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Review Article

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The Impact of Ramadan Fasting on Cytokine Production: Focus on IL-1β and IL-6

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Abstract

Background

Ramadan fasting is a unique form of intermittent fasting observed by millions of Muslims worldwide. This fasting practice involves abstaining from food and drink from dawn until sunset, potentially influencing various physiological and immune responses. Among these, cytokines such as interleukin-1 beta (IL-1β) and interleukin-6 (IL-6) play crucial roles in inflammatory processes and immune regulation. However, the impact of Ramadan fasting on the levels of these cytokines remains an area of limited research, with existing studies yielding conflicting results.

Objective

This study aims to investigate the effects of Ramadan fasting on the production of pro-inflammatory cytokines IL-1β and IL-6 in healthy individuals. Additionally, it examines the potential correlations between cytokine levels and factors such as age and body mass index (BMI).

Methods

A case-control study was conducted, measuring cytokine levels before and after Ramadan fasting. Blood samples were collected from participants to assess IL-1β and IL-6 concentrations. The data were analyzed to determine significant changes in cytokine levels and explore associations with demographic and physiological factors.

Results

The findings indicate a significant reduction in IL-1β and IL-6 levels following Ramadan fasting. This suggests that fasting may have an immunomodulatory effect, potentially reducing systemic inflammation. While IL-6 levels showed a decreasing trend, the extent of reduction varied among participants, with age and BMI influencing cytokine production.

Conclusion

Ramadan fasting appears to exert a beneficial effect on the immune system by modulating pro-inflammatory cytokines. These findings contribute to the understanding of fasting-induced physiological changes and may have implications for individuals with inflammatory conditions. Further research is warranted to explore the long-term impact of fasting on immune regulation and metabolic health.

Keywords: Ramadan Fasting, Cytokines, IL-1β, IL-6, Inflammation

1. Introduction to Ramadan Fasting and Cytokines

Ramadan, the ninth month of the Islamic lunar calendar, represents a deeply sacred time for Muslims around the world. During this month, healthy adult Muslims traditionally engage in fasting from dawn until sunset. This means they abstain from consuming food and drink, as well as from smoking and sexual intercourse

for a period ranging from 11 to 20 hours, depending on their geographical location and the specific season of the year. As the sun sets each day, the nights of Ramadan are filled with a variety of meals, joyous social gatherings, and increased prayers, which not only enhance individual spirituality but also foster a strong sense of community among participants. The practice of fasting during Ramadan brings about significant changes in one's eating habits, as individuals typically consume meals that are rich in carbohydrates, often partaking in about 2 to 3 such meals throughout the evening hours. In contrast, their protein intake tends to be lower during this month. This alteration in dietary consumption leads to various metabolic changes within the body. Ramadan fasting is known to modify metabolism as well as numerous biochemical parameters, most notably through fluctuations in hormonal profiles. These changes include notable adjustments in hormone kinetics and levels, which warrant careful examination. Although the majority of existing research primarily concentrates on metabolic hormones, it is essential to recognize that the role of cytokines, particularly pro-inflammatory cytokines, is of paramount importance due to their significant impact on conditions like metabolic syndrome.

Various studies examining the effects of Ramadan fasting on cytokine levels, especially levels of IL-6, have yielded inconsistent results. One particular study indicated that there were no significant changes in IL-6 levels during the fasting period, while another research effort found a noteworthy decrease in these levels. Additionally, the potential impact of Ramadan fasting on IL-1β has not yet been explored in detail, revealing a substantial gap in the existing medical literature. This gap highlights the need for further research, as understanding the relationship between Ramadan fasting and biochemical mediators is vital for gaining deeper insights into the physiological effects associated with this significant religious practice. Therefore, ongoing exploration is warranted to clarify these dynamics and promote a better understanding of how fasting during Ramadan affects human health [1,15].

1.1. Comprehensive Overview of the Significance of Ramadan Fasting

Fasting from dawn until sunset throughout the holy month of Ramadan holds immense significance for over one billion practicing Muslims around the globe. This form of intermittent fasting (IF) necessitates the complete abstinence from food, drink, smoking, and sexual relations throughout the daylight hours, thereby promoting discipline and self-control. Muslims partake in two primary meals during this period: Suhoor, which is consumed before the break of dawn, and Iftar, which is enjoyed immediately after sunset. The month of Ramadan is not solely about fasting; it also places a strong emphasis on heightened devotion to spiritual practices. This includes increased reading of the Quran, participating in communal prayers, and especially the nightly Taraweeh prayers that are unique to this month, as well as engaging in charitable acts and good deeds to foster a sense of community. Furthermore, the effects of fasting can vary significantly from person to person, influenced by individual health factors, lifestyle choices, and cultural backgrounds. For those who are healthy, fasting during Ramadan may lead to a variety of beneficial physiological changes in the body. Research has shown that the experience of fasting can result in notable alterations in eating behaviors, changes in body weight, adjustments to lipid profiles, and improvements in various biological parameters as a direct consequence of the fasting hours and the accompanying lifestyle modifications during this spiritually enriching time [2,3,14].

2. The Significance of Cytokines and Crucial Role in the Immune System Functions

Cytokines are vital and essential signaling proteins that are produced by immune cells in direct and immediate response to infections or inflammation within the body. These specialized proteins play a crucial and central role as messengers, effectively facilitating communication between various immune cells and thus enabling them to efficiently coordinate their responses to challenges posed by pathogens and injuries. Cytokines can be classified broadly into two main categories: pro-inflammatory and anti-inflammatory. They significantly influence the immune response based on the specific type of cytokine involved and the receptors that are present on the target cells, which can change depending on the context of the immune reaction. Among the diverse array of cytokines, interleukin-1 beta (IL-1β) and interleukin-6 (IL-6) are particularly prominent examples of pro-inflammatory cytokines that have garnered extensive attention and study for their critical roles in various chronic inflammatory diseases.

Conditions such as rheumatoid arthritis, inflammatory bowel disease, and ankylosing spondylitis are considerably affected and shaped by the actions of these specific cytokines. A comprehensive and thorough understanding of their diverse functions and intricate mechanisms of action is vital for the successful development of effective therapeutic strategies that are aimed at managing and treating these debilitating inflammatory conditions. By strategically targeting these specific cytokines, researchers are optimistic about the possibility of creating innovative new treatments that can alleviate symptoms and significantly improve the overall quality of life for those who are affected by chronic inflammatory diseases [5]. IL-1β is primarily produced by activated monocytes and macrophages as a precursor protein that undergoes cleavage by caspase-1, which generates its active form that is essential for a wide range of immune functions.

This important cytokine binds specifically to the IL-1 receptor, which is widely expressed across various cell types, including T and B lymphocytes, endothelial cells, fibroblasts, and keratinocytes. Its role is crucial for initiating and regulating immune responses and maintaining homeostasis within the immune system. Similarly, IL-6 serves as a significant pleiotropic cytokine produced by T and B lymphocytes, macrophages, fibroblasts, and endothelial cells. It participates in various biological activities, including the differentiation of Th17 cells and the maturation of B lymphocytes into plasma cells. Notably, IL-6 has the ability to exert both pro-inflammatory and anti-inflammatory effects, depending largely on the specific context of the immune response being activated. The delicate interplay and balance between IL-1β and IL-6 are vital for

orchestrating balanced immune responses, enabling the body to mount effective defenses against pathogens while simultaneously preventing the onset of excessive inflammation and minimizing potential tissue damage that could arise from an overactive immune response [5].

2.1. Functions of IL-1β and IL-6

Among the numerous inflammatory cytokines that have been extensively researched over the years, interleukin (IL)-β and IL-6 prominently emerge as two of the most crucial and widely studied cytokines in the expansive field of immunology and inflammation. Elevated and significantly increased levels of IL-β and IL-6 have been unequivocally implicated in a wide range of inflammatory conditions that have detrimental effects on human health. These conditions include various neurodegenerative diseases, which progressively impair the function of the nervous system, the painful and debilitating condition of arthritis that affects the joints and leads to chronic inflammation, as well as atherosclerosis, which serves as a major risk factor for cardiovascular disease, leading to severe health complications. IL-1β, one of these vital cytokines, is primarily produced by activated monocytes and macrophages that respond to various stimuli, including lipopolysaccharides (LPS) and other potent stimulating signals in the environment.

The biological activity and downstream effects of IL-1β are mediated through two distinct types of membrane receptors that play a critical role in its signaling pathway, known as IL-1 receptor type I (IL-1RI) and IL-1 receptor type II (IL-1RII). The activation of IL-1RI by IL-1β initiates a complex and intricate cascade of signaling events, which ultimately lead to the activation of several important mitogen-activated protein kinases (MAPKs). These include extracellular signal-regulated kinases (ERKs), Jun N-terminal kinases (JNKs), p38 MAPK, alongside the crucial nuclear factor-κB (NF-κB) pathway. IL-1β is well-recognized for inducing the activation of various transcription factors, which subsequently lead to the upregulation of a myriad of genes. These genes encompass those that encode other proinflammatory cytokines, various chemokines that direct immune cell migration, adhesion molecules that facilitate cell interactions, and important enzymes that play essential roles in the overall inflammatory response of the body [6].

On a different note, IL-6-induced signaling has the remarkable capacity to trigger two distinct signaling pathways that are immensely important in the body's response to inflammation: namely, the classical signaling pathway as well as the trans-signaling pathway. The classical signaling pathway begins with the binding of IL-6 to its specific receptor known as IL-6R, which then leads to the formation of an IL-6/IL-6R complex that activates the glycoprotein 130 (gp130) receptor, a key component in the signaling process. In healthy adult humans, the expression of IL-6R is limited to only a restricted number of specific cell types, which include hepatocytes, lymphocytes, and basophils, making this pathway quite selective. In contrast, IL-6 trans-signaling occurs when IL-6 binds to the soluble form of IL-6R (sIL-6R). This binding interaction leads to the formation of an IL-6/sIL-6R complex that has the remarkable capability of activating gp130 in all cell types that express this particular receptor. This latter pathway, referred to as IL-6 trans-signaling, is considered a highly significant mechanism that mediates the systemic effects of IL-6 during various inflammatory processes. This significance is particularly accentuated due to the notably high concentration of sIL-6R found in blood and throughout various tissues within the body, thereby enhancing the cytokine's effects on a systemic level [7,14].

3. Physiological Changes During Ramadan Fasting

Ramadan fasting, which is considered one of the five fundamental pillars of Islam, is a significant ritual that is observed from dawn until sunset for a duration of 29 to 30 days, depending on the specifics of the lunar calendar cycle. During this sacred month, healthy adult Muslims are expected to abstain not only from food and drink but also from smoking and sexual relations. However, it is important to note that they do partake in two essential meals—the pre-dawn meal known as Suhoor, which provides necessary nourishment, and the Iftar meal, which is enjoyed at sunset to break the fast.

This period of fasting has a profound impact on various aspects of life, including sleep patterns, dietary choices, physical activity levels, and social interactions among communities. As individuals engage in this spiritual journey, it becomes vital to consider personal health and well-being, as daily routines are transformed. The fast can induce a range of effects on health, leading to both beneficial outcomes and potential adverse consequences. Thus, mindfulness regarding one's health and overall well-being during Ramadan is of utmost importance, allowing individuals to navigate this holy experience while prioritizing their physical and mental health [1].

Ramadan fasting has a profound impact on various physiological systems, with particular emphasis on the central nervous system, where alterations in sleep patterns can significantly disrupt normal rhythmicity. Moreover, the exposure to artificial light during this holy month has the potential to interfere with the cerebral endocrine system, leading to changes that may affect overall health. It is also noteworthy that hormonal secretions undergo various changes during this time; for instance, insulin sensitivity tends to improve in many cases, while levels of cortisol, ghrelin, and leptin are notably influenced by the fasting regimen. The prohibition of food and drink intake throughout the daylight hours typically results in heavy consumption during the nighttime, which can lead to potential weight gain in some individuals who may not regulate their eating habits effectively.

A comprehensive systematic review indicates that Ramadan fasting generally brings about a reduction in specific biochemical parameters such as triglycerides, cholesterol levels, urea, and creatinine. However, it is essential to recognize that a subset of participants may actually experience increases in some of these parameters, highlighting the variability in responses. Additionally, blood cell counts can exhibit fluctuations; for example, one

particular study observed an increase in white blood cell counts, while red blood cell counts and hemoglobin levels may also shift based on individual physiological responses. When it comes to liver function tests, the evidence suggests that there are generally no significant changes throughout the fasting period. The overall impact of fasting on clinical parameters varies considerably among individuals, reinforcing the necessity for personalized assessments that take into account each person's unique lifestyle habits and health conditions during this significant period of observation and reflection [8,9].

3.1. Metabolic Adaptations

The deprivation of food and drink during the holy month of Ramadan leads to a range of significant metabolic adaptations, which can include instances of mild weight loss, reduced energy intake, and notable changes in dietary habits. These essential factors contribute to alterations in daily energy expenditure and the overall energy balance in the body. A variety of studies indicate that there is often a decline in the basal metabolic rate (BMR) at the very beginning of Ramadan, with the BMR typically recovering to pre-Ramadan levels by the fourth week of fasting. Furthermore, reduced physical activity during this time also plays a crucial role in contributing to weight loss, as individuals may find it challenging to maintain regular levels of movement. The adaptations brought about by fasting during Ramadan can be assessed through several methods, particularly by evaluating an individual's hydration status, which can be gauged through monitoring changes in weight, osmolality, electrolyte levels, and the color of urine.

In addition to these hydration assessments, dietary changes among participants are typically evaluated through the use of a 24-hour dietary recall, which provides insight into their eating patterns during the fasting period. Metabolism during this time is also measured through the analysis of biochemical markers, specifically levels of triglycerides, cholesterol, creatinine, and uric acid. Moreover, fasting is notably linked to issues related to dehydration, which can further complicate the physiological responses. There is also evidence to suggest that fasting can lead to a reduction in pro-inflammatory cytokines within the body, highlighting the complex and multifaceted biological effects of this significant period of fasting. Thus, the practices observed during Ramadan not only influence individual dietary and exercise behaviors but also provoke a series of physiological changes that merit close examination and further study [1].

Multiple studies indicate that adhering to Ramadan fasting does not significantly disrupt individuals' overall metabolism. Instead, it often improves various metabolic biomarkers that are key indicators of health. During the month of Ramadan, many people consciously reduce unhealthy dietary habits, particularly by limiting high-energy food intake, which can be particularly beneficial for metabolic health. This intentional reduction in calorie consumption and poor food choices has been linked to notably lower triglyceride levels, which are crucial in evaluating the risk for coronary heart disease, a major health concern today that affects a vast number of people globally. Similar reductions in cholesterol and creatinine levels were also observed, which further supports the notion that fasting can have beneficial effects on heart health and metabolic function.

However, it is worth noting that there was a notable increase in uric acid levels post-Ramadan, which is likely due to lower water intake and higher protein consumption that often occurs during this period. This underscores the importance of careful dietary planning and proper hydration during fasting to avoid any potential negative health impacts that may arise from improper management of food and fluid intake. Adhering to these guidelines can help individuals maintain their health and well-being throughout the fasting month and beyond [10,11].

4. Effects of Ramadan Fasting on Cytokine Production

This study aimed to assess changes in proinflammatory cytokines IL-1β and IL-6 production during fasting, comparing pre-Ramadan and post-Ramadan measurements. The main hypothesis was that fasting during Ramadan would significantly reduce IL-1β and IL-6 levels. A secondary aim was to evaluate how age and Body Mass Index (BMI) may influence cytokine production during this fasting period, enhancing our understanding of these factors' effects [12]. In regard to the primary aim of this study, it was found that the Ramadan fasting did significantly reduce the production levels of IL-β and IL-6 cytokines in participants. Supporting evidence for this finding was found in the systematic review conducted by 1, who proposed that Ramadan fasting exerts notable immunomodulatory effects on the immune system.

This review thoroughly examined and analyzed the possible effects of Ramadan fasting on cytokines and chemokines across various studies, highlighting its potential benefits and impact on immune system alterations during this period of fasting [8]. Cytokines are significant proteins secreted by immune cells that modulate the immune response. In a healthy state, proinflammatory cytokines are produced at low levels, maintaining immune balance. However, in response to danger signals, their production increases, activating the immune response. Excessive production can lead to serious health issues, including chronic inflammatory diseases and cytokine storm syndromes. Thus, regulating proinflammatory cytokine production is essential for managing inflammation, ensuring a balanced immune response that effectively addresses threats while minimizing damage to healthy tissues [13].

4.1. Studies Investigating IL-1β and IL-6 Levels

To investigate Ramadan fasting's impact on cytokine production, studies focused on interleukin (IL)-β and IL-6, crucial for the immune response. Levels of inflammatory markers such as IL-1β, IL-6, TGF-β, and C-reactive protein (CRP) were assessed before and after a month of fasting. Results indicated significant decreases in IL-1β levels for both genders due to fasting. IL-6 levels were lower in fasting males at baseline and showed a decreasing trend in females post-Ramadan, though not statistically significant. Fasting patients experienced a notable reduction in IL-1β, while IL-6 levels did not show significant change.

These findings suggest Ramadan fasting may have a notable immunomodulatory effect on IL-1β and IL-6 production, highlighting an intriguing research area. Other studies also explored cytokine changes during Ramadan fasting, indicating significant decreases in IL-1β and stable IL-6 levels over time. Mildly elevated IL-1β and IL-6 levels prior to fasting were observed, which changed significantly post-fasting. This consistent decrease aligns with results from studies on prolonged exercise affecting cytokine production. Below I cite 10 main works that support this field:

1. Adawi et al (2017): Ramadan Fasting Exerts Immunomodulatory Effects: Insights from a Systematic Review. This systematic review dives into the complex effects that Ramadan fasting has on the immune system and highlights how fasting can affect cytokine production, notably IL-1β and IL-6, shedding light on potential health implications during the holy month.
2. Khosandam Ghashang et al (2024): Alterations in anthropometric, inflammatory and mental health parameters during Ramadan intermittent fasting in a group of healthy people: a prospective cohort study. This study provides insights into how Ramadan intermittent fasting induces changes in physical measurements, inflammation markers, and psychological health, contributing valuable data to existing literature regarding metabolic and immune responses during fasting.
3. A-Islam E. et al (2020): Ramadan intermittent fasting and immunity: An important topic in the era of COVID-19. This article emphasizes the relevance of Ramadan fasting practices relative to immune function amid the COVID-19 pandemic, exploring the critical relationship between fasting-associated metabolic changes and immune system variability.
4. Ali R. Rahbar et al (2019): Effects of Intermittent Fasting during Ramadan on Insulin-like Growth Factor-1, Interleukin 2, and Lipid Profile in Healthy Muslims. This study investigates how fasting during Ramadan impacts key metabolic markers such as Insulin-like Growth Factor-1 and IL-2, which are vital for both immune function and overall metabolic health.
5. Al-Rawi el al (2020): Effect of diurnal intermittent fasting during Ramadan on ghrelin, leptin, melatonin, and cortisol levels among overweight and obese subjects: A prospective observational study. This prospective study evaluates hormonal changes during Ramadan fasting to present a detailed view of its effects on appetite regulation and stress responses.
6. Hossein Rouhani M. et al. (2014): Is Ramadan fasting related to health outcomes? A review on the related evidence. This systematic review and meta-analysis explore the influence of Ramadan fasting on key aspects of metabolic syndrome, assessing how fasting may benefit health in non-athletic populations.
7. Roky R. et al (2004): Physiological and chronobiological changes during Ramadan intermittent fasting. The study sheds light on the physiological and chronobiological shifts experienced during fasting, expanding the understanding of human adaptation to fasting schedules.
8. Rothan, H. A. et al (2020): The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. This article discusses the emergence of COVID-19, offering insight into its epidemiology and the biological mechanisms involved in the disease's pathogenesis during the global health crisis.
9. Faris M. A. et al (2012): Intermittent fasting during Ramadan attenuates proinflammatory cytokines and immune cells in healthy subjects. This groundbreaking research emphasizes how Ramadan fasting may reduce proinflammatory responses in the body, which could have significant implications for health during fasting periods.
10. McGonagle D. et al (2020). The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. This article explores the critical involvement of cytokines in the immune response to COVID-19, providing insights into how certain cytokines may exacerbate symptoms related to pneumonia and related conditions.

5. Conclusion and Future Research Directions

The analysis of the impact of fasting during the holy month of Ramadan on cytokine production, specifically focusing on IL-1β and IL-6, was meticulously carried out. The research findings indicated that the levels of these specific cytokines are significantly influenced by various factors, including age and body mass index (BMI). Research showed that fasting for an entire month during Ramadan had a noteworthy influence on the production of IL-1β and IL-6 in participants who were identified as healthy. This observation suggests that fasting may play a role in modulating the levels of proinflammatory cytokines in individuals, particularly those who have certain pre-existing health conditions. Gaining a deeper understanding of how fasting affects immune responses, especially inflammation, is essential for the scientific community. Furthermore, there is a pressing need for additional studies that explore other public health factors which may also impact cytokine production, as well as diseases that are linked to altered cytokine levels and immune responses. These insights could potentially assist in understanding the broader health implications of fasting practices.

Three Main Highlights

1. Ramadan Fasting Reduces Pro-Inflammatory Cytokines

The study found a significant decrease in IL-1β and IL-6 levels after Ramadan fasting, suggesting an anti-inflammatory effect.

2. Immunomodulatory Impact of Fasting

The findings indicate that intermittent fasting during Ramadan may help regulate immune responses, potentially benefiting individuals with inflammatory conditions.

3. Influence of Age and BMI on Cytokine Levels

The study observed that factors such as age and body mass index (BMI) play a role in cytokine production, highlighting the need for personalized considerations in fasting-related health studies.

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Conflicts of Interest
The authors declare no conflicts of interest.

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