The central role of stress-induced

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The central role of stress-induced inflammation and hyperglycemia to COVID-19 severity

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Abstract

As a global burden, the coronavirus disease 2019 (COVID-19) pandemic is going on spread. It has many clinical manifestations and impacts on humans worldwide. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection causes systemic illness through its known receptor binding to angiotensin-converting enzyme 2 (ACE2) which is expressed in various tissue types in the human body. Its infection and systemic condition lead to physical and psychological stress for the patients. During critical illness, and ongoing inflammation, physical and psychological stress both contribute to the patient's outcome. Pre-existing or underlying psychological conditions also affect COVID-19 patients and lead to poorer prognosis. Stress causes several imbalances including neurohormonal, pro-inflammatory, and metabolic alteration. Ongoing stress and COVID-19 both increase systemic inflammation through interleukin 6 (IL-6), hyperglycemia, and uncontrolled sympathetic drive. These conditions pile up into the vicious cycle of poor prognosis and even mortality. This review article discusses the mechanism of stress to induce inflammation and hyperglycemia that correlated with the poorer outcome in COVID-19 patients. Because of its important role in COVID-19, approaches should be made to overcome stress and homeostatic imbalance caused by stress conditions in COVID-19 patients.

Key words: COVID-19, stress, hyperglycemia, inflammation, IL-6.

Introduction

Critical illness is characterized by chronic pathologic stress, inducing neuroendocrine, inflammation, and hormonal changes. (1,2) Stress is classified as multiple forms of trauma, surgery, and infection that stimulate the neural and hormonal response significantly, leading to homeostatic imbalance. (2)

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Prior studies have investigated a biphasic metabolic response to stress. The first phase was termed the ebb phase, representing an acute response for survival with the activation of blood transfer from peripheral to central circulation to conserve haemodynamics. The second phase was marked by hypermetabolism, which lasted for a week and was acknowledged for the increase in total body oxygen consumption and carbon dioxide (CO2) production, which led to catabolism of gluconeogenesis and protein synthesis. (3)

Under the stress condition, both psychologically and physically, a subsequent increase in blood glucose concentration occurs. The increase of blood glucose concentration under critical illness is termed as stress-induced hyperglycemia. Several studies proved that interleukin 6 (IL-6) played an important role in the development of hypercytokinemia present in critical illness and also correlated with hyperglycemia and difficulty to control blood glucose levels in patients with severe inflammation like sepsis. (4,5) Cytokine overpro-

duction caused multiple organ failures through the activation of humoral mediators and vascular endothelial impairment. (4)

The renowned coronavirus disease 2019 (COVID-19), which has been a global burden since the year 2019, has a global case fatality rate (CFR) of 2%, with the highest prevalence among people in their productive age of 40-49 years old. (6) Various manifestations of COVID-19 have been documented since the beginning of the pandemic, from asymptomatic, mild, moderate, to severe and critical illness. (7) A case also reported pneumothorax complication in a COVID-19 patient. (8) Several COVID-19 detection methods had been developed to differentiate its particular characteristics from other respiratory infections, and several approaches had been addressed as a warning system to detect COVID-19 patients who were at a greater risk of worse outcomes. (9-11) Several managements during this pandemic have also developed, as well as the robotic intensivist development. (12) Prognosis and severity of COVID-19 were also depending on various factors, both externally and internally. COVID-19 patients who were admitted to the health care facilities also could have a particular stress response. Stress management and approach, both physically and physiologically, in critically ill COVID-19 patients should be taken more attention. A study by Kyle et al. showed that on the first day of COVID-19 care as much as 68.2% of the patients underwent moderate to severe stress, marked by the increase in cortisol levels, glucagon levels, and the decrease of anabolism, measured by the decrease of insulin-like growth factor 1 (IGF-1). (13) Another study showed the increase of IL-6 in these populations, which was the dominant cytokine from brown adipocytes. (14) This article mainly discusses the role of stress in severe and critically ill COVID-19 patients.

Stress

Psychological stress happens when anybody feels external pressure and becomes their burden or more than their adaptive capacity. It is a negative influence of events. (15) Generally, stress affects the pathogenesis of physical illness by causing negative effects, such as anxiety and depression, which in turn directly affects biological processes or behavioral pattern that leads to the severity of a disease. Stress exposure could alter the emotional, physiological, and behavioral responses chronically or permanently.

Behavioral change becomes the adaptation coping response toward stressors, for example, a smoker who smokes to reduce their stress, lack of exercise due to depression, lack of sleep, and also lack of compliance to medications. (15)

Stress response during critical illness

All forms of trauma, surgery, and infection initiate neural and hormonal responses markedly, leading to impairment in maintaining homeostasis and preventing patients from the healing process. (2) Stress will produce and integrate various cognitive, emotional, neurosensory, and somatic responses transmitted to the brain via various pathways. Stress system activation caused physical and behavioral alterations. Marik et al. observed similar biological, physical, and physiological responses to stress, namely general adaptation syndrome. (16)

General adaptation syndrome described the chronology of body response to stress while occurring continuously. The first phase of general adaptation to stress was initiated with a shock phase or alarm reaction, followed by the second phase of resistance or contra-shock, and the last phase was exhaustion. The human body could resist stress in the second phase by compensating and bringing back to homeostasis balance. (17)

Physiologically, a stress response is adaptive and immediate which is needed for survival. (16)

Stress response during critical illness was also investigated by Cuthbertson and Moore, who explained that the first 24 hours (ebb phase) was marked by the blood circulation from peripheral to central (heart and central nervous systems) and electrolyte maintenance. The next phase was called phase flow, which was characterized by hypermetabolism which lasts for 6-7 days, and an increase in oxygen consumption and CO2 production, skeletal muscle and visceral muscle catabolism, gluconeogenesis, and protein synthesis. The last phase was the chronic phase, which could last for months and was characterized by the decrease of pituitary hormones, peripheral resistance to growth hormones, insulin, thyroid, and cortisol. These hormonal changes affected energy metabolism as well as protein and lipid metabolism. (2)

Critical illness is marked by the chronic pathological stress response. (16) A good stress response management will lead to a better outcome in critically ill patients, especially during phase 1 of the stress response, as the golden period of stress management to prevent multiorgan damage and counteracts stress to bring back the physiologic state. Cellular protection strategies to overcome pathological stress responses could be supported by managing hypercapnia, hypotension, hypoxemia, oliguria, and anemia. After balancing stress in phases 1 and 2, phase 3 is focused on therapeutic treatments based

on the underlying disease. (17) Patients' progressivity in undergoing stress during critical illness is linear. Clinical approaches are individual and depend on the stress phase in each patient.

Metabolism and neuroendocrine alteration during stress

Metabolic responses during stress involve neuroendocrine, inflammation, and hormonal from the adipose tissue via leptin, resistin, and adiponectin, as well as gastrointestinal via ghrelin and cholecystokinin. (1,2) Catabolism, which was measured by the increase of glucagon and cortisol, was studied and reported in patients admitted to the intensive care unit with moderate to critical illness. Anabolism reduction was also documented in these patients which was characterized by a decrease in IGF-1. (13)

Neuroendocrine response to stress is mainly generated through the hypothalamic-pituitary-adrenocortical (HPA) pathway and sympathetic-adrenal-medullary (SAM) pathway. Cortisol is a primary effector in the activation of the HPA pathway, and largely regulates the physiological factors, including the anti-inflammatory response, carbohydrate metabolism, lipid, and protein, and its relation to gluconeogenesis. These connecting events lead to homeostatic imbalance. Peripheral tissue damage like hypoxemia, hypercapnia, and hypovolemia stimulate signals in afferent nerves. Catecholamines are also released during this phase as a response to the SAM activation. SAM and the autonomic nervous system both regulate the cardiovascular, pulmonary, and immunological response toward stress response. HPA and SAM activation not only leads to the deterioration of physiological controls that influence the physical impairments, but also psychological deterioration. (15)

The increase in the sympathetic nervous system will subsequently increase the catecholamine release. The adrenal medulla releases norepinephrine and epinephrine to the bloodstream coincident with the increase of pituitary hormone secretion (adrenocorticotropin, growth hormones, and vasopressin), while glucocorticoid is increased in peripheral tissues. (2) Corticotropin-releasing hormone (CRH), released by the hypothalamus, stimulates the adrenocorticotropin release from the anterior pituitary to the bloodstream, and the adrenal produces cortisol, which is called the stress hormone. Negative feedback regulation of the HPA pathway is marked by the cortisol suppressing the CRH and adrenocorticotropic hormone (ACTH). Cortisol is a catabolic hormone that alters the energy storage to prepare the counteraction of stressors and stimulate gluconeogenesis in the liver, thus increasing the blood sugar level. (18)

Hyperglycemia attenuates the healing process and is related to infections and other comorbidities, including ischemia, sepsis, and mortality. Intercellular adhesion molecule 1 (ICAM-1) and lymphocyte function-associated antigen 1 (LFA-1), which play an important role in orchestrating healing and repair, are significantly reduced in hyperglycemia. (19) In the severe stress response, cortisol is markedly increased, catabolizing the muscle protein to provide a substrate for gluconeogenesis. This substrate is prepared for lipid degradation and subsequently prepared as the gluconeogenic substrate. (2)

Growth hormone-releasing hormone (GHRH) is released from the hypothalamus to stimulate the release of growth hormone (GH) that subsequently regulates catabolism and induces protein synthesis and lipolysis. Cortisol increases blood glucose levels in a similar fashion to GH by inducing glycogenolysis. (2)

Vasopressin is a main anti-diuretic released from neurohypophysis during stress. Vasopressin stimulates the insertion of aquaporin into the renal wall, allowing water exchange from the renal tubule to the systemic circulation. Serum thyroxin and triiodothyronine are decreased during critical illness mostly because of the lack of thyrotropin. The alteration of thyrotropin-thyrotropin-releasing hormone (TRH) imbalance leads to insulin resistance, hypertriglyceridemia, lethargy, pleural effusion, glucose intolerance, and muscle protein synthesis. (2)

Stress and inflammation

Stress is involved in the regulation of immune response to inflammation, and correlates with depression, infection, autoimmunity, cardiovascular disease, and certain cancers. Psychological stress alters the immunity through direct intervention to lymphatic tissue, via HPA and SAM, which bind and conform to the active immune cells' function, or through the behavioral changes induced by stress, such as smoking habits as coping to reduce stress. (20) During stress conditions, IL-6 and tumor necrosis factor α (TNF-α), which are the pro-inflammatory cytokines, are released in a large number. These pro-inflammatory cytokines stimulate proteolysis and lipolysis. (1,2)

Catecholamines and glucocorticoids could activate immune responses to release anti-inflammatory cytokines. Glucocorticoid, norepinephrine, and epinephrine inhibit interleukin 12 (IL-12) cytokine production from antigen-presenting cells (APC), but not interleukin 10 (IL-10). TNF-α stimulates T helper 1 response (Th1) and cellular immunity,

while IL-10 suppresses the production of IL-12 and the activity of Th1 and suppresses T helper 2 (Th2) and humoral immune response. (21) Thus, cellular immunity is suppressed during stress conditions.

In acute stress conditions that last for minutes or hours, innate and adaptive immune responses are activated, mediated by dendritic cells, neutrophils, macrophages, and lymphocytes. On the contrary, chronic exposure to stress suppresses innate and adaptive immune responses by altering type 1-type 2 cytokine balance, thus inducing continuous low-grade inflammation and dysregulating immune protective cells. (22)

COVID-19 pathologic mechanism

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) life cycle consists of 5 stages: adhesion, penetration, biosynthesis, maturation, and release. After attaching to the host cell, SARS-CoV-2 enters the host cell by endocytosis or membrane fusion, namely penetration. SARS-CoV-2 releases its genetic material, which was RNA, to hijack the host cell and is followed by its replication. SARS-CoV-2 mainly consists of 4 structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N). Spike consists of trimetric glycoprotein which is prominent from the surface.

Spike protein is responsible for the diversity of this virus, it consists of 2 subunits: S1 has a role to bind host's cell receptor and S2 subunit for the virus membrane fusion. (23) Prior studies showed that SARS-CoV-2 needed angiotensin-converting enzyme 2 (ACE2) as the portal to enter the host's cell. (24) SARS-CoV-2, with the aid of its surface glycoprotein (peplomer) which was known as the spike, accesses the host cells. ACE2 receptor expression in each tissue type correlates significantly with the virulence of SARS-CoV-2. ACE2 is highly expressed in the lungs, heart, ileum, renal, and urinary bladder, but mostly in the lungs' epithelial cells mainly in alveolar cells. (23) Alveolar cells, together with macrophage and dendritic cells, play an important role in the innate immune response as the first line of counterattack for SARS-CoV-2. (23)

T cell activation was initiated with the antigen presentation by the APC. Dendritic cells and macrophages function as the APC and present the antigen of the SARS-CoV-2 to T-cells. These cells phagocyte the apoptotic-infected cells. This APC continues to move in lymphatic nodes to present the antigen to T-cells. CD4+ cells activate B cells to improve specific antibodies against SARS-CoV-2. Some cytokines and chemokines are reported to have the main role in COVID-19. They are IL-6, granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein (MIP) 1α, and TNF-α. Prior study has shown a significant correlation between the increasing IL-6 levels with the severity of COVID-19. (23)

Stress, inflammation, and hyperglycemia in COVID-19 severity

Despite its primary infection in the lower respiratory tract, several systemic factors lead to COVID-19 severity. The worse prognosis was reported in bacterial co-infection, hyperinflammatory state, hyperglycemia, and chronic stress. (6,25,26) Psychological conditions also increase inflammation and hyperglycemia and thus may worsen COVID-19 outcomes. (6,27)

SARS-CoV-2 is known for its binding receptor in ACE2, which is found in many tissue types in the human body. In normal conditions without SARS-CoV-2 binding, the signaling of angiotensin II through its receptor of angiotensin II type 1 receptor (AT1R) is balanced by angiotensin 1-7 and the ACE2 angiotensin I proteolysis products, that have an anti-inflammatory effect. SARS-CoV-2's binding to the ACE2 receptor leads to downregulation of ACE2, which in turn affects the angiotensin II accumulation in the absence of angiotensin 1-7. Therefore, the progression of the inflammatory effect occurs. AT1R binding to angiotensin II promotes the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase resulting in the increase of free radicals and direct stimulation of IL-6 cytokine production. IL-6 has a positive feedback loop to further upregulation of AT1R, moreover, they exacerbate hypertension, edema, infiltration of immune cells, hyperpermeability of the membrane, and continuing the inflammation process. (28) The primary site of SARS-CoV-2 infection is the lower respiratory tracts. SARS-CoV-2's spike protein binds to ACE2 and causes an inflammation process that leads to the increase of pro-inflammatory cytokines, mainly IL-6. It also leads to the increase of alveolar cell permeability and allows the virus' spread to the bloodstream, thus promoting the systemic spread of the virus antigens in many organs containing ACE2 receptors. Like another respiratory viral infection, antigen-presenting cells (alveolar cells and macrophages) present the virus antigen to CD4+ cells (CD4+ cells then will activate macrophages), CD8+ cells, and B-cells. These immune cells release IL-6 in SARS-CoV-2 infection. (29) IL-6, in turn, reactivates and stimulates CD4+ differentiation to maximize its pro-inflammatory role. (30) Spreading of SARS-CoV-2 drives it to the pancreatic cells which also express ACE2, and causes

the hyperglycemia and release of pro-inflammatory cytokine IL-6, via a disintegrin and metalloprotease 17 (ADAM-17) activation. (31)

Stress during COVID-19, both because of COVID-19 or the pre-existing stress prior to COVID-19, increase IL-6 release and hyperglycemia state. Stress condition, without the presence of SARS-CoV-2 infection, activates corticotropin-releasing hormone (CRH) by the hypothalamus and the subsequent ACTH by the hypophysis to increase glucocorticoid production. Glucocorticoid production increases IL-6 production via glucocorticoid receptors in macrophage and also increase blood glucose levels. An increase in blood glucose levels also leads to further inflammation. Besides hormonal change, stress also stimulates sympathetic nervous system activation through adrenergic receptors, allowing the release of pro-inflammatory cytokine IL-6 through the activation of the nuclear factor kappa B (NF-KB) pathway. (32) SARS-CoV-2 infection during stress conditions, moreover, will increase the risk of cytokine storm and systemic immune response syndrome. SARS-CoV-2, through the toll-like receptor (TLR) in macrophages, will directly stimulate the activation of inflammation through the activation of the extracellular signal-regulated kinase (ERK) and NF-KB pathways. Together with stress and overlapping hyperglycemia (due to stress and/or inflammation), increased pro-inflammatory cytokines, marked by the continuing inflammation, increase of chemokines, acute phase reactants, and adhesion molecules have systemic effects and cause multiple organ dysfunctions (MODS). (6,25,29,32,33)

Pathomechanism of stress, inflammation, and hyperglycemia in COVID-19 severity is described in **Figure 1**.

Conclusion

Stress, both psychologically and physically, has the central role that could significantly worsen COVID-19 through the overlapping stimulation of inflammation through IL-6 and together with SARS-CoV-2 infection worsen the hyperglycemia state, which in turn also increases the inflammatory state. Chronic stress leads to the deregulation of immune response to infections. Poor outcomes of COVID-19 patients with overt psychological stress and hyperglycemia have been proven. This vicious cycle causes the cytokine storm and potential MODS and mortality in COVID-19 patients with stress conditions. Stress condition is a very essential condition that needs attention. Several approaches should be addressed to overcome these imbalances made by stress conditions in COVID-19 patients.

Conflict of interest

None to declare.

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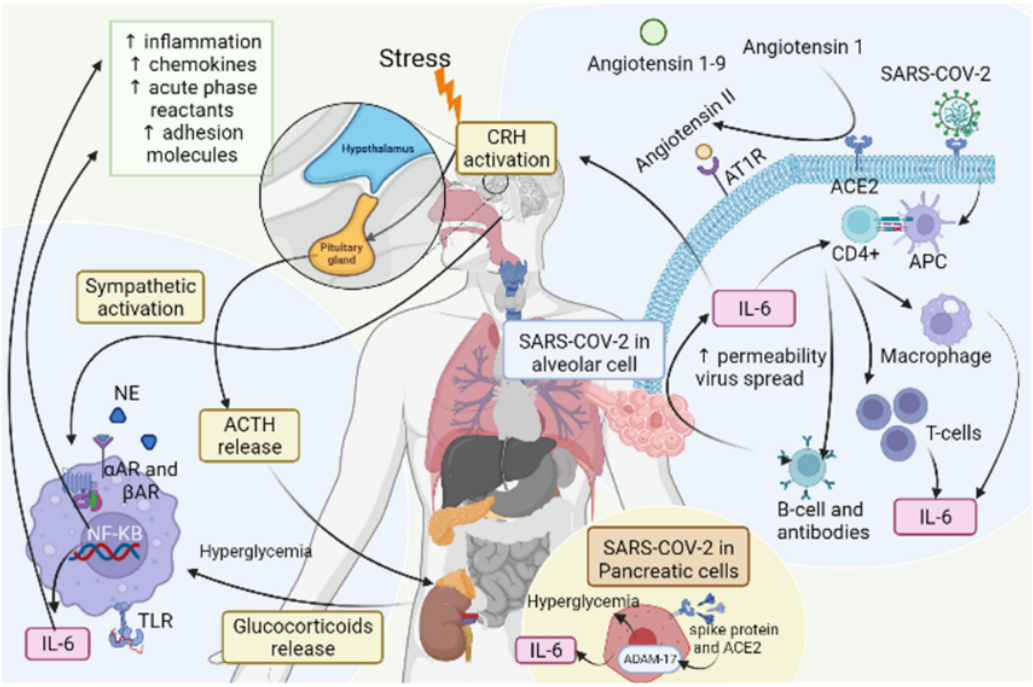
Figure 1. Stress and its relation to inflammation, hyperglycemia, and SARS-CoV-2 infection



Legend: SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2; NE=norepinephrine; αAR=α-adrenergic receptor; βAR=β-adrenergic receptor; NF-KB=nuclear factor kappa B; TLR=toll-like receptor; IL-6=interleukin 6; ACTH=adrenocorticotropic hormone; CRH=corticotropin-releasing hormone; ADAM-17=a disintegrin and metalloprotease 17; AT1R=angiotensin II type 1 receptor; ACE2=angiotensin-converting enzyme 2; APC=antigen-presenting cells.

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