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Review

The Impact of Ramadan Fasting on Cytokine Production, with a 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, is a sacred time when healthy adult Muslims fast from dawn until sunset, abstaining from food, drink, smoking, and sexual intercourse for 11 to 20 hours depending on location and season. Nights are filled with meals, social gatherings, and increased prayers, enhancing community and spirituality. This fasting leads to a shift in eating habits, with individuals consuming 2 to 3 carbohydrate-rich meals, while protein intake is lower. Ramadan fasting alters metabolism and various biochemical parameters, notably hormonal profiles, with changes in hormone kinetics and levels. While most research focuses on metabolic hormones, the role of cytokines, especially pro-inflammatory ones, is crucial as they impact metabolic syndrome. Studies on Ramadan fasting's effects on cytokine levels, particularly IL-6, present conflicting results. One study found no significant changes in IL-6 levels, while another noted a significant decrease. The impact of Ramadan fasting on IL-1β remains unexplored, highlighting a gap in literature. Overall, the relationship between Ramadan fasting and biochemical mediators warrants further exploration to understand the physiological effects of this religious practice. [1]

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1.1. Comprehensive Overview of the Significance of Ramadan Fasting

Fasting from dawn until sunset during Ramadan is vital for over a billion Muslims. This form of intermittent fasting (IF) involves abstaining from food, drink, smoking, and sexual relations during daylight, with two main meals: Suhoor before dawn and Iftar after sunset. Ramadan also emphasizes increased devotion, including reading the Quran, communal prayers, especially the nightly Taraweeh, and charitable acts. The effects of fasting can vary based on individual health, lifestyle, and cultural background. For healthy individuals, fasting may lead to positive physiological changes. Research indicates alterations in eating behaviors, body weight, lipid profiles, and biological parameters due to fasting and lifestyle changes. [2,3]

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

Cytokines are essential signaling proteins produced by immune cells in response to infections or inflammation. They act as messengers, allowing immune cells to communicate and coordinate their responses effectively. Cytokines can be pro-inflammatory or anti-inflammatory, significantly influencing the immune response based on the type of cytokine and its receptors on target cells. Interleukin-1 beta (IL-1β) and interleukin-6 (IL-6) are prominent pro-inflammatory cytokines extensively studied for their critical roles in chronic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, and ankylosing spondylitis. Understanding their functions is vital for developing therapeutic strategies for managing these inflammatory conditions. [4]

IL-1β is primarily produced by activated monocytes and macrophages as a precursor protein, which is cleaved by caspase-1 to generate its active form essential for immune functions. This cytokine binds to the IL-1 receptor, widely expressed on various cell types, including T and B lymphocytes, endothelial cells, fibroblasts, and keratinocytes, crucial for immune responses and homeostasis. Similarly, IL-6 is a significant pleiotropic cytokine produced by T and B lymphocytes, macrophages, fibroblasts, and endothelial cells, participating in various activities, including Th17 cell differentiation and B lymphocyte maturation into plasma cells. IL-6 can exert pro-inflammatory and anti-inflammatory effects, depending on the immune context. The interplay between IL-1β and IL-6 is vital for balancing immune responses, enabling effective pathogen defense while preventing excessive inflammation and tissue damage. [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

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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]

3. Physiological Changes During Ramadan Fasting

Ramadan fasting, one of Islam's five pillars, is observed from dawn until sunset for 29 to 30 days based on the lunar calendar. During this holy month, healthy adult Muslims abstain from food, drink, smoking, and sexual activity. However, they consume Suhoor before dawn and Iftar at sunset, which are important meals for nourishment. This fasting period significantly affects sleep, dietary choices, physical activity, and social interactions. It's essential to consider individual health as routines change, as the fasting can lead to both positive and negative health impacts. Mindfulness regarding health and well-being is crucial. [8]

Ramadan fasting significantly affects physiological systems, especially the central nervous system, where sleep pattern changes alter rhythmicity. Exposure to artificial light can disrupt the cerebral endocrine system. Hormonal secretions also change; insulin sensitivity typically improves, while cortisol, ghrelin, and leptin levels are influenced by fasting. Food and drink intake is prohibited during the day, leading to heavy consumption at night, which may result in weight gain for some individuals. A systematic review shows that Ramadan fasting generally reduces certain biochemical parameters like triglycerides, cholesterol, urea, and creatinine, although some participants may experience increases. Blood cell counts vary, with one study noting an increase in white blood cells, while red blood cells and hemoglobin may fluctuate based on individual responses. Liver function tests generally show no significant changes. The impact of fasting on clinical parameters varies widely among individuals, emphasizing the importance of personalized assessments based on unique lifestyle habits during this period. [9]

3.1. Metabolic Adaptations

Deprivation of food and drink during Ramadan leads to significant metabolic adaptations, including mild weight loss, decreased energy intake, and changes in dietary habits. These factors result in altered daily energy expenditure and energy balance. Studies indicate a decline in basal metabolic rate (BMR) at the start of Ramadan, recovering to pre-Ramadan levels by the fourth week of fasting. Reduced physical activity also contributes to weight loss. Fasting adaptations can be assessed through hydration status via weight, osmolality, electrolytes, and urine color. Dietary changes are evaluated through 24-hour dietary recall, while metabolism is measured by levels of triglycerides, cholesterol, creatinine, and uric acid. Fasting is linked to dehydration and a reduction in pro-inflammatory cytokines, highlighting the complex biological effects of this period. [10]

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Multiple studies indicate that adhering to Ramadan fasting does not significantly disrupt individuals' overall metabolism. Instead, it often improves metabolic biomarkers. During Ramadan, many people reduce unhealthy dietary habits, particularly limiting high-energy food intake. This reduction is linked to lower triglyceride levels, indicating a decreased risk of coronary heart disease, a major health concern today. Similar reductions in cholesterol and creatinine levels were observed. However, there was a notable increase in uric acid post-Ramadan, likely due to lower water intake and higher protein consumption. This underscores the importance of careful dietary planning and hydration during fasting to avoid negative health impacts. [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. Thus, these insights into cytokine modulation during Ramadan fasting warrant further exploration of fasting practices' immunological effects.

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5. Conclusion and Future Research Directions for Continued Study in the Field

The impact of fasting during Ramadan on cytokine production, specifically IL-1β and IL-6, was analyzed. The research indicated that these cytokine levels are significantly affected by age and body mass index (BMI). Fasting for a month during Ramadan notably influenced the production of IL-1β and IL-6 in participants classified as healthy. This suggests that fasting may modulate proinflammatory cytokine levels in individuals with certain health conditions. Understanding how fasting affects immune responses, particularly inflammation, is crucial. Moreover, additional studies are needed to explore other public health factors impacting cytokine production and diseases linked to altered cytokine and immune responses, potentially aiding insights into fasting's broader health implications.

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