

Effects of Ramadan Fasting on the Regulation of Inflammation

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ARTICLE INFO	ABSTRACT
<p><i>Article type:</i> Review article</p> <hr/> <p><i>Article History:</i> Received: 20 Jan 2016 Accepted: 15 Mar 2016 Published: 20 Mar 2016</p> <hr/> <p><i>Keywords:</i> Cardiovascular disease Inflammation Metabolic syndrome Ramadan fasting</p>	<p>As a model of intermittent fasting, the month of Ramadan is a valuable opportunity to investigate the effects of dietary modifications on human metabolism. Fasting improves insulin sensitivity, while reducing the risk of atherogenesis, oxidative stress, and inflammation. Inflammation plays a pivotal role in the pathogenesis of different disorders, including atherosclerosis, metabolic syndrome, and cardiovascular diseases. Ramadan fasting could positively modulate cardiovascular risks and improves the features of metabolic syndrome through the suppression of inflammatory responses. This review aimed to explore recent studies evaluating the regulatory role of the nutritional status of fasting in the regulation of inflammation in patients with inflammatory diseases. According to the literature, fasting has significant anti-inflammatory effects and could be a complementary therapeutic approach in the treatment of inflammatory disorders.</p>

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Introduction

Fasting in the month of Ramadan, the ninth month in the lunar Islamic year, is the religious duty of all healthy adult Muslims. While fasting from sunrise (Sahur) to sunset (Iftar), Muslims refrain from eating, drinking liquids, smoking, and sexual activity (1). Fasting is recommended as a medical treatment for various conditions, including weight control (2,3), resting the digestive tract, and reducing lipid levels (4-7).

A constant dietary restriction could positively influence the biochemical and physiological functions, as well as the inflammatory state of the body (6, 8). Inflammatory status of the body, which is characterized by the up-regulation of cytokines, chemokines, and other inflammatory mediators, contributes to the pathogenesis of some proinflammatory disorders, such as atherosclerosis (9), insulin resistance (10),

cardiovascular diseases (11), and cancer (12).

Several experimental studies have confirmed the numerous health benefits of fasting in Ramadan. According to the literature, Ramadan fasting could enhance insulin sensitivity (13), while reducing the risk of atherogenesis, oxidative stress, and inflammation (14, 15). Furthermore, it has been suggested that fasting attenuates the inflammatory status of the body through inhibiting the expression of proinflammatory cytokines and chemokines (16, 17).

The majority of the studies in this regard have focused on the effect of fasting on inflammation through investigating the serum levels of inflammatory markers, such as C-reactive protein (CRP), leukocyte count, cytokines, and chemokines. These markers could be used to differentiate between healthy individuals and those with

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inflammatory diseases. Studies in this regard have suggested that Ramadan fasting through down-regulation of the expression of proinflammatory molecules could beneficially affect inflammation and decrease the destructive symptoms of inflammatory diseases in the patients.

This review aimed to update recent findings regarding the regulatory effects of Ramadan fasting on inflammation and the safety of this practice for patients with inflammatory disorders.

Fasting and inflammation

Extensive research has been conducted to investigate the effects of Ramadan fasting on inflammation. For instance, in one report by Aksungar et al., it was demonstrated that inflammatory biomarkers, such as interleukin-6 (IL-6) and CRP, had a significant reduction after the month of Ramadan in male and female fasting individuals compared to the basal values (one week before Ramadan). Therefore, they concluded that prolonged intermittent fasting in Ramadan could positively affect the inflammatory state of the body (15).

These findings are in line with the results obtained by Faris et al., who stated that Ramadan fasting led to a significant reduction in the circulating levels of proinflammatory cytokines, including IL-1 β , IL-6, and tumor necrosis factor alpha (TNF- α) (16). Low level of reactive oxygen species and down-regulation of nuclear factor κ B (NF- κ B) signaling may result in the reduction of cytokine levels during Ramadan fasting (18). NF- κ B is a major proinflammatory signaling pathway, which regulates the expression of proinflammatory cytokines, such as IL-1 β , IL-6, and TNF- α (19).

In another study, Unalacak et al. reported that some inflammatory mediators, such as IL-2, IL-8, and TNF- α , decreased after fasting (6). Furthermore, Mohajeri F et al. stated that during Ramadan fasting, serum levels of CXC chemokines (CXCL1, CXCL10, and CXCL12) decreased (17), which is suggestive of the fact that through the suppression of inflammatory chemokines, fasting could inhibit inflammatory responses in individuals. Moreover, fasting has been shown to reduce oxidative stress and inflammation in different body tissues, including the brain (18).

In an animal model of stroke, Arumugam et al. indicated that the production of TNF- α and IL-6, the

cytokines involved in neuronal degenerative processes, was suppressed through intermittent fasting in young mice, resulting in the protection of neurons against ischemic injury. In rats, intermittent fasting and calorie restriction were observed to improve cardiovascular complications and protect the myocardium against ischemia-induced cell damage and inflammation (20, 21).

In overweight adults, caloric restriction has been shown to decrease disease symptoms in patients with moderate asthma, as well as the markers of oxidative stress and inflammation in the blood, including TNF- α and brain-derived neurotrophic factor (BDNF) (22). Studies conducted on asthma patients and animal models of asthma have confirmed TNF- α and BDNF (23, 24) as important mediators of airway inflammation. Interestingly, calorie restriction has also been shown to slow the process of aging effectually and protect the heart of rats against age-induced inflammation and fibrosis via inhibiting oxidative damage and NF- κ B activation (25).

In general, these findings indicate that fasting could effectively reduce inflammatory processes through the down-regulation of pro-inflammatory cytokines and chemokines.

Fasting and metabolic syndrome

Metabolic syndrome is caused by a combination of several medical conditions, including abdominal obesity, hyperlipidemia, hypertension, insulin resistance, and hyperglycemia. Metabolic syndrome is considered a major risk factor for type II diabetes mellitus (26). Inflammation is directly associated with the occurrence of metabolic syndrome (27). According to the literature, IL-6 and CRP increase the risk of hyperglycemia, insulin resistance, and type II diabetes (28). As mentioned earlier, inflammatory cytokines, such as IL-6 and CRP, reduce significantly as a result of short-term and long-term intermittent fasting (15). Therefore, it could be concluded that fasting improves the features of metabolic syndrome through the down-regulation of inflammatory responses.

In support of this hypothesis, Faris et al. claimed that the expression of TNF- α and IL-6 is likely to decrease with Ramadan fasting in healthy volunteers, which is positively correlated with weight loss and reduced body fat percentage during the month of Ramadan (16).

Furthermore, it is believed that TNF- α and IL-6 inhibit lipoprotein lipase (LPL) activity leading to the down-regulation of TNF- α and IL-6 in fasting individuals. This will result in increased LPL activity, which is accompanied by the reduction of the body fat mass (29). Increased LPL activity during the month of Ramadan has been shown to increase LPL-catalyzed reaction products, such as free fatty acids (30).

Since the concentration of blood glucose is low in fasting individuals, fat oxidation increases more significantly compared to carbohydrates. As such, body fat percentage and body weight are expected to decrease (16, 31). In this regard, a clinical trial was performed to evaluate the effect of Ramadan fasting on the plasma levels of high-sensitivity CRP (hs-CRP) and fibrinogen in patients with obesity and metabolic syndrome (32). According to the findings, fasting plasma glucose, fibrinogen, hs-CRP, body mass index, and waist circumference had a significant reduction after the month of Ramadan, which is suggestive of the beneficial effects of fasting on obese individuals with metabolic syndrome.

In another study, Feizollahzadeh et al. investigated the mechanism through which Ramadan fasting improves human health. According to the results, intermittent fasting in Ramadan significantly increased the serum adiponectin levels of high-risk individuals for type II diabetes (33). Adiponectin is a protein hormone released by the adipose tissue; this hormone plays a regulatory role in the mechanism of insulin resistance (34). Previous studies have demonstrated that the expression of adiponectin decreases in patients with type II diabetes (34). These findings indicate that through the up-regulation of adiponectin, Ramadan fasting could reduce insulin resistance, attenuating the development and severity of type II diabetes in high-risk patients.

In another research in this regard, Ugochukwu NH et al. stated that caloric restriction was effective in reducing diabetic complications through the suppression of inflammatory responses in streptozotocin-induced diabetic rats (35). Moreover, they reported that inflammatory cytokines, such as IL-1 β , IL-4, IL-6, and TNF- α , tended to up-regulate in diabetes; however, the levels of these cytokines significantly decreased due to caloric restriction. Other findings of these researchers indicated that caloric restriction could

reduce IL-6 and TNF- α in the brain of streptozotocin-induced type II diabetic rats (36). It is recommended that further investigation be performed in this regard in order to determine the exact effects of Ramadan fasting on the proinflammatory state of diabetic patients.

Fasting and cardiovascular diseases

Inflammation plays a pivotal role in the pathogenesis of cardiovascular diseases (37). According to the literature, Ramadan fasting positively modulates cardiovascular risk factors in the patients through the suppression of inflammatory responses (15, 16, 38). Previous studies have reported that the levels of inflammatory biomarkers, hs-CRP, and homocysteine significantly decrease during the month of Ramadan compared to the phase before this month (15). Moreover, TNF- α level has been shown to reduce during Ramadan in fasting individuals. TNF- α expression decreases the concentration of high-density lipoprotein (HDL) and increases the level of low-density lipoprotein (LDL) cholesterol, which leads to the regulation of proatherogenic processes in the cardiovascular system (39).

It has been well established that low HDL levels are a major risk factor for atherosclerosis in patients with coronary artery disease (CAD) (40). HDL is associated with several atheroprotective effects. Furthermore, through the down-regulation of endothelial adhesion molecules, HDL inhibits the recruitment of monocytes to the arterial wall (41, 42), while it could also neutralize the proinflammatory activity of CRP (43). Several studies have reported an elevation in HDL and apolipoprotein A-I (apo A-I) levels during Ramadan fasting (44-47).

Recent studies have suggested that serum amyloid-A (SAA) is essentially involved in the process of atherogenesis (48, 49). SAA displaces apo A-I from HDL, converting HDL from a protective agent to a pro-atherogenic molecule. Furthermore, SAA enhances the recruitment of monocytes to the arterial wall increasing the delivery of cholesterol to arterial wall cells, which contributes to the initiation and progression of atherosclerotic lesions (48). Level of SAA increases due to inflammatory conditions, such as obesity (49, 50), insulin resistance (51), metabolic syndrome (52), diabetes (50, 51), and rheumatoid arthritis (53).

In a cross-sectional study, Asadi et al. evaluated the level of SAA as an inflammatory biomarker in patients with cardiovascular disease who practiced fasting during the month of Ramadan (53). According to the findings, the level of SAA, as an acute-phase inflammatory protein and useful indicator of cardiovascular risk, was significantly lower after the month of Ramadan (54). This was indicative of the fact that Ramadan fasting exerts protective effect on the cardiovascular system partially through the down-regulation of SAA level.

Previous research has demonstrated that Ramadan fasting regulates inflammatory responses, leukocyte infiltration, and pro-inflammatory cytokine production during myocardial ischemia (MI). In this regard, Ruiqian Wan et al. claimed that through the inhibition of inflammatory responses, intermittent fasting diminished myocardial tissue damage in a model of myocardial infarction (55). Furthermore, they observed that plasma IL-6 levels were significantly lower following MI in rats preserved on an intermittent fasting diet compared to those with a controlled dietary plan. Similarly, the results of another study indicated that intermittent fasting diet with energy restriction diminished the myocardial damage induced by ischemic injury in an experimental acute myocardial infarction in rats (56).

In general, the findings of the aforementioned studies confirm the positive and protective effects of fasting on atherosclerotic diseases, as well as patients with CAD.

Conclusion

According to the results of this review, Ramadan fasting not only regulates the biochemical and physiological processes of the body, but it also elicits potent anti-inflammatory responses in both human and animal models. Intermittent fasting during Ramadan down-regulates the expression of proinflammatory cytokines, chemokines, and other proinflammatory mediators. The results of cellular and animal studies presented in this review revealed that Ramadan fasting could elicit potent anti-inflammatory responses under inflammatory conditions, such as metabolic syndrome and cardiovascular disorders. However, further studies are required as to clarify the molecular mechanism of the

protective signaling functions of Ramadan fasting in order to consider this practice as a complementary therapeutic approach in the treatment of inflammatory disorders

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