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Inflammatory Markers: Promising Tools for Diagnosis of Eating Disorders and Response to Treatment

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Eating disorders are important psychiatric conditions with serious implications for physical and mental health. These disorders may be seen in all age groups but are more common in adolescents and young adults. Anorexia nervosa, bulimia nervosa, and binge-eating disorder are the main eating disorders. These disorders are triggered by acute stress regarding distorted body image and identified by persistent changes in eating behaviors. While each eating disorder involves different clinical features, they all share some common risk factors, including genetic predisposition, environmental factors, and psychological triggers. Inflammation is a core mechanism that underlies the pathophysiology of eating disorders. This editorial essay discusses the evidence linking inflammatory markers to eating disorders' etiology, diagnosis, and treatment.

The immune system has a critical role in maintaining the body's homeostasis and responding to outside threats. Inflammatory responses are a form of immune response, aimed at protecting the body from infections, physical, or mental damage. Inflammation is a highly complex process, involving the activation of immune cells, the release of cytokines, and the recruitment of leukocytes to the affected site (1). Acute inflammation is a beneficial response that helps the body to deal with injury, infection, and threats. However, when inflammation persists, it can lead to chronic inflammation, which can trigger tissue damage and impair organ function(2).

The association between inflammation and anorexia nervosa is complex and likely involves multiple pathways (3). One hypothesis is that inflammation may arise as a consequence of severe psychological stress, malnutrition, intestinal dysbiosis, infection, and oxidative stress in anorexia nervosa. Inadequate nutrition and weight loss can cause hormonal and metabolic disturbances that lead to immune system dysregulation and chronic inflammation. Another hypothesis is that neuro-inflammation may underlie the progress of eating disorders. Inflammation can impair brain function and mood regulation, leading to depression and anxiety, which are commonly associated with eating disorders (4). Moreover, inflammation can affect appetite and satiety signals, resulting in disrupted food intake and abnormal eating behaviors (5).

In recent years, several studies have demonstrated a significant relationship between eating disorders especially anorexia nervosa and inflammatory markers. The most studied inflammatory markers that have been linked to anorexia nervosa are interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α)(6). These pro-inflammatory factors are cytokines produced by immune cells. Severe mental stress regarding distorted body image may trigger the neuro-inflammation, activate the toll-like receptors (TLRs), and enhance the production of IL-6 and TNF-α, thereby releasing them into the bloodstream (Figure-1). Raised serum levels of IL-6 and TNF-α have been documented in patients with anorexia nervosa (7). Other inflammatory markers that have been proposed to be altered in patients with anorexia nervosa are interleukin-1 beta (IL-1β), interleukin-10 (IL-10), interleukin-15 (IL-15), tumor necrosis factor-beta (TNF-β), and vascular cell adhesion molecule (VCAM)-1 (6, 7).

Another important inflammatory marker, which its levels in the serum of patients with anorexia nervosa is well documented, is C-reactive protein (CRP). In these patients, the inflammatory response is chronic and low-grade due to ongoing stressors such as social pressure, body image concerns, and fear of weight gain (3). Meanwhile, malnutrition and hormonal changes, such as leptin associated with anorexia nervosa, compromise the

CRP production by the liver, resulting in decreased levels of CRP in the serum (Figure-1). By treating malnutrition in these patients and increasing the BMI, the CRP production by the liver returns to the normal levels. However, there is a controversy about CRP levels in patients with anorexia nervosa. In chronic cases of anorexia nervosa, there may be an increase in CRP due to the severe inflammation, chronic stress, and development of complications such as infections or organ damage. On the other hand, CRP could fluctuate regarding the different course of the disease, comorbid inflammatory conditions, and medications. It is essential to note that CRP levels alone cannot diagnose anorexia nervosa or any other medical condition, and a comprehensive evaluation by a psychiatrist is necessary for accurate diagnosis and management.

Understanding the link between inflammatory markers and eating disorders has important clinical implications. Inflammation markers can be used as a confirmatory tool for diagnosing anorexia nervosa. Additionally, elevated levels of IL-6 and TNF-α and decreased CRP levels have been proposed as potential markers for anorexia nervosa. Along with clinical signs and diagnostic interviews, these markers can help clinicians to identify patients with anorexia nervosa and determine the stage of disease and monitor their progress during treatment.

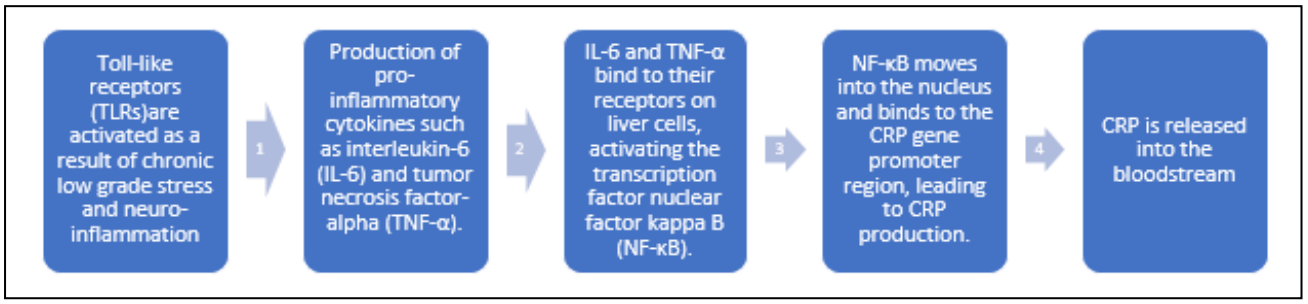

Figure1. The Inflammation Pathway as a Result of Acute and Chronic Low-Grade Stress in Anorexia Nervosa. Steps 1 and 2 are Upregulation of IL-6 and TNF-α as a Result of Inflammation; However, Steps 3 and 4 are Compromised Production of CRP Resulting from Malnutrition and Hormonal Change

There is limited research on the relationship between inflammation and bulimia nervosa (BN) or binge eating disorder (BED). However, clinical manifestations such as dry skin, calluses on the back of the hands (known as Russell's sign), edema, chronic sore throat, inflammation of esophagus and dental erosion due to reflux, and swelling of salivary glands-- especially parotid and submandibular glands due to frequent vomiting-- could be indicative of bulimia nervosa (8, 9). The inflammation may occur due to recurrent episodes of binge eating and self-induced purging in bulimia nervosa, which can lead to gastrointestinal distress and inflammation (8). Moreover, clients with bulimia nervosa may be more susceptible to infections and inflammation due to malnutrition and nutrient deficiencies. Similarly, individuals with binge eating disorder may encounter inflammatory conditions due to severe distress, abdominal fat accumulation, and change in gastrointestinal microbiota (10). However, there is still no consensus in relation to specific markers of inflammation in patients with bulimia nervosa and binge eating disorder. More research is needed to fully understand the role of inflammation and inflammatory markers in these disorders and their potential implications for treatment.

There is limited evidence to support the use of inflammatory markers in assessing eating disorders, and the cost-effectiveness of doing so is unclear. Additionally, the accuracy and reliability of inflammatory marker tests in this context are still being investigated. Although the initial cost of testing for inflammatory markers may be higher, early diagnosis and effective treatment of inflammatory conditions can lead to lower overall healthcare costs by preventing complications and reducing the need for more expensive treatments. Hence, monitoring inflammatory markers for diagnosis and assessing responses to treatment can be cost-effective in certain situations. At this time, there is no recommendation for routinely monitoring inflammatory markers as a diagnostic or treatment tool for eating disorders. However, considering the growing evidence in favor of CRP, IL-6, and TNF-α measurements, such monitoring can be helpful and cost-effective, especially for inpatients suffering from anorexia nervosa. Furthermore, regular monitoring of these inflammatory markers can help healthcare providers adjust treatment plans as needed, which can improve outcomes and reduce the risk of treatment failure or relapse. However, the cost-effectiveness of inflammatory marker monitoring will depend on factors such as the severity of condition, the availability and accuracy of testing methods, and the overall healthcare system context.

Accordingly, we can suggest targeting inflammation as a new therapeutic approach for clinical studies on eating disorders, as well as in clinical settings. Anti-

inflammatory drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), cytokine inhibitors, probiotics, and nutritional interventions that aim to reduce inflammation, such as omega-3 fatty acids, antioxidants and polyphenol rich diets could be used in future studies as potential treatments for decreasing the inflammation and even improving clinical signs of eating disorders.

In conclusion, the pathophysiology and intensity of eating disorders involve an inflammatory response to severe stress. Altered levels of inflammatory markers have been well documented especially in patients with anorexia nervosa. Understanding the pathway of inflammation and the complicated relationship of IL-6, TNF-α, and CRP levels regarding the stage of diseases and treatment is very important. This highlights the importance of addressing inflammation in the treatment of this condition and emphasizes inflammatory markers as indicators of response to treatment. Hence, markers of inflammation can be used as confirmatory tools along with diagnostic interviews and as potential therapeutic targets for eating disorders, especially anorexia nervosa. Additional studies are required to clarify the pathways underlying the association between inflammatory markers and eating disorders and to develop novel treatments that specifically target inflammation.

Conflict of interest

None.

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