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Review Paper

Interaction of Allostatic Load With Immune, Inflammatory, and Coagulation Systems

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ABSTRACT

Dysregulation of the immune system, as well as the endocrine, metabolic, and coagulation systems, has been linked to stress. The type of stressor (acute or chronic) may have a differential effect on immune function, with brief acute stress enhancing some parameters of immunity and chronic stress having a negative effect on many parameters of immune function. The hypothalamic-pituitary-adrenal axis and autonomic (sympathetic and parasympathetic) nervous systems mediate stress and immune functions. Exposure to frequent stressors can lead to repeated physiological arousal, failure to adapt to repeated stressors, failure to terminate the stress response after the stressor has ceased, and inadequate allostatic load to the stressor. The allostatic load provides an overall and body system-specific mechanistic relationship between stressor exposures and health outcomes that may explain minority health disparities. Multiple physiological systems interact at differing levels of activity in this condition. Principally, the severity of allostatic load is determined by using biomarkers of numerous body systems that depict physiological disturbances. There is a substantial connection between stress, immune function, inflammation, and coagulation. Consequently, immune/inflammatory/coagulation biomarkers may play crucial roles in the calculation of allostatic load, and the recommendation of additional biomarkers may improve the estimation accuracy of allostatic load.

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1. Introduction

Several studies have assessed the link between stress and immunological function in recent decades [1-4]. Chronic stress has been related to a dysregulation of the immune and neuroendocrine systems. This dysregulation has been shown to have a role in the development of different diseases. Immune dysregulation and chronic inflammation are also linked to an increased risk of premature death from any cause [2, 5-7].

There are several mechanisms, by which stress can affect the immune system. Both the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS; adrenergic activation) are involved in the immune responses. Depending on the nature of the stress, the body's response to it may be different, or it may even go wrong. Short-term or acute stress causes a widespread reorganization of the immune system. Immune cells (such as lymphocytes) normally reside in the marginated pool, spleen, bone marrow, and lymph nodes; however, when acute stressors occur, stress hormones initiate a cascade of events and induce the trafficking of immune cells (e.g. lymphocytes) out of these compartments and into the blood, where they eventually reside in target organs where an individual is most likely to be injured. The result is a boost in immune cell defenses against infection [8-10].

Chronic stressors are among the most dangerous environmental hazards because of their long-lasting impact on mental, emotional, and physical health. Stress causes not only mental and behavioral shifts but also physical modifications [11, 12]. When the HPA system is activated for an extended period, it might throw off the body's ability to regulate other systems, such as the immune system. Individuals who are under chronic stress are more likely to have a cold and reduced immunological response to immunization and take longer to recover following standardized wound inductions [1, 2]. They also experience low-grade, nonspecific inflammation. This increase in inflammation is likely due to decreased anti-inflammatory feedback [13]. When the immunological response is no longer necessary, the HPA axis acts as a negative feedback mechanism to dampen it. Increases (rather than decreases) in inflammation are related to the HPA axis; however, glucocorticoid resistance or inadequate glucocorticoid signaling may emerge in chronic stress settings. If the HPA axis is overactive, the adrenal gland may pump out so much cortisol that cell receptors that normally detect cortisol and turn off become resistant and do not "hear" the cortisol as well (i.e. they are less sensitive). This would result in a decrease in anti-inflammatory feedback [14-16].

In contrast to acute activation of the immune system in response to stress, which is homeostatically regulated by neuroendocrine mechanisms, chronic activation of the immune system due to continuous stress exposure can lead to an allostatic load with an inflammatory diathesis that is involved in the pathophysiology of various disorders. The term "allostatic load" is used to describe the overall effect of prolonged emotional and psychological strain. Several physiological systems must coordinate their efforts, each operating at a different intensity level [17]. Allostatic overload occurs when an individual is confronted with environmental demands that are greater than their reserves. Adrenal corticosteroids, in conjunction with catecholamines, help maintain homeostasis in the immune system by directing immune cell "trafficking" to sites where they will be most effective in fighting infection or other threats and by regulating the expression of cytokines and chemokines, the immune system's hormones [18]. Allostatic load, which includes immunosuppressive effects, occurs with chronic over-activity of these same mediators when they are secreted continuously or not shut off appropriately [18, 19].

This study aimed to review the relationships between stress, immunity, inflammation, and coagulation, and their effects on allostatic load. This review may show the importance of using more immune, inflammatory, and coagulation markers in allostatic load score calculations.

Acute stress and immunity

Stress has been conceptualized as a constellation of events, commencing with a stressor, which triggers a brain reaction, which in turn activates a physiological or biological stress response to enable the body to deal with the threat or opportunity. The body prepares for potential injury in response to acute stress by rapidly activating the sympathetic nervous system, which transmits efferent projections to the bone marrow and lymphoid tissues [20]. The innate immune response provides rapid defense against infections or tissue damage. Granulocytes, monocytes, macrophages, and natural killer (NK) cells mediate this innate immunity by emitting inflammatory molecules (such as cytokines and reactive oxygen species) and phagocytosing pathogens [21]. Innate immunity responds rapidly to acute stress, whereas acquired immunity can take days to develop a response to a particular disease [22]. Different subsets of lymphocytes, each with antigen-specific receptor sites, mediate the development of acquired immunity. When the body detects stress, the sympathetic-adrenal-medullary axis secretes adrenaline and noradrenaline, which activate monocytes, macrophages, and lymphocytes through

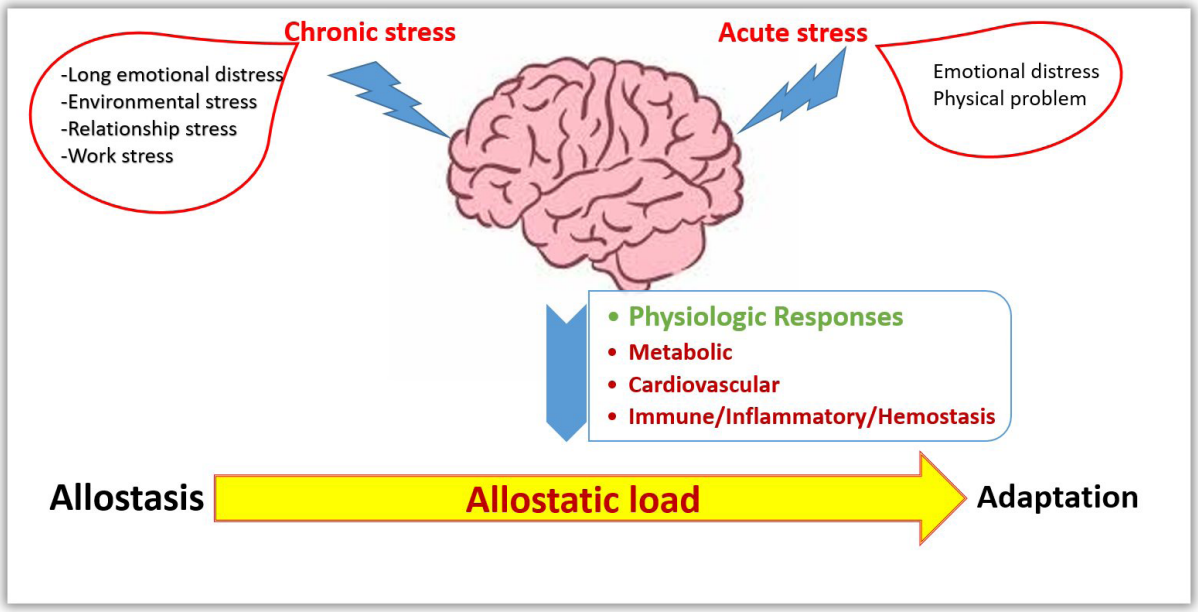

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Figure 1. Schematic view of the stress effects in physiologic systems and their influence on the allostatic load

Note: The brain is a principal organ that responds to stress. The main function of allostasis mediators is to provide adaptation. However, overuse and/or dysregulation among the allostasis mediators causes allostatic load (or overload) and exacerbates the disease processes.

beta-adrenergic receptors [23]. Signaling via adrenaline and noradrenaline induces rapid changes in the absolute quantity and percentage of circulating leukocytes that serve to transport immune cells to lesion sites [24]. The redistribution of leukocytes within immune system compartments occurs simultaneously, with an increase in lymphocytes and monocytes in the blood followed by a decrease as these cells enter organ compartments, including the epidermis, lungs, and lymph nodes as the sites for pathogen infiltration. There is an increase in the expression of pro-inflammatory genes, such as tumor necrosis factor (TNF), interferon-gamma (IFN_Y), and interleukins 1 β (IL-1β) and 6 (IL-6) at the site of this acute stress-induced redistribution of immune cells [25]. NF-B, a mediator of the effects of acute stress on gene expression, increases the production of pro-inflammatory cytokines from mononuclear cells and enhances its activity. Acute stress can increase noradrenaline levels, which can then activate NF-B and lead to the release of IL-6 [25, 26]. In turn, the released cytokines enter the brain through permeable regions of the blood-brain barrier, active transport molecules, and afferent nerve fibers, which transmit information through the nucleus tractus solitarius. Environmental stress induces the withdrawal of inhibitory motor vagal input, as well as the release of acetylcholine, which binds to the nicotinic acetylcholine receptor. In response to stress, aldosterone is secreted, and by acting on mineralocorticoid receptors [16], it inhibits the activity of neutrophils, helper T cells, and natural killer (NK) cells. In addition, the secretion of the adrenaline and noradrenaline hormones will occur at this time. In response to stress, the adrenal cortex produces and secretes cortisol, which modulates the distribution and activity of immune cells via glucocorticoid receptors on immune cells. At the level of the glucocorticoid receptor, negative feedback mechanisms decrease the levels of NF-B and the production of pro-inflammatory cytokines. This restores homeostasis and allows the immune system to respond to the acute stress-induced release of glucocorticoids [27-29].

Chronic stress and immunity

During chronic stress, stressors can stimulate the paraventricular nucleus (PVN) to produce corticotropin-releasing hormone (CRH), which activates the HPA axis. CRH stimulates the secretion of adrenocorticotropic hormone (ACTH), which in turn stimulates the secretion of glucocorticoids, particularly cortisol. Cortisol exerts significant immunosuppressive effects.

Chronic stress inhibits glucocorticoid-mediated negative feedback regulation of immune activation, thereby promoting allostasis and increasing systemic inflam-

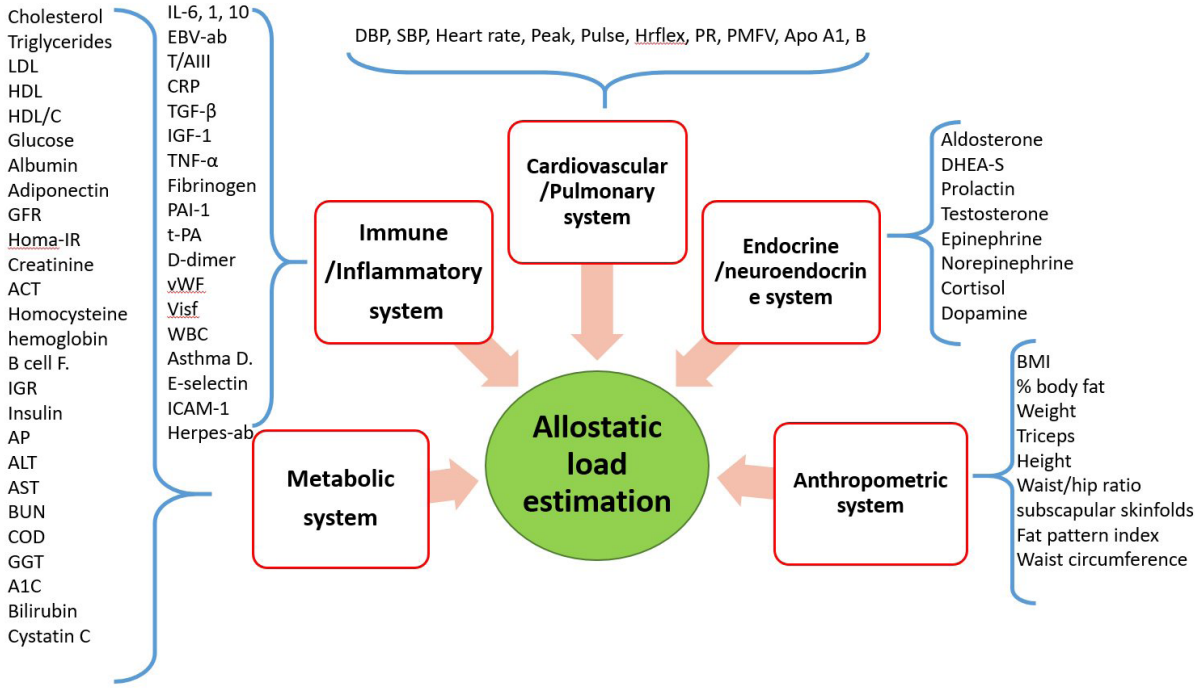

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Figure 2. Physiologic systems and related parameters involved in allostatic load estimation

A1C: Hemoglobin A1c; ACT: Alpha-1-antichymotrypsin; ALT: Alanine transaminase; AP: Alkaline phosphatase; Apo A1, B: Apolipoprotein A1 & B; Asthma D: Asthma diagnosis; AST: Aspartate aminotransferase; B cell F: β-cell functioning; BMI: Body mass index; BUN: Blood urea nitrogen; COD: Cytomegalovirus optical density; CRP: C-reactive protein; DHEA-S: Dehydroepiandrosterone-sulfate; DBP: Diastolic blood pressure; EBV-ab: Epstein-Barr virus antibodies; GFR: Glomerular filtration rate; GGT: Y-glutamyl Transferase; HDL: High-density lipoprotein cholesterol; HDL/C: Total cholesterol to HDL ratio; Herpes-ab: Herpes antibody; HRflex: Cardiovascular physical fitness; ICAM-1: Intercellular adhesion molecule 1; IGR: Insulin–glucose ratio; IL-6: Interleukin-6; IGF-1: Insulin-like growth factor-1; IR: Insulin resistance; LDL: Low-density lipoprotein; PAI-1: Plasminogen activator inhibitor 1 antigen; PMFV: Peak menstrual flow volume; PR: Pressor response; Peak: Peak expiratory flow; SBP: Systolic blood pressure; T/AIII: Thrombin/antithrombin III complex; TNF-α: Tumor necrosis factor-alpha; t-PA: Tissue-type plasminogen activator antigen; Visf: Visfatin; vWF: von Willebrand factor.

mation. Due to glucocorticoid resistance, chronic stress lessens HPA axis negative feedback. Glucocorticoid resistance may be caused by stress-induced epigenetic modifications of molecules that regulate the glucocorticoid receptor and cytokine-induced receptor inhibition. Hypercortisolemia and immune system activation as a result of glucocorticoid resistance can elevate pro-inflammatory cytokine levels and pathogen-induced disease [17, 30-32].

Poor social status modifies the immune gene expression patterns of natural killer (NK) cells, helper T cells, B cells, and cytotoxic T cells to increase lymphocyte proliferation, innate immune responses, and cytokine responses [33]. Resting pro-inflammatory gene expression is most affected by social stress in NK and helper T cells [34, 35]. Prolonged stress modifies the chromatin structure and glucocorticoid responsiveness of DNA. However, these findings suggest that chronic stress exposure may generate pro-inflammatory states that contribute to stress-related psychopathology and other health issues, such as chronic low-grade inflammation, delayed wound healing, poor vaccine responses, and increased susceptibility to infectious diseases [36].

Stress and allostatic load

Allostatic load was first proposed in 1993, and is defined as the "cost of chronic exposure to fluctuating or heightened neural and neuroendocrine responses." The individual's reaction to what they consider to be extremely severe environmental situations over an extended period of time triggers these reactions. It derives from allostasis, the idea that an organism can achieve stability through change, and the premise that a healthy body requires regular modifications to its internal physiological environment [37, 38].

Allostatic load is a term used to describe the cumulative effect of daily experiences, including subtle and longstanding life events as well as major challenges, on a person's physiology, including but not limited to poor sleep and circadian disruption, lack of exercise, smoking, alcohol consumption, and an unhealthy diet [39]. When an individual's coping mechanisms are overwhelmed by their surroundings, a condition known as allostatic overload sets in [40]. This is an extremely stressful state, in which the body's stress response systems are perpetually activated and buffering elements are insufficient [40]. Exposure to frequent stressors can establish a state of chronic stress and repeated physiological arousal, failure to adapt to repeated stressors, failure to terminate the stress response after the stressor has ceased, and insufficient allostatic response to the stressor can all lead to allostatic load/overload [41]. In response to environmental stimuli, several physiological systems interact at varying levels of activity. Both the nervous and immune systems help the body to persevere against hardship [42]. The hypothalamic-pituitary-adrenal axis has been implicated in the etiology of allostasis [43]. Brain structure and neurochemical activity are affected by both hereditary and non-genetic factors. Immune system modifications (such as leukocytes, cytokines, and inflammation), both short- and long-term, can have immunosuppressive effects [44]. Cardiovascular function, gastrointestinal health, endocrinemetabolic harmony, and sleep are all potentially affected [37].

The allostatic load has been characterized using two different approaches: the first approach is the use of biomarkers that depict physiological derangements, while another approach focuses on the most severe symptoms associated with allostatic overload. The use of biological indicators for the diagnosis of allostatic stress has been the subject of several studies [45-47]. Juster et al. (2010) reviewed 58 allostatic load studies and reported using 4-18 biomarkers in five physiologic systems of neuroendocrine, immune (inflammatory and clotting factors), metabolic, cardiovascular/respiratory, and anthropometric for allostatic load calculation [48]. In another review, 26 various biomarkers in 18 different ways were used to calculate allostatic load in 21 previous studies. The number of biomarkers in each calculation varied between 7 and 14 with at least one biomarker from three categories: cardiovascular, metabolic, and immune [49]. The allostatic load was also expanded by Karimi et al. (2019) into a multisystem biological health score that measures characteristics of the endocrine, inflammatory, cardiovascular, and metabolic systems, as well as the function of two key organs (the liver and the kidney). They measured 16 different biomarkers [50]. Nasiri et al. (2021 and 2022) also used the same systems with little modification of the number (18 biomarkers) and type of biomarkers [51, 52]. However, the complexity and dynamic nature of this multisystem network means that this measure of allostatic stress has several limitations [46], despite being a more accurate predictor of mortality and decreased physical functioning than single biomarkers [48, 53, 54]. Figure 1 shows a schematic view of the stress effects in physiologic systems and their influence on the allostatic load.

Involvement of immune/inflammatory/hemostasis biomarkers in allostatic load estimation

There is a strong relationship between stress, immune function, and inflammation [55-57]. As Figure 2 represents, immune/inflammatory parameters are used in the calculation of allostatic load, indicating that chronic stress and subsequent allostatic load are related to inflammation. The immune system relies on inflammation to function properly. It is the first automatic and broad response of the innate immune system [58]. There are both pro-inflammatory (such as interleukin [IL]-1, IL-6, and tumor necrosis factor [TNF]-a) and anti-inflammatory (such as IL-4 and IL-10) indicators involved in the inflammatory response. C-reactive protein (CRP) is an example of an acute-phase reactant that is produced in response to inflammatory stimulation. Chronic or excessive inflammation may be harmful to health during periods of chronic stress, even though it is a vital response to acute illness or injury [36, 59]. Epidemiological studies have linked elevated inflammatory markers in the blood to an increased risk of developing cardiovascular disease, diabetes, cancers, autoimmune diseases, and death [36]. Therefore, the use of inflammatory parameters in allostatic load calculation can both indicate the severity of chronic stress and the serious situation of the body in the occurrence of cardiovascular, metabolic diseases, and cancer [60]. CRP, IL-6, and fibrinogen were the most frequently used immune/inflammatory system biomarkers in allostatic load estimation [48].

As Figure 2 shows, many hemostasis factors are also used as biomarkers in the immune/inflammatory system to calculate the allostatic load. During stress, the sympathetic nervous system exerts significant effects on hemostasis. Within a few minutes, catecholamines, particularly epinephrine, stimulate vascular endothelial 2-adrenergic receptors, resulting in the release of factor VIII (FVIII), von Willebrand factor (VWF), and tissue plasminogen activator (t-PA) from endothelial storage pools into the circulation [61]. Catecholamines also stimulate the release of FVIII from the liver and affect

the elimination of t-PA and D-dimer from the liver. Another important source of acute stress-induced release of t-PA into the circulation is sympathetic nerves in densely innervated resistance arteries and arterioles, and there is a direct correlation between stress-induced increases in norepinephrine and D-dimer [62]. Changes in D-dimer are significantly correlated with alterations in FVII:C, FVIII:C, FXIX:C, VWF:Ag, and soluble tissue factor (sTF) [61, 63].

Inflammation and coagulation are closely intertwined processes that can significantly influence one another. This interaction occurs at the levels of platelet activation, fibrin formation, fibrin resolution, and physiological anticoagulant pathways [62]. Activation of coagulation generates proteases that interact not only with coagulation protein zymogens but also with specific cell receptors to induce signaling pathways that mediate inflammatory responses [64]. By binding to protease-activated receptors (PARs), coagulation proteases exert their greatest effect on inflammation. Recent experiments demonstrated that the administration of recombinant factor VIIa to healthy human subjects increases plasma levels of IL-6 and IL-8 by three to four times [65]. PARs play a role in coagulation and inflammation in the context of coronary artery thrombosis and its subsequent complications [66]. Activated platelets serve a crucial role in inflammation, particularly in the chronic inflammation associated with atherosclerosis. Platelet adhesion to the sub-endothelial matrix promotes leukocyte rolling, adhesion, and transmigration via the interaction between platelet P-selectin and leukocyte P-selectin glycoprotein ligand-1. A lack of P-selectin delays the formation of atherosclerotic plaques. Platelet-activating factor-mediated activation of macrophage 1 antigen (Mac-1) and interaction of this integrin with fibrinogen bound to the platelet glycoprotein IIb/IIIa receptor stimulate leukocyte adhesion to the vessel wall [67]. In addition, activated platelets generate a variety of pro-inflammatory cytokines (such as CD40 ligand and IL-1) and chemokines (such as RANTES and platelet factor-4), which may result in the activation of monocyte integrins and lead to monocyte recruitment to atherosclerotic plaques [68]. Nonetheless, these studies provide evidence of a strong connection between stress, the immune system, inflammation, and allostatic burden.

2. Conclusion

Stress has been related to a dysregulation of the immune system as well as the endocrine, metabolic, and coagulation systems. Exposure to frequent stressors can establish a state of repeated physiological arousal, failure to adapt to repeated stressors, failure to terminate the stress response after the stressor has ceased, and insufficient allostatic response to the stressor can all lead to allostatic load/overload. In this condition, many physiological systems interact at varying levels of activity. The use of biomarkers of many body systems that depict physiological derangements is the main approach to identifying the severity of allostatic load. There is a strong relationship between stress, immune function, inflammation, and coagulation. Then, immune/inflammatory/coagulation biomarkers may play critical roles in the calculation of allostatic load, and the recommendation of more mentioned biomarkers could increase the accuracy of allostatic load estimation.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Conflicts of interest

The author declared no conflict of interest.

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