with the adverse effects of RF exposure being significantly higher in the sedentary group. The study suggests that elderly individuals who continue to train at least three times per week during Ramadan may improve their cognitive performance, despite the impairment of sleep quality.

The second study aimed to compare the clinical characteristics and outcomes of patients who experienced an ischemic stroke during Ramadan and non-Ramadan months in a tertiary academic center in an Islamic country.<sup>59</sup> A total of 1,058 patients were retrospectively reviewed, with 960 patients in the NRG and 98 patients in the RG over a period of 4 consecutive years (February 2016 to June 2019). The mean age of patients during Ramadan was 59 years, and most non-Ramadan ischemic stroke patients were male. Both groups showed no significant difference in vascular risk factors and medical history. However, patients during Ramadan had higher median National Institute Stroke Scale (NIHSS) scores at discharge, and more ICU admissions were noted among them. Gender-specific analysis for Ramadan patients revealed a statistically significant difference in smoking and urinary tract infections. The study found no significant difference between patients with ischemic stroke during Ramadan and non-Ramadan months, except for higher NIHSS scores at discharge and more ICU admissions during Ramadan. The authors recommend future studies with larger sample sizes, longer duration, and inclusion of all types of strokes.

The third study investigated the impact of RF on the frequency of various types of seizures. The ketogenic diet is based on the practice of fasting, and IF is gaining recognition as a potential treatment for epilepsy.<sup>60</sup> This was a prospective observational study on Muslim patients with active epilepsy intended to observe RF in 2019. The patients fasted for an average of 16 hours per day. They were monitored for seizure frequency for 3 months: 1 month before Ramadan, during Ramadan, and 1 month after Ramadan, while ensuring compliance with prescribed medication. Three hundred and twenty-one Muslim patients with active epilepsy with a median age of 33 years were included (some patients had more than one type of seizure). During Ramadan,  $\geq 50\%$  reduction in seizure frequency was observed in 86 out of 224 patients with focal seizures, 17 out of 38 patients with myoclonic seizures, and 6 out of 10 patients with absence seizures. In Shawwal, such improvement continued to include 83, 13, and 4 patients with focal, myoclonic, and absence seizures, respectively. Compared to Shaaban,

focal and myoclonic seizures were significantly reduced in Ramadan and Shawwal. However, only Ramadan significantly improved absence seizures compared to the pre-Ramadan period. There was no significant difference in the frequency of generalized tonic-clonic seizures between the 3 months. These results suggest that RF may benefit patients with active focal, myoclonic, and absence seizures during and after fasting.

Additionally, a systematic review also evaluated the effect of sex on epilepsy and headache frequency during RF.<sup>8</sup> Six studies on headaches looked at the sex difference. Most of these studies reported that in the baseline condition, the headache was more frequent in women and that RF was a triggering factor for headaches. Out of the four studies that assessed the impact of RF on epilepsy, two studies yielded no significant difference. In contrast, one study demonstrated a rise in epilepsy frequency and another indicated a decrease. However, no sex differences were reported in any of the studies.

### Mental Health

Two studies focused on mental health and quality-of-life changes during Ramadan. The number of hospitalizations in psychiatry during Ramadan was studied in a cross-sectional and retrospective study in Tunis over five lunar years.<sup>61</sup> A significant 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 hospitalizations over the years, mainly enforced hospitalizations. However, Ramadan stands out not on a spiritual and social level. Whether, during RF, reminders of food can impair the fasters' reaction time and accuracy on a non-food-related test of cognitive control was investigated.<sup>62</sup> Using a repeated measures design in a sample of fasters ( $N = 190$ ), they found that when food is made salient, fasters are slower and less accurate during Ramadan than after Ramadan. Control participants perform similarly across time. Furthermore, during Ramadan, performances vary by how recently people had their last meal. Potential mechanisms are suggested, grounded in research on resource scarcity, commitment, and thought suppression, as well as the psychology of rituals and self-regulation, and implications for people who fast for religious or health reasons are discussed.

### Infections and Inflammations:

Antibiotic prescribing patterns before, during, and after Ramadan in a primary care setting within the Pakistani and Bangladeshi populations in the United Kingdom, most of who were Muslims, were compared to those who do not observe Ramadan.<sup>63</sup> Retrospective controlled interrupted time series analysis of electronic health record data from primary care practices was performed. The study consists of two groups: Pakistanis/Bangladeshis and white populations. For each group, they constructed a series of aggregated, daily prescription data from 2007 to 2017 for the 30 days preceding, during, and after Ramadan, respectively. Controlling for the

rate in the white population, there was no evidence of increased antibiotic prescription in the Pakistani/Bangladeshi population during Ramadan, compared to before Ramadan (IRR: 0.994) or after Ramadan (IRR: 1.006). Slimani et al<sup>64</sup> explored the effect of COVID-19 and Ramadan on physical activity and burnout in teachers and the relationship between them in 57 secondary school teachers from public education centers. They were aged between 29 and 52 years. The International Physical Activity Questionnaire—BREF and the Maslach Burnout Inventory—Human Services Survey were used to assess physical activity intensities and burnout, respectively. The data revealed that total physical activity, vigorous metabolic equivalent of task (MET), and moderate MET were higher before COVID-19 and Ramadan than during Ramadan.

Regarding burnout subscales, emotional exhaustion was higher before Ramadan than before COVID-19 and during Ramadan. A lower personal accomplishment was reported before Ramadan than before COVID-19 and during Ramadan. In addition, low to high correlations were observed between physical activity intensities and burnout subscales, except for the correlation between depersonalization and all physical activity intensities. Also, a cross-sectional study investigated the influence of the COVID-19 lockdown during RF on weight change in 481 participants in Saudi Arabia.<sup>65</sup> Around 42% of the participants had gained weight, and around 38% had lost weight. Physical activity level was shown to be considered as a protective factor against weight gain (OR = 1.03), while increasing the number of meals and not adopting healthy cooking methods can both be considered as contributing factors to weight gain (OR = 1.03 and 1.03). The effects of RF on high-sensitivity CRP (hs-CRP) levels and total antioxidant status (TAOS) in HIV patients on antiretroviral therapy (ART) were examined in a prospective cohort study.<sup>66</sup> HIV-infected patients on stable ART who fasted throughout Ramadan were compared to those who did not. They included men aged 20 to 40 years, taking first-line ART for at least 6 months, Muslims intent to fast for Ramadan, no current hospitalization because of acute conditions, and not being treated for opportunistic infections. After 2 weeks, hs-CRP had decreased significantly in the FG compared to the NFG. The linear regression analysis has shown that RF contributed to 10.1% of the variance in hs-CRP value and decreased its value. TAOS changes did not significantly differ between the FG and NFG. In the FG, there were significant changes in polyunsaturated fatty acid consumption, body weight, cigarette smoking, and sleeping duration. RF reduces hs-CRP concentrations among HIV patients on ART.

Athletes' training practices (i.e., training load and training times) were assessed using predefined survey criteria/questions during the "first" COVID-19 lockdown, and compared RFL to lockdown-alone (LD) in Muslim athletes.<sup>67</sup> Specifically, a within-subject, survey-based study saw athletes' ( $n = 5,529$ ; from 110 countries/territories) training practices (comparing RFL to LD) explored by comparative variables of sex, age, continent, athlete classification (e.g., world-class), sport classification (e.g., endurance), athlete

status (e.g., professional), and level of training knowledge and beliefs/attitudes (ranked as good/moderate/poor). During RFL (compared to LD), athlete's perceptions (ranges presented given a variety of comparative variables) of their training load decreased (46–62%), were maintained (31–48%), or increased (2–13%). Decreases ( $\geq 5\%$ ,  $p < 0.05$ ) affected more athletes aged 30 to 39 years than those 18 to 29 years (60 vs. 55%); more national than international athletes (59 vs. 51%); more team sports than precision sports (59 vs. 46%); more North American than European athletes (62 vs. 53%); more semiprofessional than professional athletes (60 vs. 54%); more athletes who rated their beliefs/attitudes “good” compared to “poor” and “moderate” (61 vs. 54 and 53%, respectively); and more athletes with “moderate” than “poor” knowledge (58 vs. 53%). During RFL, athletes had different strategies for training times, with 13 to 29% training twice a day (i.e., afternoon and night), 12 to 26% at night only, and 18 to 36% in the afternoon only, with ranges depending on the comparative variables. Training loads and activities were altered negatively during RFL compared to LD. It would be prudent for decision-makers responsible for RFL athletes to develop programs to support athletes during such challenges. The combined effects of Ramadan observance and COVID-related lockdown in Muslim athletes were evaluated.<sup>68</sup> From an international sample of athletes, 1,681 Muslim athletes from 44 countries (aged 25.1 years, 38% females, 41% elite, 51% team sport athletes) answered a retrospective, cross-sectional questionnaire relating to their behavioral habits pre- and during COVID-19 lockdown, including (1) Pittsburgh, sleep quality index (PSQI); (2) insomnia severity index (ISI); (3) bespoke questions about training, napping, and eating behaviors; and (4) questions related to training and sleep behaviors during lockdown and Ramadan compared to lockdown outside of Ramadan. The survey was disseminated predominately through social media (July to September 2020). The lockdown reduced sleep quality and increased insomnia severity. Compared to non-Muslim ( $n = 2,230$ ), Muslim athletes reported higher PSQI and ISI scores during lockdown but not pre-lockdown. Muslim athletes reported longer and later daytime naps and an increase in late-night meals during lockdown compared to pre-lockdown, associated with lower sleep quality. Both sleep quality and training volume were lower during the lockdown and Ramadan compared to the lockdown outside of Ramadan in Muslim athletes. Muslim athletes reported lower sleep quality and higher insomnia severity during lockdown compared to pre-lockdown, exacerbated by Ramadan observance. Therefore, further attention to Muslim athletes is warranted when a circadian disrupter (e.g., lockdown) occurs during Ramadan. Whether COVID-19 restrictions and RF during the fourth wave of the COVID-19 pandemic were associated with poor physical activity, anxiety, well-being, and sleep-quality outcomes were tested.<sup>69</sup> A total of 510 individuals participated in an online questionnaire disseminated to adults ( $\geq 18$  years) residing in Iran 3 days after the end of Ramadan 2021. Physical activity behavior, anxiety, well-being, and sleep quality were used. Of 510 individuals included in the study (mean age: 31

years), 172 reported less physical activity during Ramadan 2021. Physical activity was associated with better well-being and sleep-quality outcomes. Also participants who fasted for all of Ramadan had less anxiety and better well-being outcomes than those who fasted a part of Ramadan or did not fast at all. However, the fasting part of Ramadan decreased the sleep quality of active participants. Ramadan 2021 was associated with poor physical activity, well-being, and sleep quality. However, physical activity was associated with better well-being and sleep-quality, and those who fasted all the month had better anxiety and well-being outcomes.

### Miscellaneous Conditions

Single articles that were reported addressed miscellaneous subjects or medical conditions.<sup>70–76</sup>

#### Eyes

Shokoohi-Rad et al<sup>70</sup> assessed the effect of RF on intraocular pressure (IOP), retinal parameters, and retinal thickness using optical coherence tomography angiography performed on a spectral domain device. All the participants ate a pre-dawn meal and drink and then fasted for at least 15 hours. They assessed 61 eyes from 31 healthy volunteers with a mean age of 32.87. A significant decrease was found in the median IOP after fasting compared to the pre-fasting value. Retinal peripapillary capillary (RPC) whole image, RPC inside the disc, and RPC mean values showed significant decreases after fasting. RPC whole vessel density (VD), RPC inside VD, and RPC VD mean values also showed significant decreases after fasting.

#### Psoriasis

Almutairi and Shaaban<sup>71</sup> investigated the impact of RF on adults with stable chronic plaque psoriasis ( $N = 121$ ). The mean PASI score was 4.36 at the beginning of the study, which was reduced to 3.51 at the end. The difference was statistically significant. There was no difference in the change of weight. Only mild adverse events were noted during the study period. Ramadan IF has beneficial effects on the severity of the disease in psoriasis patients, with a reduction in PASI score and no serious health hazards.

#### Use of Warfarin

Rabea et al<sup>72</sup> conducted a systematic review and meta-analysis to resolve the controversy of RF impact on patients taking warfarin. All relevant studies measuring the international normalized ratio (INR), time in therapeutic range (TTR), or the number of patients within the therapeutic range before, during, and after Ramadan were assessed by full-text screening for achieving all of the inclusion criteria. Five studies with 446 patients were included in the meta-analysis, with patients as their control. The pooled analyses showed no significant difference during Ramadan compared to pre-Ramadan. There was only a significant increase in the risk ratio of supratherapeutic INR when comparing post-Ramadan to pre-Ramadan. However, there was no significant risk for supratherapeutic INR during Ramadan compared to pre-Ramadan or post-Ramadan; the number of patients

within the therapeutic range of INR during Ramadan compared to pre-Ramadan; and TTR during Ramadan, pre-Ramadan, and post-Ramadan.

### Bronchial Asthma

Ghaffary et al<sup>73</sup> investigated the effect of fasting during Ramadan on the severity of the disease and spirometric parameters in patients with asthma in 120 patients with moderate to severe asthma. Patients were categorized into fasting (60) and nonfasting (60) groups. Patients underwent spirometry before and after Ramadan; asthma control status was also assessed. Spirometric measurements, including forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), peak expiratory flow, and FEV1/FVC, were not significantly different before and after Ramadan in both groups of fasting and nonfasting patients. Furthermore, the two groups had no significant difference regarding these spirometric parameter changes from the baseline. Nevertheless, FEV1 change in the FG was significantly higher than in the NFG.

### Rheumatoid Arthritis

Ben Nessib et al<sup>74</sup> assessed the sustainability of fasting effects on rheumatoid arthritis (RA) activity in a prospective study that included 35 patients who observed RF in 2019. The disease activity was compared between three time points 6 months before (T1), T2 during Ramadan (T2), and about 3.4 months after fasting (T3). The disease activity score 28 (DAS28) was used to evaluate the disease activity. After a significant decrease in all disease activity parameters between T1 and T2, a gradual increase in clinical and biological outcomes was seen between T2 and T3. The other disease activity parameter changes were not statistically significant except for CRP, which was significantly higher at T3. By reference to baseline data, the decrease of ESR, DAS28 CRP, and DAS28 ESR induced after RF was maintained until T3, with statistically significant differences.

### Cancer

Lachgar et al<sup>75</sup> reported an observational study of fasting practices in patients receiving external radiation therapy during the month of Ramadan (2018) in a radiotherapy department (Casablanca). They included all patients who received external radiotherapy during this period. They included 209 patients, mostly with breast and gynecological cancers. All of these patients were observing RF before the diagnosis of cancer. However, only 39.2% were fasting during the treatment by radiotherapy, and just 40% of patients discussed the possibility of fasting with their oncologist. In multivariate analysis, the stage of the disease was the only factor related to the fasting status of their patients. Therefore, even under treatment, many of the patients fast during the month of Ramadan.

### High-Risk Patients

Baynouna AlKetbi et al<sup>76</sup> assessed factors influencing RF in patients with CKD in a prospective before and after cohort study. CKD patients were counseled regarding fasting and

were followed up post-Ramadan for renal function status, actual fasting behavior, and other relevant outcomes. Of the 360 patients who attended the pre-Ramadan consultation, 306 were reachable after Ramadan. Of these, 67.1% fasted, 4.9% had attempted to fast but stopped, and 28% did not. Of these, 74 have a post-fasting kidney test. Of the patients, 68.1% had stage 3A CKD, 21.7% had stage 3B, 7.9% had stage 4, and only 2% had stage 5. Of those who fasted, 11.1% had a eGFR drop of 20% or more. The 16.7% who did not fast presented a similar drop. Conversely, of the few who attempted to fast and had to stop, half had a drop in eGFR of more than 20%. Linear regression revealed that fasting was not associated with post-Ramadan eGFR levels when controlling for age and baseline eGFR. There were 17 (5.6%) significant events, including one death. More events occurred in the group who fasted some days; 26.7% of the subjects experienced an adverse event; and 4.7% of the NFG had a significant adverse event compared to 4.4% among those who fasted all of Ramadan.

### Patients' Perspectives and Advocacy

Several studies considered the perceptions and attitudes of patients with different medical conditions regarding RF.<sup>77–83</sup>

Work also involved relations with work, study, and sports for physically challenged people. Mahmood et al<sup>77</sup> described which patients might benefit from pre-Ramadan consultations and consultations content and provided suggestions for risk stratification and joint decision-making. Shared decision-making about fast, safe medication administration options, reducing dehydration risk, and what constitutes adequate nutrition is crucial. If deterioration, disease exacerbation, or delayed recovery occurs during fasting, patients should be advised to break their fast, take a break from fasting, and seek medical help. Pre-Ramadan consultations for patients with existing conditions are essential. They also emphasized that scholars can offer further advice or assurance to patients about religious exemption from fasting. To et al<sup>78</sup> explored the perceptions and experiences surrounding medication management practices during Ramadan by Australian Muslims in a qualitative exploration of the views and experiences of Muslim patients hospitalized during or shortly before Ramadan 2021. Comments were provided by 88 patients born in various countries and with various medical and surgical comorbidities. The themes identified included the interpretation of RF, altering medications to facilitate fasting, perceptions about healthcare professionals, and health knowledge. Many patients altered their medications to facilitate RF, and there was considerable variability in interpreting what breaks the fast. Patients' perceptions and previous experiences with healthcare professionals determined whether they sought advice about managing their medications during Ramadan or dismissed advice and/or self-managed their medications, sometimes inappropriately. This exploration of Australian Muslim patients found diverse views and experiences around medication practices during Ramadan—past relationships with healthcare professionals influenced this practice. As there are ramifications for physical, spiritual, and family well-being, it is imperative that

healthcare professionals partner with their Muslim patients to optimize their medication management and health outcomes for Ramadan. Shalihin and Sholihin<sup>79</sup> examined the relationship between mechanical solidarity and social cohesion mediated by generosity during Ramadan. Their finding showed mechanical solidarity and social cohesion is more significant when generously mediated. In practice, the dimensions of charity strengthen mechanical solidarity (i.e., collective consciousness and cooperative spirit) to influence social cohesion. Furthermore, generosity activities supported mechanical solidarity in strengthening the social cohesion among Muslims in Indonesia. The elaboration on the factors accelerating social cohesion is an important issue for social and religious studies. It is useful for transforming the dimensions of Islamic rituals into social impacts and determining harmony between religious communities in the future. Also, Sulaiman et al<sup>80</sup> assessed Nigerian Muslims' dietary modifications during Ramadan and their related body weight and health status changes through a web-based cross-sectional study of 770 participants. They found that fruits, palm dates, homemade foods, milk products, and vegetables were more frequently consumed. Fewer energy drinks, pastries, salty snacks, and carbonated or sugary drinks were consumed during Ramadan than before. Over half of the respondents lost weight during Ramadan, 37.0% maintained weight, and 8.4% gained weight during the month. Nearly all reported having good health during Ramadan, and a minority (2.7%) reported having a poorer health state during Ramadan. An interesting study by Nuryakin et al<sup>81</sup> examined the impact of fasting on students' learning outcomes in the Indonesian context in 2018 and 2019, and Ramadan coincided with the final exams at University. After controlling for semester-course-class fixed effects, student, class, and course characteristics, they found no evidence of Ramadan's negative effects on students' test scores. Consistently, they also find no evidence of morning-afternoon differential effects. They argued that the absence of (or weak) Ramadan's effects is likely because Muslim students had adapted to the fasting environment earlier in the Ramadan period, allowing them to improve their scores as the exam period progressed. The regression results also suggest that the fasting effects are more positive among students with less good academic performance. Furthermore, Deen et al<sup>82</sup> underscored that it is important for employers in Muslim-minority countries to recognize that many Muslim employees cannot decouple practices prescribed by their faith from the workplace, and employers should engage proactively to align their workers' professional and Muslim identities. Finally, Zainudin et al<sup>83</sup> proposed that fasting Muslims, especially those experiencing health and clinical challenges, continually engage in physical activity during Ramadan. In this opinion piece, they recommend WF as the exercise of choice among fasting Muslims. WF can be played by any individual regardless of fitness, skill, and age. WF has been shown to elicit cardiovascular and metabolic stress responses suitable for populations with low fitness levels. Most importantly, WF has the inherent characteristics of being a fun team activity requiring social interactions among

participants and, hence, likely to encourage long-term consistent and sustainable participation.

## Conclusions

This review of the health implication of RF in 2022 is narrated in a concise thematic account, excluding those concerned with diabetes. The emerging themes from the review of the literature on RF published in 2022 include the pathophysiology of changes during RF, nutritional aspects including body composition and energy metabolism, CVD and risk factors, renal function and structure, endocrinology (mainly thyroid), neurological disorders, mental health, pregnancy and fetal life, infections (including COVID), and some miscellaneous clinical themes. In addition, some perspective of patients and professionals were published. The medical interest in RF remains widely spread across specialties. Cardiovascular disease and risk factors attract the most interest in terms of original articles and professional guidelines. We hope this concise summary of the scholarly work on the subject is helpful.

### Note

To the best of our abilities, we presented our perception of the published work in good faith. Original authors cannot be held responsible for any misrepresentation.

### Authors' Contribution

S.A.B. proposed the study, performed the literature searches, and drafted the manuscript. All authors reviewed the whole document for intellectual content. All authors approved its final version.

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No ethical approval is required.

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None declared.

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