



Impact of diurnal intermittent fasting during Ramadan on inflammatory and oxidative stress markers in healthy people: Systematic review and meta-analysis

Mo'ez Al-Islam E. Faris^{a,*}, Haitham A. Jahrami^{b,c}, Asma A. Obaideen^d, Mohamed I. Madkour^e

^a Department of Clinical Nutrition and Dietetics, College of Health Sciences, Research Institute of Medical and Health Sciences (RIMHS), University of Sharjah, Sharjah, United Arab Emirates

^b Rehabilitation Services, Periphery Hospitals, Ministry of Health, Manama, Bahrain

^c College of Medicine and Medical Sciences, Arabian Gulf University, Manama, Bahrain

^d Department of Clinical Nutrition, Faculty of Medicine and Health Sciences, University Putra Malaysia, Malaysia

^e Department of Medical Laboratory Sciences, College of Health Sciences/Research Institute of Medical and Health Sciences (RIMHS), University of Sharjah, Sharjah, United Arab Emirates

HIGHLIGHTS

- Ramadan fasting has a small impact on the inflammatory and oxidative stress markers in healthy subjects.
- TNF- α and IL-6 appeared to be the most impacted markers.
- High heterogeneity of retrieved studies found as a result of the different dietary and lifestyle behaviors accompanying Ramadan fasting month.

ARTICLE INFO

Keywords:

Diurnal intermittent fasting
Inflammation
Interleukin-1
Interleukin-6
Malondialdehyde
Oxidative stress
Ramadan
Tumor necrosis factor- α

ABSTRACT

Studies on the impact of diurnal intermittent fasting during Ramadan on inflammatory and oxidative stress markers have been limited and yielded contradictory results. Therefore, we performed a systematic review and meta-analysis to comprehensively examine changes in inflammatory and oxidative stress markers in healthy people before and after Ramadan. Databases searched were: PubMed/MEDLINE, ProQuest Medical, Web of Science, Scopus, EBSCOhost, Science Direct, CINAHL, Cochrane, and Google Scholar. The reference lists of identified papers were also screened. There was no date restriction for papers. The studied inflammatory markers were: interleukin (IL)-1, IL-6, tumor necrosis factor- α (TNF- α), and C-reactive protein (CRP)/high sensitivity CRP (hs-CRP). The studied oxidative stress marker was malondialdehyde (MDA). We identified 12 studies (involving 311 participants) conducted in eight countries: Iran (K = 3), Turkey (K = 2), the Kingdom of Saudi Arabia (K = 2), Jordan (K = 1), the United Arab Emirates (K = 1), Denmark (K = 1), the Netherlands (K = 1), and Indonesia (K = 1). Diurnal fasting during Ramadan resulted in very small reductions in IL-1 (Hedge's $g = 0.016$), CRP/hs-CRP (Hedge's $g = 0.119$), and MDA (Hedge's $g = 0.219$), and small reductions in TNF- α (Hedge's $g = 0.371$) and IL-6 (Hedge's $g = 0.407$). These results suggest diurnal intermittent fasting during Ramadan provides some protection against elevated inflammatory and oxidative stress markers. Therefore, it may offer an opportunity to reduce low-grade systemic inflammation and oxidative stress, and subsequent adverse health effects in healthy people.

1. Introduction

Fasting is defined as voluntary abstinence from eating for variable time intervals [1,2] and has been associated with potential beneficial

impacts on human health, including increased longevity [3]. Religious fasting involves a fasting regimen undertaken for spiritual or religious purposes, and is defined as a nutritional model characterized by variable degrees of caloric restriction and abstinence from specific foods

* Corresponding author. Department of Clinical Nutrition and Dietetics, College of Health Sciences, Research Institute of Medical and Health Sciences (RIMHS), University of Sharjah, Sharjah, P.O. Box 27272, United Arab Emirates.

E-mail addresses: mfaris@sharjah.ac.ae, moezfaris@hotmail.com (M.A.-I.E. Faris).

<https://doi.org/10.1016/j.jnim.2018.11.005>

Received 18 August 2018; Received in revised form 17 November 2018; Accepted 22 November 2018

Available online 24 November 2018

2352-3859/© 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

[1]. Such fasting has become increasingly popular worldwide [2,4].

Intermittent fasting is a commonly practiced model of fasting used for both health-improving (non-religious) and religious purposes that has been widely studied. Cumulative research supports the health-improving effects of caloric restriction and intermittent fasting [5] on cerebrovascular and cardiovascular systems [6], including: healthy aging [7]; lowering insulin resistance and triggering insulin sensitivity and action [8]; enhancing mitochondrial health, DNA repair, and autophagy [9]; lowering body weight; enhancing cardiovascular health among people with diabetes who are obese; and reducing cardiovascular risk [5]. These benefits mean intermittent fasting is a safe and cost-effective method of lowering the risk for adverse health events [10]. However, some research has reported adverse health effects of caloric restriction and intermittent fasting [11]; particularly during Ramadan fasting among those following unhealthy eating patterns during the night hours when eating is permitted [12].

Ramadan is the ninth month in the Islamic calendar. During Ramadan, healthy adult Muslims refrain from eating and drinking (including water) each day from dawn to sunset, and abstain from smoking and sexual activity during this period. The fasting period varies depending on the season and the geographic location, and ranging from around 12 h/day to around 18 h/day. A growing body of evidence from meta-analyses, systematic reviews, and original research suggests that variable physiological changes are induced by Ramadan intermittent fasting (RIF), including: anthropometric changes (body weight) [13,14], biochemical changes (glucose homeostasis and lipid profile) [14], and immunomodulatory effects [15]. However, conflicting results have been reported for various immunomodulatory markers in healthy and patient volunteers who observe the month of Ramadan [15].

Interleukin (IL)-1, IL-6, and tumor necrosis factor- α (TNF- α) are among the important and frequently examined proinflammatory cytokines in clinical settings, and are major components of low-grade systemic inflammation that predisposes the development of cardio-metabolic diseases in people with obesity [16]. Their integral role in regulating inflammatory responses in the human body makes these cytokines potential targets for many clinical therapeutic strategies [17]. A growing body of evidence indicates that IL-6, IL-1/IL-1 β , and C-reactive protein (CRP)/high-sensitivity CRP (*hs*-CRP) are directly involved in the pathogenesis of cardiovascular disease; suppressing their activity may help ameliorate acute inflammation and improve the atheroprotective effect [18]. Further, a cumulative meta-analysis confirmed the role of elevated IL-1 β , IL-6, CRP, and TNF- α in patients with major depression compared with non-depressed controls [19]. TNF- α and IL-6 may also play crucial roles in the severity and activity of rheumatoid arthritis [20]. Malondialdehyde (MDA) is a biological marker commonly used to assess oxidative stress, and the principal product studied in the peroxidation of polyunsaturated fatty acids. MDA is a highly toxic molecule that is considered as more than just a marker of lipid peroxidation, and its interaction with DNA and proteins has been suggested to be potentially mutagenic and atherogenic [21].

The present systematic review and meta-analysis aimed to systematically revise and analyze available scientific evidence pertaining to the impact of RIF on selected proinflammatory/inflammatory and oxidative stress markers in healthy people. The results will contribute to a more stable estimate of the effect of RIF, and clarify the variability between different observational studies conducted in this area. We also aimed to assess the generalizability of the results of identified studies, perform subgroup analyses (if needed), and direct future researchers toward gaps that need further examination using other models (e.g., animal models and experimental interventional trials). Finally, this meta-analysis will help to contextualize existing knowledge by examining all similar studies [22].

2. Materials and methods

This meta-analysis used the Meta-analysis Of Observational Studies in Epidemiology statement as a guideline for reporting the protocol findings [23].

2.1. Database searches

In March 2018, two authors (MF and AO) conducted an electronic search of PubMed/MEDLINE, ProQuest Medical, Web of Science, Scopus, EBSCOhost, Science Direct, CINAHL, Cochrane, and Google Scholar from database inception to March 2018. The search strategy included relevant keywords: “diurnal fasting” OR “Ramadan intermittent fasting” OR “Ramadan model of intermittent fasting” OR “Ramadan fasting” OR “Ramadan fast” OR “intermittent prolonged fasting during Ramadan” AND “oxidative stress” OR “inflammation” OR “inflammatory” OR “interleukin” OR “cytokine” OR “immunomodulatory”. OR “CRP” OR “C-reactive protein” OR “malondialdehyde” OR “MDA”. Furthermore, the review team manually screened the references of identified papers for potential inclusion in this review.

2.2. Inclusion criteria

We included observational studies that aimed to study the impact of RIF on oxidative stress and inflammatory markers in healthy people. It may be argued that the chances of obtaining a measurable difference were low because we only selected studies involving healthy people. Also, when starting with a healthy population (i.e. “normal” inflammatory and oxidative stress markers), why should it be expected that these markers would become significantly “better” after fasting? There are two counter arguments. First, by using data from studies including healthy people, we were controlling for major factors that may induce confounding or statistical heterogeneity, such as the type of disease (inflammatory or non-inflammatory disease), effect of disease stage, comorbidities, and treatments on the outcomes of interest. Second, from a logistics point of view, published studies on the impact of RIF on patients are scarce. This is because Ramadan fasting is only required for healthy people; those with chronic and acute illnesses are exempt from observing RIF.

The inclusion criteria for study selection were: 1) original articles published in the English language; 2) publication date between the inception of the database and March 2018; 3) studies that assessed the impact of RIF on healthy people as the target population (prospective observational studies) or as healthy controls (case-control studies); 4) studies that reported numerical values (e.g., arithmetic mean with/without standard deviation) for at least one of the selected inflammatory (IL-6, IL-1 β , TNF- α and CRP/*hs*-CRP) and oxidative stress (MDA) markers. Because we were interested in data from before and after RIF, we included studies that examined the levels of inflammatory and oxidative stress markers in at least two stages: pre-fasting as the baseline (a few days or weeks before Ramadan month or the first day of the fasting month), and post fasting (after completion of 29–30 days of the fasting month or at least 2 weeks into the fasting month).

2.3. Exclusion criteria

Exclusion criteria were: 1) studies that included patients with different ailments who were observing Ramadan fasting; 2) studies on the impact of RIF on Muslim athletes who were observing Ramadan fasting; 3) lack of availability of the study or inability to obtain the full text after contacting the authors; 4) studies that expressed changes in inflammatory and oxidative stress markers using bar graphs and curves without showing exact numerical values; 5) studies that used different specimens for the same marker (e.g., serum vs. salivary MDA); 6) studies on pregnant and lactating women who were observing Ramadan

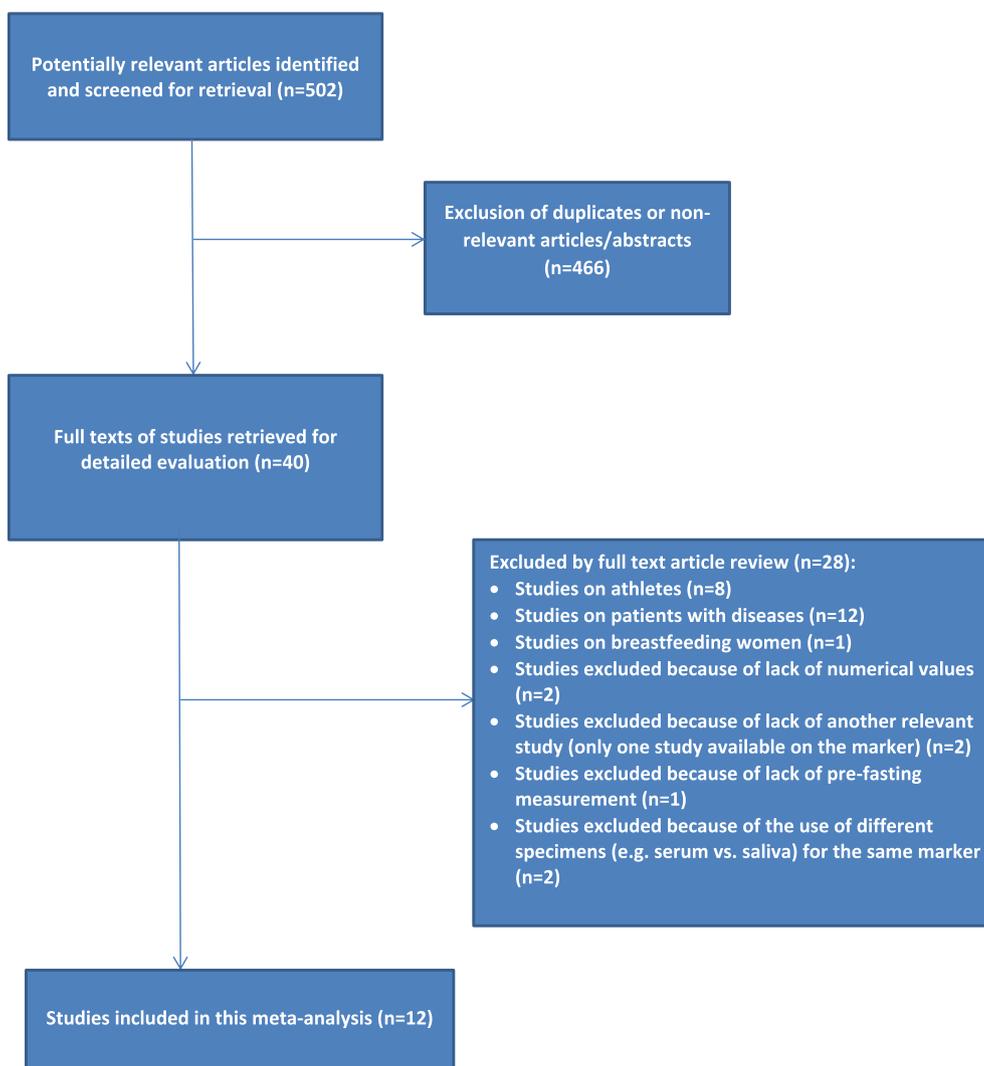


Fig. 1. Flow chart of studies included in the present systematic review and meta-analysis.

fasting; 7) being a sole study for one marker without other relevant study; and 8) lack of pre-fasting measurement. Abstracts, case reports, editorials, review articles, and non-English-language articles were excluded. Unpublished, non-peer-reviewed data were also excluded from the analysis because of potential methodology and quality issues (see Fig. 1).

2.4. Main outcomes and measures

The principal outcome of this review was to report the impact of RIF on changes in levels of inflammatory (IL-1, IL-6 and TNF- α , hs-CRP) and oxidative stress (MDA) markers. Two authors (MF and AO) independently screened the titles and abstracts of identified studies, and assessed the studies for eligibility. Two authors (MF and AO) performed the initial data extraction, which was validated by another author (MM). Any conflicts in opinion regarding study eligibility were resolved through dialogue with a fourth author (HJ) to reach consensus. To standardize data extraction, the review team collected data for: study characteristics (e.g., title, year, sample size, country; participants' characteristics (e.g., age, sex); and the main findings for inflammatory and oxidative stress markers before and at the end of RIF.

2.5. Data synthesis and statistical analyses

We performed a series of one group (pre-post) meta-analyses using

pre- and post-means, sample size, and *P*-values (paired groups). Hedge's *g* value was used for effect size measurement. An effect size of ≤ 0.2 was described as a small effect, an effect size around 0.5 as medium effect, and an effect size around 0.8 was as a large effect. In addition to Hedge's *g* values, we also presented results graphically using forest plots to illustrate point estimates of the effect size and 95% confidence intervals (CI). Random-effects modeling was used for all analyses. An assessment of heterogeneity of the selected studies using I^2 and tau² statistics was performed. Comprehensive Meta-Analysis version 2 [24] was used for all analyses. Leave-one-out sensitivity analyses were conducted by iteratively eliminating one study at a time to confirm our meta-analysis findings were not driven by any one study. Other descriptive statistical analyses were performed using Microsoft Excel (2016).

3. Results

Twelve studies including a total of 311 participants were included in our analyses (Table 1). All included studies used a pre-post design to report changes in inflammatory and/or oxidative stress markers. Approximately 86% of participants were male, and the median age was 38 years (range 12–70 years).

Table 1
Characteristics of studies on the impact of Ramadan intermittent fasting on inflammatory and oxidative stress markers.

Study No.	Author	Year	Country	Sample size n (% male)	Age, years mean (range)	Examined markers
1	Asgary et al. [62]	2000	Iran	50 (100)	(30–60)	MDA
2	Ibrahim et al. [63]	2008	UAE	14 (64)	(25–58)	MDA
3	Sülü et al. [27]	2010	Turkey	45 (51)	28.7 (21–51)	MDA
4	Ünalacak et al. [25]	2011	Turkey	20 (100)	27.4 ± 5.2 ^a	IL-1, IL-6, TNF-α, hs-CRP
5	Faris et al. [64]	2012	Jordan	50 (42)	32.70 ± 9.5 ^a	IL-1, IL-6, TNF-α
6	Lahdimawan et al. [65]	2013	Indonesia	22 (100)	20.26 ± 1.13 ^a (18–22)	TNF-α
7	Ajabnoor et al. [51]	2014	Saudi Arabia	23 (78)	(18–42)	hs-CRP
8	Radhakishun et al. [31]	2014	Netherlands	25 (100)	(12–18)	hs-CRP
9	Askari et al. [66]	2016	Iran	14 (100)	37.5 ± 7.86 ^a	hs-CRP
10	BaHammam et al. [67]	2016	Saudi Arabia	8 (100)	26.6 ± 4.9 ^a	MDA
11	Harder-Lauridsen et al. [68]	2017	Denmark	10 (100)	(18–35)	IL-6, TNF-α
12	Mohammadzade et al. [26]	2017	Iran	30 (100)	(20–35)	IL-6, hs-CRP

hs-CRP, high sensitivity-C reactive protein; IL, interleukin; MDA, malondialdehyde; TNF-α, tumor necrosis factor-α; UAE, United Arab Emirates.

^a Mean ± standard deviation.

3.1. Meta-analysis of inflammatory markers

Meta-analytic pooling for four inflammatory biomarkers (IL-1/β, IL-6, TNF-α, and CRP/hs-CRP) was performed. Hedges g values were: 0.016 ($I^2 = 0.0%$) for IL-1 (N = 70, K = 2) (Fig. 2); 0.407 ($I^2 = 0.0%$) for IL-6 (N = 110, K = 4) (Fig. 3); 0.371 ($I^2 = 19.7%$) for TNF-α (N = 102, K = 4) (Fig. 4); and 0.119 ($I^2 = 26.9%$) for CRP/hs-CRP (N = 111, K = 5) (Fig. 5). Sensitivity analyses were performed for inflammatory markers with three or more studies by removing one study at a time to determine if the pooled effect size was arbitrary or influenced by a single study. The sensitivity analysis for IL-6 indicated there was no major issue. However, the sensitivity analyses for TNF-α and hs-CRP indicated that some studies slightly skewed the effect size. The results for TNF-α were influenced by Ünalacak et al. [25], and those for hs-CRP were influenced by Mohammadzade et al. [26] and Ünalacak et al. [25]. No formal publication bias or meta-regression or subgroup analyses were performed because of the small number of studies (Table 2).

3.2. Meta-analysis of oxidative stress markers

Meta-analytic pooling for MDA was performed. Hedge's g for MDA (N = 117, K = 4) was 0.219 ($I^2 = 0.0%$) (Fig. 6). The sensitivity analysis for MDA indicated the results were influenced by Sülü et al. [27]. Hedge's g increased to 0.4 if that study was removed. No formal publication bias or meta-regression or subgroup analyses were performed because of the small number of studies (Table 2).

4. Discussion

RIF represents a unique model to explore the impact of consistent food restriction (29–30 days) for a fixed time duration (12–18 h) on different anthropometric, biochemical, and immunological aspects of the human body [3]. Although fasting during the holy month of Ramadan is an obligatory form of worship for every healthy adult Muslim, certain groups of people are exempt. These groups include: pre-pubertal

children; individuals with acute illnesses that may be adversely affected by fasting; women who are pregnant, breastfeeding, or menstruating; healthy individuals who are travelling; individuals with a chronic disease; and individuals with mental health problems [28,29]. However, some studies showed that children and adolescents, even those with diabetes, fast for a significant number of days during the month of Ramadan [30]. Therefore, we included a study in our meta-analysis that involved adolescents as part of the healthy population who were observing RIF [31].

RIF is a safe lifestyle modification that is observed annually for 1 month. RIF involves specific dietary and lifestyle modifications, such as changes in food quantity and quality, nocturnal food consumption, meal frequency, and sleep cycle [13]. Different studies have reported varying impacts of RIF on overall health [29,32]. The present review summarizes the best available evidence on the effects of RIF on proinflammatory cytokines (IL-1, IL-6, and TNF-α), a general inflammatory marker (hs-CRP), and an oxidative stress marker (MDA) in healthy people (both obese and non-obese). The studies included in our analysis showed various findings regarding the effects of RIF on these inflammatory and oxidative stress markers at the end of the Ramadan month compared with pre-fasting (baseline) levels. We found the I^2 statistics were low and suggested low heterogeneity, which confirmed that conducting a meta-analysis was appropriate.

Overall, the impact of RIF in terms of a decrease in inflammatory and oxidative stress markers was small, suggesting that fasting Muslims may develop some short-term protection against low-grade systemic inflammation and oxidative stress. This reduction in inflammatory and oxidative stress markers could be attributed to weight loss during the fasting month, as noted in a meta-analysis of body weight changes during RIF [13]. Further, increased body weight is associated with increased levels of inflammation and oxidative stress in the human body, with IL-6, IL-1, and TNF-α among the common proinflammatory adipokines that predispose the metabolic derangements associated with obesity [33].

Another possible mechanism for the role of RIF in lowering inflammatory and oxidative stress markers is through lowering the

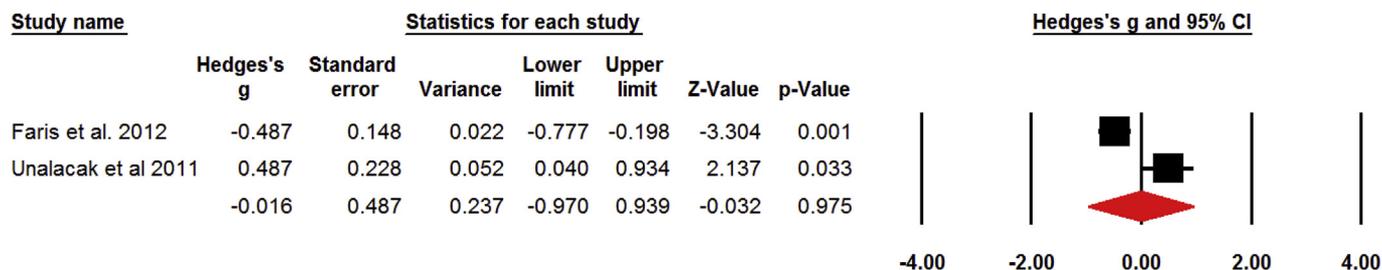


Fig. 2. Forest plot of studies that examined the impact of Ramadan intermittent fasting on interleukin-1 (α and β).

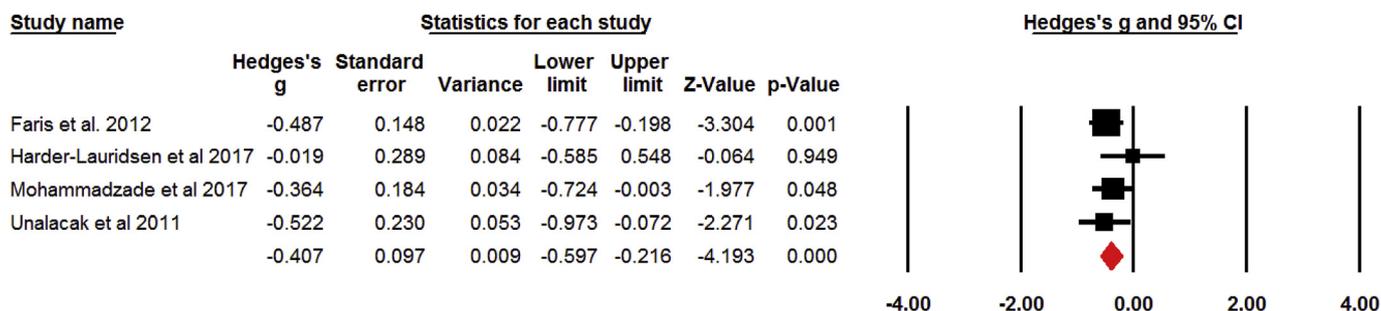


Fig. 3. Forest plot of studies that examined the impact of Ramadan intermittent fasting on interleukin-6.

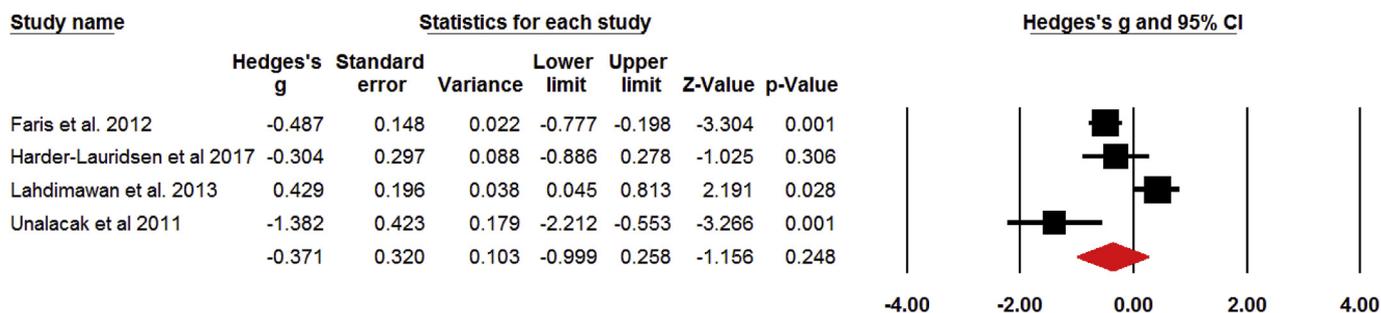


Fig. 4. Forest plot of studies that examined the impact of Ramadan intermittent fasting on tumor necrosis factor- α .

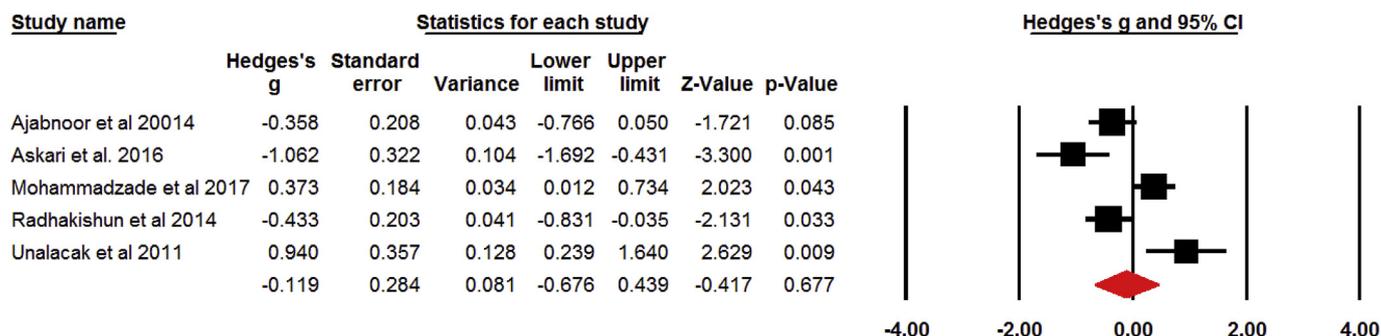


Fig. 5. Forest plot of studies that examined the impact of Ramadan intermittent fasting on C-reactive protein/high-sensitivity C-reactive protein.

insulin/insulin-like growth factor 1 (IGF-1) axis that predisposes inflammation and oxidative stress among people with obesity [34]. Obesity may promote chronic diseases through the induction of pro-inflammatory cytokines and onset of insulin and insulin/IGF-1 resistance, which is associated with increased production of reactive oxygen species and increased oxidative stress and inflammatory states [34]. Several reports have indicated RIF is associated with reduced serum glucose, insulin, and insulin resistance (measured by homeostasis model assessment as an insulin resistance index) levels in people with metabolic syndrome who are obese [25,35,36]. In a recent study, we showed that RIF was associated with a significant (about 30%) reduction in IGF-1 factor at the end of the Ramadan fasting month (Faris et al., 2018. Unpublished data). At the genetic level, Wegman and colleagues [37] reported a marginal increase in the expression of the *SIRT3* gene associated with aging, which also helps in alleviating oxidative stress and inflammation. This finding was further confirmed in our institution, where RIF in healthy people with obesity was associated with a significant ($P < 0.05$) upregulation in the expression of the three anti-oxidant genes *TFAM*, *SOD2* and *Nrf2*, with percent increments of 90.45%, 54.1% and 411.5%, respectively (Faris et al., 2018. Unpublished data).

The significant reduction of total body and visceral fat reported at the end of the Ramadan fasting month [38–41] may also help to explain the reductions in oxidative stress and inflammatory markers reported in

the present meta-analysis. It has been established that adipocytes are a source of IL-6, IL-1, TNF- α , and most people with obesity secrete superfluous amounts of this pro-inflammatory “cocktail” [42]. These three adipokines in turn generate reactive oxygen species; therefore, adipose tissue is considered an independent factor for the generation of systemic oxygen species responsible for the increased level of oxidative stress in people with obesity [33].

Overall, the slight improvement in inflammatory and oxidative stress markers reported in the present analysis may reflect short-term protection against cancer initiation and atherogenesis in healthy fasting people, as these markers are known to be involved in cancer initiation and cardiovascular events, especially among people who are obese [33].

During RIF, changes in the timing of fluid and food intake, along with the reduction in meal frequency, may result in various behavioral and chronobiological changes, such as the circadian distribution of body temperature, melatonin, cortisol, and glycemic control, as well as changes in daytime alertness and nocturnal sleep [43]. These physiological changes have been reported to modulate the inflammatory and oxidative stress levels in the human body [44].

Caloric restriction is a significant change that ameliorates the inflammatory and oxidative stress markers that are predisposing factors for chronic diseases, such as cancer and cardiovascular events [45]. Caloric restriction and decreased food intake during RIF were not

Table 2
Summary of changes in inflammatory and oxidative stress markers from baseline (pre-fasting) to the end of Ramadan month reported in the included studies.

Author and year	Country	Study design	Sample size and sex	Mean age/age range, years	Before Ramadan, mean \pm SD	End of Ramadan, mean \pm SD	Description
Asgary et al. (2000) [62]	Iran	Prospective observational	M: 50	30–60	MDA: 1.9 \pm 0.51 NR: IL-1, IL-6, TNF- α ; hs-CRP	MDA: 1.73 \pm 0.38	Significant reduction ($P = 0.009$) observed at the end of Ramadan compared with baseline
Ibrahim et al. (2008) [63]	United Arab Emirates	Prospective observational	M: 9 F: 5	25–58	MDA: 1.41 \pm 0.13 NR: IL-1, IL-6, TNF- α ; hs-CRP	MDA: 1.31 \pm 0.15	No significant changes observed at the end of Ramadan compared with baseline
Silili et al. (2010) [27]	Turkey	Prospective observational	M: 23 F: 22	28.7 (21–5) M: 30.5 \pm 7.1 F: 26.9 \pm 3.8	MDA: 5.8 \pm 2.2– 7.0 \pm 3.2 NR: IL-1, IL-6, TNF- α ; hs-CRP	MDA: 8.9 \pm 6.8– 9.3 \pm 3.2	No significant changes ($P = 0.26$) observed for M; significant increase ($P = 0.03$) observed for F at the end of Ramadan compared with baseline
^b Ünalacak et al. (2011) [25]	Turkey	Prospective cohort with control group	M: 20 (10 obese and 10 non-obese controls)	27.4 \pm 5.2	IL-1: 5.0 \pm 0.0 IL-6: 4.03 \pm 0.30–4.13 \pm 1.20 TNF- α : 10.56 \pm 3.84–10.87 \pm 2.60 hs-CRP: 1.85 \pm 1.51–2.83 \pm 1.39	IL-1: 5.0 \pm 0.0 IL-6: 3.56 \pm 0.78–3.76 \pm 0.99 TNF- α : 7.57 \pm 2.60–7.70 \pm 2.52 hs-CRP: 2.41 \pm 1.98–2.70 \pm 1.29	No change reported in either obese or control groups No significant changes reported in either obese or control groups Significant ($P < 0.001$) changes reported in both obese and control groups post-Ramadan compared with baseline
Faris et al. (2012) [64]	Jordan	Prospective observational	M: 21 F: 29	32.7 \pm 9.5 M: 18–49 F: 18–51	NR: MDA IL-1 β : 17.84 \pm 17.92 IL-6: 156.0 \pm 121.0 TNF- α : 179.6 \pm 129.6 NR: hs-CRP, MDA	IL-1 β : 3.89 \pm 4.84 IL-6: 67.0 \pm 51.0 TNF- α : 52.2 \pm 57.3	No significant change reported in the obese group; non-obese controls showed significant ($P < 0.01$) increment after Ramadan compared with baseline
Lahdimawan et al. (2013) [65]	Indonesia	Prospective observational	M: 22	20.3 \pm 1.1 18–22	TNF- α : 15.456 \pm 7.1458	TNF- α : 19.607 \pm 6.0916	No significant change reported at day 21 of Ramadan compared with baseline
Ajabnoor et al. (2014) [51]	Saudi Arabia	Prospective observational	M: 18 F: 5	18–42	NR: IL-1, IL-6, hs-CRP, MDA hs-CRP: 1.33 \pm 0.32–1.68 \pm 0.47	hs-CRP: 0.97 \pm 0.22– 1.13 \pm 0.35	Significant ($P < 0.001$) reduction at the end of Ramadan compared with baseline Significant ($P < 0.001$) reduction at the end of Ramadan compared with baseline Significant ($P < 0.001$) reduction at the end of Ramadan compared with baseline
Radhakishun et al. (2014) [31]	Netherlands	Prospective cohort	M: 25	12–18	NR: IL-1, IL-6, TNF- α , MDA hs-CRP: 3.36	hs-CRP: 2.59	Significant ($P < 0.05$) reduction reported after Ramadan compared with baseline
^c Askari et al. (2016) [66]	Iran	Case-control study	M: 14	37.5 \pm 7.9	NR: IL-1, IL-6, TNF- α , MDA hs-CRP: 2.08 \pm 0.52	hs-CRP: 1.24 \pm 0.29	Significant ($P < 0.001$) reduction reported after Ramadan compared with baseline
BaHammam et al. (2016) [67]	Saudi Arabia	Prospective observational	M: 8	26.6 \pm 5	NR: IL-1, IL-6, TNF- α , MDA MDA: 75.5	MDA: 70.1	No significant change at 2 weeks into Ramadan compared with baseline
Harder-Lauridsen et al. (2017) [68]	Denmark	Non-randomized, crossover, intervention study	M: 10	18–35	NR: IL-1, IL-6, TNF- α ; hs-CRP IL-6: 0.3 TNF- α : 4.6	IL-6: 0.3 TNF- α : 4.4	No change reported at the end of Ramadan compared with baseline No significant change reported after Ramadan compared with baseline
					NR: IL-1, hs-CRP, MDA		

(continued on next page)

Table 2 (continued)

Author and year	Country	Study design	Sample size and sex	Mean age/age range, years	Before Ramadan, mean \pm SD	End of Ramadan, mean \pm SD	Description
Mohammadzade et al. (2017) [26]	Iran	Prospective observational	M: 30	20–35	IL-6: 1.09 \pm 1.63 hs-CRP: 1.72 \pm 1.67 NR: IL-1, TNF- α , MDA	IL-6: 0.79 \pm 0.26 hs-CRP: 1.99 \pm 1.45	No significant reduction at the end of the third week of Ramadan month compared with baseline No significant change at the end of Ramadan compared with baseline

F, Female; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; M, male; MDA, malondialdehyde; NR, not reported; SD, standard deviation; TNF- α , tumor necrosis factor- α .

^a Only serum MDA was included, salivary MDA was excluded.

^b Study included both IL-1 α and IL-1 β .

^c Control healthy group for comparison with asthmatic patients.

reported in all studies included in this analysis (one-third of the studies showed decreased energy intake during RIF), despite most studies systematically reviewed elsewhere reporting decreased meal frequency [13]. Variations in the caloric intake during RIF may also be helpful in interpreting the heterogeneity of the present findings with regard to the varying changes in inflammatory and oxidative stress markers reported at the end of the fasting month. Further, there was geographical heterogeneity in the populations examined in the studies included in our analysis (Iran, Turkey, the Netherlands, Denmark, Jordan, Saudi Arabia, United Arab Emirates, and Indonesia). This suggests that health outcomes associated with the Ramadan fasting month are affected by various factors, including: variations in the length of fasting (e.g., 16–20 h in the same year) and daytime temperature [43,46]; differences in traditional foods and dietary habits/customs during Ramadan [3,43,47]; differences in amounts and types of fluid intake (e.g., sweetened drinks or water/juices) [48,49]; variations in sleep duration and sleeping patterns [50,51]; differences in working hours, job conditions, and physical activity levels [47,52]; different Ramadan religious rituals and social behaviors [53] that affect levels of activity/setting durations during Ramadan; and the age of participants [3].

It is worth noting that the studies included in the present analysis may be criticized in that they included more than one confounding factor that might have affected the impact of RIF on inflammatory and oxidative stress markers. For example, factors that were not controlled in the studies we analyzed included changes in sleep duration and circadian rhythm hormones [43,50,51,54–58] and changes in physical exercise levels [59–61] during the fasting month of Ramadan. These factors have been reported to be changeable and have a significant influence on the metabolic outcomes of RIF. Factors such as these should be considered in future studies and reviews.

By combining RIF studies, our meta-analysis increased the total sample size, thereby increasing the power of the studies in showing the effects of diurnal intermittent fasting during Ramadan. However, the present meta-analysis had some limitations. First, the analysis of IL-1 only included two studies, which is the minimum number of studies that can be meta-analyzed; therefore, the impact of RIF on this pro-inflammatory cytokine cannot be generalized. More studies are needed to examine the impact of RIF on IL-1. Second, the results of the sensitivity analyses revealed that some studies had more power, but overall they did not significantly influence the conclusion; this needs to be explored in a future meta-analysis with a larger number of studies to allow for subgroup analyses and meta-regression techniques. In addition, we recommend that research methodology (design), country of the study, and season or timing of the study (as per the Gregorian calendar) should be examined in future studies.

5. Conclusions

Findings of the present meta-analysis demonstrate that RIF ameliorates inflammatory and oxidative stress markers to a small extent. This may provide a slight short-term protective effect against the adverse health consequences of systemic low-grade inflammation and high levels of oxidative stress that are predisposing factors for different chronic diseases associated with affluent societies.

Funding sources

This work did not receive any funding or support from any grant or funding body.

Statement of authorship

HJ and MF contributed to the conception and design of the work. MF and AO participated in the article reviews and data extraction. HJ performed all data analyses. MF and HJ contributed to drafting the manuscript, and MM contributed to critically revising the manuscript

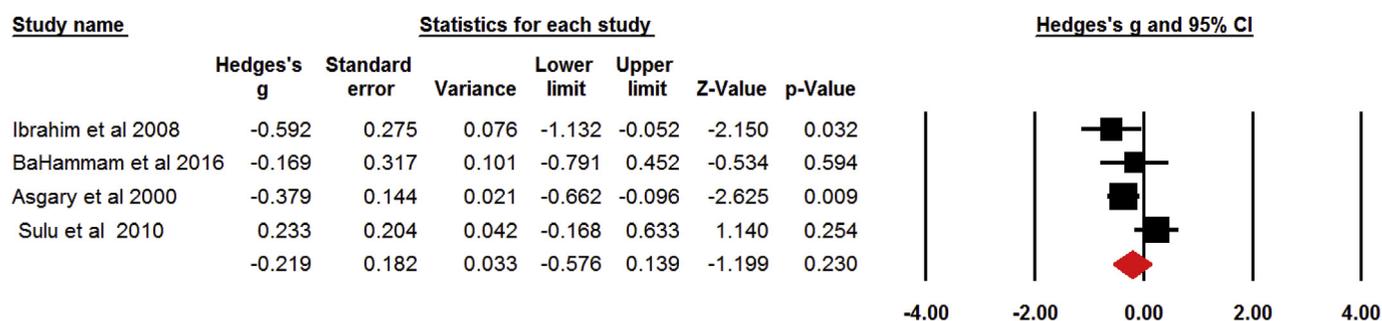


Fig. 6. Forest plot for studies that examined the impact of Ramadan intermittent fasting on malondialdehyde.

and provided intellectual contributions to strengthen the manuscript. All authors were involved in writing the paper and approved the final version for publication.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical statement

- This article does not contain any studies with human participants performed by any of the authors.
- For this type of study formal consent is not required.

List of abbreviations

hs-CRP	high-sensitivity C-reactive protein
IL-1	interleukin-1
IL-6	interleukin-6
IGF-1	insulin-like growth factor 1
MDA	malondialdehyde
RIF	Ramadan intermittent fasting
TNF- α	tumor necrosis factor- α

References

- J.F. Trepanowski, R.J. Bloomer, The impact of religious fasting on human health, *Nutr. J.* 9 (2010) 57.
- A. Persynaki, S. Karras, C. Pichard, Unraveling the metabolic health benefits of fasting related to religious beliefs: a narrative review, *Nutrition* 35 (2017) 14–20.
- J.F. Trepanowski, R.E. Canale, K.E. Marshall, M.M. Kabir, R.J. Bloomer, Impact of caloric and dietary restriction regimens on markers of health and longevity in humans and animals: a summary of available findings, *Nutr. J.* 10 (2011) 107.
- T. Koufakis, S.N. Karras, V. Antonopoulou, E. Angeloudi, P. Zebekakis, K. Kotsa, Effects of Orthodox religious fasting on human health: a systematic review, *Eur. J. Nutr.* 56 (2017) 2439–2455.
- R.E. Patterson, D.D. Sears, Metabolic effects of intermittent fasting, *Annu. Rev. Nutr.* 37 (2017).
- M.P. Mattson, R. Wan, Beneficial effects of intermittent fasting and caloric restriction on the cardiovascular and cerebrovascular systems, *J. Nutr. Biochem.* 16 (2005) 129–137.
- B. Martin, M.P. Mattson, S. Maudsley, Caloric restriction and intermittent fasting: two potential diets for successful brain aging, *Ageing Res. Rev.* 5 (2006) 332–353.
- N. Halberg, M. Henriksen, N. Soderhamn, B. Stallknecht, T. Ploug, P. Schjerling, et al., Effect of intermittent fasting and refeeding on insulin action in healthy men, *J. Appl. Physiol.* 99 (2005) 2128–2136.
- M.P. Mattson, V.D. Longo, M. Harvie, Impact of intermittent fasting on health and disease processes, *Ageing Res. Rev.* 39 (2017) 46–58.
- J.E. Brown, M. Mosley, S. Aldred, Intermittent fasting: a dietary intervention for prevention of diabetes and cardiovascular disease? *Br. J. Diabetes Vasc. Dis.* 13 (2013) 68–72.
- A.J. Dirks, C. Leeuwenburgh, Caloric restriction in humans: potential pitfalls and health concerns, *Mech. Ageing Dev.* 127 (2006) 1–7.
- P. Maideen, N. Mohamed, Ab Jumale, R. Balasubramaniam, Adverse health effects associated with Islamic fasting—A literature review, *J. Fasting Health* 5 (2017) 113–118.
- S. Sadeghirad, S. Motaghipisheh, F. Kolahdooz, M.J. Zahedi, A.A. Haghdoost, Islamic fasting and weight loss: a systematic review and meta-analysis, *Publ. Health Nutr.* 17 (2014) 396–406.
- S. Kul, E. Savaş, Z.A. Öztürk, G. Karadağ, Does Ramadan fasting alter body weight and blood lipids and fasting blood glucose in a healthy population? A meta-analysis, *J. Relig. Health* 53 (2014) 929–942.
- M. Adawi, A. Wataf, S. Brown, K. Aazza, H. Aazza, M. Zouhir, et al., Ramadan Fasting exerts immunomodulatory effects: insights from a Systematic Review, *Front. Immunol.* 8 (2017).
- J.I. León-Pedroza, L.A. González-Tapia, E. del Olmo-Gil, D. Castellanos-Rodríguez, G. Escobedo, A. González-Chávez, Low-grade systemic inflammation and the development of metabolic diseases: from the molecular evidence to the clinical practice, *Cir. Cir.* 83 (2015) 543–551.
- M. Akdis, A. Aab, C. Altunbulakli, K. Azkur, R.A. Costa, R. Cramer, et al., Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β , and TNF- α : receptors, functions, and roles in diseases, *J. Allergy Clin. Immunol.* 138 (2016) 984–1010.
- P.M. Ridker, From C-reactive protein to interleukin-6 to interleukin-1: moving upstream to identify novel targets for atheroprotection, *Circ. Res.* 118 (2016) 145–156.
- R. Haapakoski, J. Mathieu, K.P. Ebmeier, H. Alenius, M. Kivimäki, Cumulative meta-analysis of interleukins 6 and 1 β , tumor necrosis factor α and C-reactive protein in patients with major depressive disorder, *Brain Behav. Immun.* 49 (2015) 206–215.
- S.-T. Wei, Y.-H. Sun, S.-H. Zong, Y.-B. Xiang, Serum levels of IL-6 and TNF- α may correlate with activity and severity of rheumatoid arthritis, *Med. Sci. Mon. Int. Med. J. Exp. Clin. Res.: Int. Med. J. Exp. Clin. Res.* 21 (2015) 4030.
- D. Del Rio, A.J. Stewart, N. Pellegrini, A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress, *Nutr. Metabol. Cardiovasc. Dis.* 15 (2005) 316–328.
- Student, Six reasons for conducting a meta-analysis, *Pediatrics* 83 (1989) 100.
- D.F. Stroup, J.A. Berlin, S.C. Morton, I. Olkin, G.D. Williamson, D. Rennie, et al., Meta-analysis of observational studies in epidemiology: a proposal for reporting, *Jama* 283 (2000) 2008–2012.
- M. Borenstein, L. Hedges, J. Higgins, H. Rothstein, *Comprehensive Metaanalysis* (Vers. 2), Biostat. Inc, Englewood Cliffs, NJ, 2005.
- M. Ünalacak, I.H. Kara, D. Baltacı, Ö. Erdem, P.G.E. Bucaktepe, Effects of Ramadan fasting on biochemical and hematological parameters and cytokines in healthy and obese individuals, *Metab. Syndrome Relat. Disord.* 9 (2011) 157–161.
- F. Mohammadzade, M. Vakili, A. Seyediniaki, S. Amirhanloo, M. Farajolahi, H. Akbari, Effect of prolonged intermittent fasting in Ramadan on biochemical and inflammatory parameters of healthy men, *J. Clin. Basic Res. (JCBR)*. 1 (2017) 38–46.
- B. Süli, B. ÖZTÜRK, A. Güven, K. Kilic, The effect of long-term controlled fasting (the Ramadan model) on body mass index, blood biochemistry and oxidative stress factors, *Turkiye Klinikleri J. Med. Sci.* 30 (2010) 855–863.
- M. Ibrahim, M.A. Al Magd, F.A. Annabi, S. Assaad-Khalil, E.M. Ba-Essa, I. Fahdil, et al., Recommendations for management of diabetes during Ramadan: update 2015, *BMJ Open Diabetes Res. Care* 3 (2015) e000108.
- F. Azizi, Islamic fasting and health, *Ann. Nutr. Metabol.* 56 (2010) 273–282.
- A. Deeb, N. Al Qahtani, M. Akle, H. Singh, R. Assadi, S. Attia, et al., Attitude, complications, ability of fasting and glycemic control in fasting Ramadan by children and adolescents with type 1 diabetes mellitus, *Diabetes Res. Clin. Pract.* 126 (2017) 10–15.
- N. Radhakishun, C. Blokhuis, M. van Vliet, I. von Rosenstiel, O. Weijer, M. Heymans, et al., Intermittent fasting during Ramadan causes a transient increase in total, LDL, and HDL cholesterol and hs-CRP in ethnic obese adolescents, *Eur. J. Pediatr.* 173 (2014) 1103–1106.
- M. Toda, K. Morimoto, RAMADAN FASTING—EFFECT ON HEALTHY MUSLIMS, *Soc. Behav. Pers.: Int. J.* 32 (2004) 13–18.
- A. Fernández-Sánchez, E. Madrigal-Santillán, M. Bautista, J. Esquivel-Soto, Á. Morales-González, C. Esquivel-Chirino, et al., Inflammation, oxidative stress, and obesity, *Int. J. Mol. Sci.* 12 (2011) 3117–3132.
- L.J. Spielman, J.P. Little, A. Klegeris, Inflammation and insulin/IGF-1 resistance as the possible link between obesity and neurodegeneration, *J. Neuroimmunol.* 273 (2014) 8–21.
- Z.V. Shariatpanahi, M.V. Shariatpanahi, S. Shahbazi, A. Hossaini, A. Abadi, Effect of Ramadan fasting on some indices of insulin resistance and components of the metabolic syndrome in healthy male adults, *Br. J. Nutr.* 100 (2008) 147–151.
- V. Ziaee, M. Razaee, Z. Ahmadinejad, H. Shaikh, R. Yousefi, L. Yarmohammadi, et al., The changes of metabolic profile and weight during Ramadan fasting, *Singap. Med. J.* 47 (2006) 409.

- [37] M.P. Wegman, M.H. Guo, D.M. Bennion, M.N. Shankar, S.M. Chrzanowski, L.A. Goldberg, et al., Practicality of intermittent fasting in humans and its effect on oxidative stress and genes related to aging and metabolism, *Rejuvenation Res.* 18 (2015) 162–172.
- [38] A. Yucel, B. Degirmenci, M. Acar, R. Albayrak, A. Haktanir, The effect of fasting month of Ramadan on the abdominal fat distribution: assessment by computed tomography, *Tohoku J. Exp. Med.* 204 (2004) 179–187.
- [39] A. Celik, E. Saricicek, V. Saricicek, E. Sahin, G. Ozdemir, S. Bozkurt, et al., Effect of Ramadan fasting on serum concentration of apelin-13 and new obesity indices in healthy adult men, *Med. Sci. Mon. Int. Med. J. Exp. Clin. Res.: Int. Med. J. Exp. Clin. Res.* 20 (2014) 337.
- [40] S.A. Saleh, S.A. Elsharouni, B. Cherian, M. Mourou, Effects of Ramadan fasting on waist circumference, blood pressure, lipid profile, and blood sugar on a sample of healthy Kuwaiti men and women, *Malays. J. Nutr.* 11 (2005) 143–150.
- [41] A. Norouzy, M. Salehi, E. Philippou, H. Arabi, F. Shiva, S. Mehrnoosh, et al., Effect of fasting in R amadan on body composition and nutritional intake: a prospective study, *J. Hum. Nutr. Diet.* 26 (2013) 97–104.
- [42] O. Nov, H. Shapiro, H. Ovadia, T. Tarnowski, I. Dvir, E. Shemesh, et al., Interleukin-1 β regulates fat-liver crosstalk in obesity by auto-paracrine modulation of adipose tissue inflammation and expandability, *PLoS One* 8 (2013) e53626.
- [43] R. Roky, I. Houti, S. Moussamih, S. Qotbi, N. Aadil, Physiological and chronological changes during Ramadan intermittent fasting, *Ann. Nutr. Metab.* 48 (2004) 296–303.
- [44] B. Klop, S.D. Proctor, J.C. Mamo, K.M. Botham, M. Castro Cabezas, Understanding postprandial inflammation and its relationship to lifestyle behaviour and metabolic diseases, *Int. J. Vasc. Med.* 2012 (2012).
- [45] E.P. Weiss, L. Fontana, Caloric restriction: powerful protection for the aging heart and vasculature, *Am. J. Physiol. Heart Circ. Physiol.* 301 (2011) H1205–H1219.
- [46] B.A. Bakhotmah, The puzzle of self-reported weight gain in a month of fasting (Ramadan) among a cohort of Saudi families in Jeddah, Western Saudi Arabia, *Nutr. J.* 10 (2011) 84.
- [47] J. El Ati, C. Beji, J. Danguir, Increased fat oxidation during Ramadan fasting in healthy women: an adaptive mechanism for body-weight maintenance, *Am. J. Clin. Nutr.* 62 (1995) 302–307.
- [48] J.B. Leiper, A. Molla, Effects on health of fluid restriction during fasting in Ramadan, *Eur. J. Clin. Nutr.* 57 (2003) S30.
- [49] K. Gumaa, K. Mustafa, N. Mahmoud, A. Gader, The effects of fasting in Ramadan: 1. Serum uric acid and lipid concentrations, *Br. J. Nutr.* 40 (1978) 573–581.
- [50] S.O. Qasrawi, S.R. Pandi-Perumal, A.S. BaHammam, The effect of intermittent fasting during Ramadan on sleep, sleepiness, cognitive function, and circadian rhythm, *Sleep Breath.* 21 (2017) 577–586.
- [51] G.M. Ajabnoor, S. Bahijri, A. Borai, A.A. Abdulkhalig, J.Y. Al-Aama, G.P. Chrousos, Health impact of fasting in Saudi Arabia during Ramadan: association with disturbed circadian rhythm and metabolic and sleeping patterns, *PLoS One* 9 (2014) e96500.
- [52] A.A. Haghdoost, M. Poorranjbar, The interaction between physical activity and fasting on the serum lipid profile during Ramadan, *Singap. Med. J.* 50 (2009) 897–901.
- [53] D. Oman, Public Health Nutrition, Religion, and Spirituality. Why Religion and Spirituality Matter for Public Health, Springer, 2018, pp. 165–173.
- [54] A. BaHammam, M. Alrajeh, M. Alabtain, S. Bahammam, M. Sharif, Circadian pattern of sleep, energy expenditure, and body temperature of young healthy men during the intermittent fasting of Ramadan, *Appetite* 54 (2010) 426–429.
- [55] T. Reilly, J. Waterhouse, Altered sleep–wake cycles and food intake: the Ramadan model, *Physiol. Behav.* 90 (2007) 219–228.
- [56] R. Roky, F. Chapotot, M.T. Benckekroun, B. Benaji, F. Hakkou, H. Elkhalfi, et al., Daytime sleepiness during Ramadan intermittent fasting: polysomnographic and quantitative waking EEG study, *J. Sleep Res.* 12 (2003) 95–101.
- [57] A. Bahammam, Does Ramadan fasting affect sleep? *Int. J. Clin. Pract.* 60 (2006) 1631–1637.
- [58] A.S. BaHammam, K. Almushailhi, S.R. Pandi-Perumal, M.M. Sharif, Intermittent fasting during R amadan: does it affect sleep? *J. Sleep Res.* 23 (2014) 35–43.
- [59] H. Chtourou, O. Hammouda, A. Chaouachi, K. Chamari, N. Souissi, The effect of time-of-day and Ramadan fasting on anaerobic performances, *Int. J. Sports Med.* 33 (2012) 142.
- [60] H. Al-Hourani, M. Atoum, Body composition, nutrient intake and physical activity patterns in young women during Ramadan, *Singap. Med. J.* 48 (2007) 906.
- [61] A. Haghdoost, M. Poorranjbar, The interaction between physical activity and fasting on the serum lipid profile during Ramadan, *Singap. Med. J.* 50 (2009) 897–901.
- [62] S. Asgary, F. Aghaei, G.A. Naderi, R. Kelishadi, M. Gharipour, S. Azali, Effects of Ramadan fasting on lipid peroxidation, serum lipoproteins and fasting blood sugar, *Med. J. Islam. World Acad. Sci.* 13 (2000) 35–38.
- [63] W.H. Ibrahim, H.M. Habib, A.H. Jarrar, S.A. Al Baz, Effect of Ramadan fasting on markers of oxidative stress and serum biochemical markers of cellular damage in healthy subjects, *Ann. Nutr. Metabol.* 53 (2008) 175–181.
- [64] M.A.-I. Faris, S. Kacimi, A. Refat, M.A. Fararjeh, Y.K. Bustanji, M.K. Mohammad, et al., Intermittent fasting during Ramadan attenuates proinflammatory cytokines and immune cells in healthy subjects, *Nutr. Res.* 32 (2012) 947–955.
- [65] A. Lahdimawan, K. Handono, M.R. Indra, S.R. Prawiro, Effect of Ramadan fasting on classically activated, oxidative stress and inflammation of macrophage, *IOSR J. Pharm.* 3 (2013) 14–22.
- [66] V. Askari, A. Alavinezhad, M.H. Boskabady, The impact of “Ramadan fasting period” on total and differential white blood cells, haematological indices, inflammatory biomarker, respiratory symptoms and pulmonary function tests of healthy and asthmatic patients, *Allergol. Immunopathol.* 44 (2016) 359–367.
- [67] A.S. BaHammam, S.R. Pandi-Perumal, M.A. Alzoghbi, The effect of Ramadan intermittent fasting on lipid peroxidation in healthy young men while controlling for diet and sleep: a pilot study, *Ann. Thorac. Med.* 11 (2016) 43.
- [68] N.M. Harder-Lauridsen, A. Rosenberg, F.B. Benatti, J.A. Damm, C. Thomsen, E.L. Mortensen, et al., Ramadan model of intermittent fasting for 28 d had no major effect on body composition, glucose metabolism, or cognitive functions in healthy lean men, *Nutrition* 37 (2017) 92–103.