Review Article

Work Stress, Dysbiosis, and Immune Dysregulation: The Interconnected Triad in COVID-19 Infection in the Medical Team Staff – A Mini-Review

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Abstract

The COVID-19 pandemic has hit most of the communities around the globe. Earlier researches have reported the psychological effects of pandemics either on the general populations or on specific communities such as students and health professionals. A scanty number of papers have focused on the interaction among complex factors underlying the pathogenesis of the disease. In this review, we aimed to integrate the accessible data about the possible mechanistic processes predisposing to COVID-19 infection in the health professions. We summarized these factors as "stress, microbiota, and immunity triad." We utilized the PubMed database, Google, and Google Scholar search engines to search the literature related to combinations of these keywords: "pandemics, COVID-19, coronavirus, SARS-CoV2;" "gut microbiota, gut-lung axis, dysbiosis, nutrition;" "work stress, workload, health workers, health professions, and medical team;" and "immunity, cytokine storm, and viral load." We detected no discussions combining the suggested triad concerning the medical team personnel. We cast light, for the first time to our knowledge, on the potential pathogenic role of "stress, microbiota, and immunity triad" in COVID-19-infected health workers.

Keywords: Coronavirus, COVID-19, cytokine storm, dysbiosis, immunity, microbiota, work stress

Introduction

The COVID-19 pandemic has compelled people to stay home to stay safe. On the other side, regarding the medical team personnel, it was their commitment to work by their full capacity to save the infected people. Many reports have documented the health worker affection by COVID-19. It may be underestimated, however, a considerable percentage of the health team workers have died by COVID-19.[1-3] The pandemic negatively impacts the mental health of the medical team due to the extraordinary physical and mental stress.[4]

Interestingly, the gut microbiota and the immune system are double-bladed natural weapons. Both can defend the body against the invading microorganisms. On the other side, both can render the diseases more severe and may be lethal.[5] The environment, the host, and the presence of other ailments are amid the contributing factors that modulate the microbiota composition.[6] Disturbed community of intestinal microbiota (dysbiosis) has been reported to have a link to multiple chronic diseases including autoimmune disorders and various psychiatric disorders like depression.[7] There is a possible interaction between the gut and lung, hence the name "gut-lung axis." This gut-lung cross-talk is bidirectional. Thereby, the disturbances in the lungs by inflammations could affect the gut from one side, and the passage of endotoxins or metabolites of microbes that harbor the gut to the blood could affect the lung function from the other side.[8-10] Many studies have reported that patients with COVID-19 displayed

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perturbations in the gut microbiota and gastrointestinal disturbances. An interesting finding was the presence of angiotensin type 2 receptors (the target for COVID-19) in the lung, especially in the alveolar epithelium and also in the gut in the enterocytes.[8] The gut microbiota has a role in developing humoral and cellular immunity. This is done through the released signals by commensal microbes that trigger the hematopoietic and nonhematopoietic cells of the immune system to initiate several physiological responses.[11] It was recently discovered that respiratory tract viral infections such as influenza and the respiratory syncytial virus can change the gut microbiome and enhance the host susceptibility to other secondary bacterial infections, which worsen the clinical course. It was evident that many pro-inflammatory cytokines and chemokines, tumor necrosis factor-alpha (TNFα), and interferon-gamma (IFNγ) are found to be elevated infected patients' plasma in comparison to the healthy controls.[12] *In vivo,* chemokines (CXCL8, CCL2, and CXCL10) and cytokines (interleukin [IL]-1, IL-6, and IL-12) were found to be higher in SARS-CoV patients.[13] From the pathophysiological view, there is an interesting observation that viral titers seem to decline, in the severe forms of the disease in animal and human models.[14]

There are a plethora of papers that studied the effect of pandemics either in general or specifically on the health team workers in relation to the COVID-19 pandemic. Yet, there is still a deficit in the studies that assessed the cross-talk among the factors underlying the viral–host interaction. To our knowledge, we are the first to discuss the interaction among "work stress, dysbiosis, and immune dysregulation" triad in COVID-19-infected medical team workers. This review is an attempt to provide a better perception of the disease pathogenesis and prognosis to help in lessening the disease severity to improve the outcome of the treatment. We summarized these factors in Figure 1.

Background

Types of stressors in health team personnel daily work

Stress is a broad term that refers to exposure to challenging conditions.[15] Stress can be defined as any condition that can alter homeostasis and elicit many adaptive responses for its restoration. It is present ubiquitously in our daily life but with variable extents.[16] Stress can occur during pandemics due to various reasons including the sense of being uncertain, despairing about family members, and colleagues and the probable shortage in foodstuffs.[17] COVID-19 pandemic has affected the psychological well-being of people all over the planet. Insomnia and disturbed sleep pattern, generalized anxiety, and major depressive disorders were reported in different social groups. The age and gender have been correlated to these psychological problems.[18] Many articles addressed the stressors and burnout to which the medical team staff is exposed during COVID-19 pandemic.[3,19-21] These stressors include the increased work hours and load, the absence of specific treatment and vaccination to the disease, and the improper infection control systems appliances. Additionally, the startling issue is the exaggerated aggressiveness and insult from patients in the form of rude attitude or exposing the medical staff to infection intentionally by, for example, coughing in their faces.[19,22] In a study, the younger medical staff members (aged between 31 and 40 years) displayed worries related to the safety of their families. Whereas, the older members (41–50 years) showed worries related to the fear of dying from infection, the lack of protective clothing, or the high workload.[23] Early studies reported an increased risk of posttraumatic stress disorders, addiction, depression, and divorce among health-care providers due to the higher level of stress and burnout.[21,22,24] Of the major issues that affect health-care personnel during the COVID-19 crisis are the feeling of guilt, grieving, loss, and uncertainty.[24] Stigma, social isolation from their families, helplessness, and deaths of their relatives or colleagues are amid the psychological

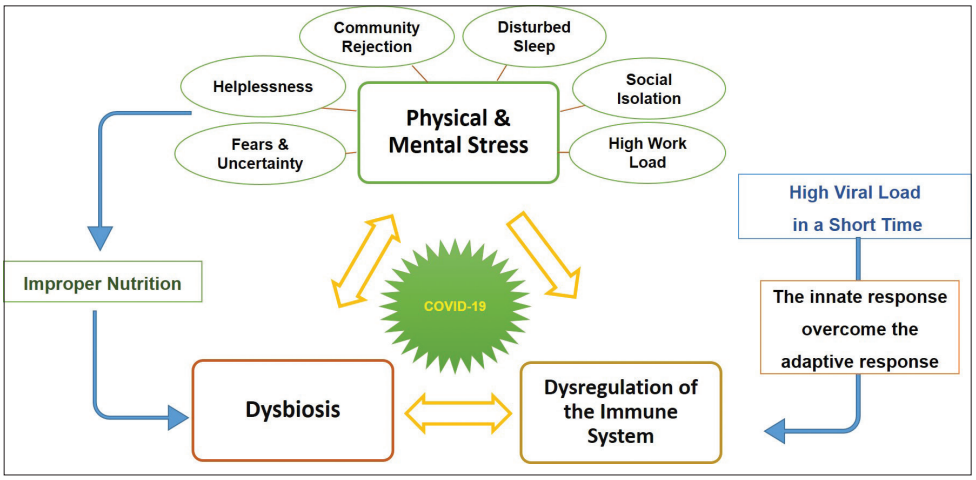

Figure 1: This figure summarizes the interplay among the suggested pathogenic triad for COVID-19 in medical staff personnel. The variable stressors play a role in causing gut dysbiosis and dysregulation of the immune system. The disturbed gut microbiota could affect mental health as well. In addition, these types of stressors could predispose to improper nutritional status in the form of increased fast food consumption. This, in turn, disturbs the gut microbiota. The interplay between the gut microbiota and the immune system is bidirectional and the dysregulation of either of them affects the other. The viral load plays an important role in disturbing the function of the immune system

stressors.[2] Many doctors and nurses have been infected and died with coronavirus in many countries all over the globe. Cases of committing suicide from the infected medical staff teams have been reported. This could be attributed to anxiety and fear of infecting the others.[20] The cultural and community supports are important factors in the psychological well-being of the medical staff. Social support could be described as the feeling the individual gets from the other people. Hence, the lack of community support and probably the rejection of some communities and cultures to the health staff due to the fear of catching an infection is one of the major stressors faced by the medical staff.[25] Adding to all that has been discussed, the presence of comorbidities can aggravate the immune response to the infection and make the individual more liable to be infected or have complications.[26]

The interplay between stress and the immune system

The effect of short-term stress on the immune system

In the early stage, stress activates the hypothalamic–adrenal axis (HPA), sympathetic–adrenal–medullary axis, and the vagus system, which then upregulates glucocorticoids (GCs) from the adrenal cortex and provokes the release of catecholamines (CAs) from the medulla of the adrenal glands to the brain and blood. Surfaces and the cytoplasm of immune cells, monocytes, and neutrophils are responsive to GC and CAs through GC and adrenergic receptors, which inhibit pro-inflammatory cytokines and promote the release of the anti-inflammatory cytokines.[27,28] Cortisol and GC receptors within the nucleus inhibit transcription control pathways such as nuclear factor-kappa B (NF-κB), AP-1, Janus kinase-signal transducer and activator of transcription (STAT) factors, mitogen-activated protein kinases, STAT3, signal transducer, and other pathways,[29] which then decrease the pro-inflammatory cytokines. In addition, motor vagus nerves secrete acetylcholine, inhibiting IL-1β, IL-6, and TNF-α.[29,30]

For regulating the inflammatory cytokines, Th1 to Th2 shift also plays its role. Th1 cells promote cellular immunity by secreting IL-2, IL-6, TNF-α, and INF-γ, activates cytotoxic T-cells, natural killer cells, and macrophage. Th2 cells boost humoral immunity on the other hand by secreting cytokines, primarily IL-4, IL-10, and IL-13.[28] GCs and CAs also act on their classic receptors on antigen-presenting cells (APCs) leading to the suppression of production of the inducer of Th1 responses, IL-12. In addition, the invasion by pathogens also leads to the suppression of IL-12 secretion from the APC. Therefore, all leads to Th1 to Th2 shift, in turn, suppressing the secretion of pro-inflammatory cytokines and enhancing the anti-inflammatory cytokines. Recently, several studies have reported that GCs do promote the secretion of IL-1β, IL-6, and TNF-α, but this does omit the possibility of involvement of other signaling pathways in the inflammatory process.[28,31] Besides, upregulation of different hormones, such as corticotrophin-releasing hormone, adrenocorticotrophic hormone, GCs, and CAs, because of stress is already a fact, which again supports that acute stress plays a definitive role in downregulating the pro-inflammatory cytokines.[32]

The effect of prolonged stress on the immune system

Very interestingly researchers have found that stress can increase pro-inflammatory cytokines. For example, the researchers who performed a meta-analysis using 300 studies about chronic stress have detected an increased production of IL-6 and INF-γ during the times of chronic stress, and these findings were very consistent in several paradigms they adopted.[33]

Accordingly, the arising question is whether chronic stress upregulates or downregulates the pro-inflammatory cytokines? In our understanding, the prolonged stress is a series of different stages, and each of these stages defines how the inflammatory cytokines will be influenced in variable ways. The early stage of chronic stress downregulates the pro-inflammatory cytokines and upregulates the anti-inflammatory cytokines. On the other hand, prolonged stress leads to HPA axis fatigue, and when prolonged, it will cause GC resistance and a diminishment in the sensitivity of the immune system to cortisol.[29] Furthermore, activated NF-κB provokes pro-inflammatory cytokines to further enhance the inflammatory response. These events influence and increase pro-inflammatory cytokines and so inflammation, which may be the activating factor in various diseases[34] [Conceptual Figure 1].

Effect of stress on the gut microbiota

Recent reports have revealed that stressors negatively influence gut microbiota leading to a shift in the microbiome composition (dysbiosis). In general, stress is thought to change the gastrointestinal environment through physical, immune, and neurochemical mechanisms, making it more attractive for certain species, and less attractive to others and thus is considered a "dysbiosis promoter."[35] The role of gut microbiota in modulating chronic stress response is suggested to be through several mechanisms, including intestinal hyperpermeability, exaggerated response of HPA axis, altered cognition, and altered social behavior.[7]

Earlier animal studies have reported that different types of stresses such as maternal separation, noise, crowding, acoustic stress, restrain, and heat stress can alter intestinal microbiota composition. Decreased levels of *Lactobacillus* have been detected after chronic restrain and maternal separation which has been correlated to stress and not to cortisol levels, indicating the role of stress in its modulation. Following these results, improvements were found in biochemical, behavioral, and cognitive parameters in animal models of stress after oral administration of *Lactobacillus*.[36]

As previously stated, the stressors applied to the health workers include stigma as well as inverted circadian rhythm and high workload.[2,23] There is a two-way cross-talk between the gut microbiota and the circadian rhythms of the host. The disturbed light-dark cycle could affect microbiota homeostasis. On the other hand, the microbial metabolites including polyphenolics, vitamins, and butyrate could affect the host circadian rhythm.[37,38] In their study, Voigt *et al*. have reported that disturbed circadian rhythm affected the function

of the gut microbiota, a matter that could have implications on the inflammatory conditions of the host.[39] Many studies have linked the improper nutrition to the disturbance of the microbiota. No doubt, the long periods of work stress and the long time the medical staff pass wearing the face masks and the protective clothes may affect their nutritional status due to the narrow time allowed for them to rest and have a healthy diet, a matter that makes it easier for them to devour fast foods that include too much fat content with low dietary fibers, vitamins, and minerals.[40,41] The lack of dietary fibers and the increased consumption of fatty food has been reported to lead to the flourishing of the pathogenic gut microbes[42-44] [Conceptual Figure 1].

The effect of gut dysbiosis on the immune system

Gut microbiota has many influences on the human body physiology and can modulate our immune system. Roughly 70%–80% of our immune cells are located in the gut; the body immune system interacts with the gut microbiota to support and help each other in defending the body's against invaders and tolerates beneficial microbes.[45] The gut microbiota such as *Bacteroides*, *Lactobacillus*, and *Bifidobacterium* species have several advantages, such as improving gut barrier integrity, metabolism, and increasing the body defense mechanism against virulent pathogens.[46]

The intestinal wall is not just an ordinary physical barrier. However, it is a barrier with a strong interplay between both the gut microbiota and the immune system.[47] This barrier is formed of intestinal epithelial cells, the mucus that they secrete, as well as the inflammatory cytokines, antibodies, and antimicrobials released by immune and epithelial cells. These epithelial cells identify microbe-produced substances through pattern recognition receptors (PRRs). By this mechanism, they can cause alteration in the epithelial activity according to the chemicals produced from microbiota. In addition, they can improve the antimicrobial response of the epithelial cells and help to destroy the pathogen and the infected cells.[48] Epithelial cells interact with the gut microbiota through the metabolites produced by these microbiota, such as short-chain fatty acids, polyamines, and amino acids.[49,50] Gut flora metabolites can affect the development, maturation, and function of immune cells in different organs, through passing the intestinal barrier, and then, they are absorbed to the blood and lymph and reach these organs. By the effect of microbial metabolites, the gut microbiota can modify the responses of the innate immunity in the body.[51]

The metabolites of the gut flora depend on its composition. Therefore, dysbiosis which is microbial imbalance can influence the interaction between the gut microbiota and the body's physiological pathways. Dysbiosis is caused by several factors, such as the uncontrolled use of antibiotics, environmental factors, dietary composition, genetic factors, and stress. It causes interruption of the epithelial barrier which increases our vulnerability to infections or stimulates abnormal immune reactions to gut microbiota causing chronic inflammatory state, autoimmune diseases, or dysfunction of other organs.[52]

Microbiota and innate immunity have a special two-way interaction. PRRs, named Toll-like receptors (TLRs), can feel the microbial signals at the time of infection to stimulate the appropriate immune response. Despite that, the commensal microbiota can produce ligands to PRRs during healthy colonization. TLRs are part of the body's defense mechanism against invaders and regulate normal microbes to keep the integrity of the tissues. Polysaccharide A is made by the commensal *Bacteroides fragilis* and is a single molecule that endorses symbiosis and host immune system.[53]

The interacting triad "stress, dysbiosis, and immune system"

The dysbiosis and COVID-19

The microbiota plays a crucial role in direct elimination or suppression of the virus within or outside the intestine. Such microbiota–viral interaction could suppress or enhance the viral infectivity directly or indirectly via modulating the immune response to the virus. Additionally, the viruses could lead to disturbance in the microbiota function and the resulting dysbiosis (disturbed microbiota homeostasis) eventually can affect the viral infectivity.[54,55] There is still a great controversy regarding the relationship between the gastrointestinal symptoms and the severity of COVID-19 disease. Some studies have documented that the gastrointestinal symptoms are present in severe cases, while others related the severity to the presence of the gastrointestinal symptoms.[56] Saleh *et al*., 2020, have reported that the iron dysregulation in patients with COVID-19 leads to the release of reactive oxygen species and aggravation of oxidative stress. This, in turn, predisposes to mitochondrial dysfunction. The latter could be a contributing factor in microbiota dysbiosis.[57] Xu *et al*., 2020, have documented that some patients with COVID-19 showed disturbances in gut microbiota with a reduction in the probiotic bacteria *Lactobacillus* and bifidobacteria.[58] In their study, Gu *et al*., 2020, have reported a change in the microbiota diversity in COVID-19 patients compared to the healthy controls. They documented a relative increase of the opportunistic pathogenic microbiota such as *Streptococcus*, *Veillonella*, *Rothia*, *Actinomyces*, and Erysipelatoclostridium.[59] Changes in the composition of fecal microbiomes were found in COVID-19 patients relative to controls. The most interesting note was the increased opportunistic pathogens and reduction of useful commensals during hospitalization in COVID-19 patients. Adding to this, gut dysbiosis was still present even after being negative COVID-19 in throat swabs and improvement of all respiratory symptoms.

The chemokines and coronavirus

Cytokines are involved in the pathogenesis of SARS-CoV patients. More importantly, CXCL10, CCL2, and TNFα blood titers (but not those of IFNγ) were reported to be significantly elevated in severe disease as compared to patients with mild symptoms.[12] In SARS disease progression, CXCL10 was also regarded to be an effective prognostic marker. Moreover,

CXCL10 serum level was found to increase significantly in early stage and persisted until the resolution in SARS infection. Persistently raised levels of CXCL10 during follow-up predict the outcome of the infection.[60] SARS-CoV could also enter macrophages and dendritic cells, and leads to an abortive infection, eliciting the release of pro-inflammatory chemokines.[61] This is then followed by a depressed IFNβ response, in parallel to a moderate rise of pro-inflammatory cytokines TNF-α and IL-6. Eventually, this leads to more upregulation of chemokines.[62] Chemokine upregulation leads to immune evasion by SARS-CoV due to the depressed response to antiviral INFs.[63] That is why direct exposure to the epithelial lining of the lung or peripheral blood mononuclear cells causes a rapid release of many chemokines.[62,63] An age-related enhancement in the symptoms' severity, which is related to enhanced levels of pro-inflammatory cytokines and chemokines and so diminished T-cell responses, was also noticed even in humans.[64] The aforementioned refers to that the severity of infection might be due to dysregulation of the immune system, rather than viremia.

The interplay among microbiota, stress, and immune system and disease severity

The severity of COVID-19 has been correlated with the degree of abundance of *Coprobacillus*, *Clostridium ramosum*, and *Clostridium hathewayi*. At the same time, the severity of the disease was negatively correlated to the abundance of *Faecalibacterium prausnitzii* (an anti-inflammatory bacterium).[65] COVID-19 patients who were presented with diarrhea had also inflammatory responses in the gut which was supported by the detection of calprotectin in the fecal samples.[66] COVID-19 virus enters the host through using angiotensin-converting enzyme 2 (ACE-2) receptors which are greatly expressed in the respiratory and gastrointestinal tract.[67] Moreover, ACE-2 is used to control intestinal inflammation and gut microbial biology. The gut microbiome can regulate immune response through regulating gene expression and metabolism.[25,68] *Actinomyces viscosus,* the opportunistic infection, was found in the oral cavity and respiratory tract in COVID-19 patients, which explains the transmission of extra-intestinal microbes into the intestine[65] [Figure 1].

The role of the viral load in increasing the severity of infection by COVID-19

Together, the innate and adaptive immune responses come into action in response to SARS-CoV-2 infection.[69] The exposure to a high viral load of SARS-CoV-2 increases the severity of the infection. This is attributed to the inability of the adaptive immune system to build up a sufficient immune response against the virus in the form of antibodies and cytotoxic CD-8 cells in a short period. Therefore, the innate response which is less specific and less developed overcomes the adaptive immune response. Hence, the evolving cytokine storm leads to severe immune reaction, which is reflected in disease severity and prognosis, leading to a severe form of the disease and even death.[69,70]

Conclusion

Collectively, it is reasonable that persistent stressors applied to the health team workers could make them more apt to catch severe infection via the modulatory effect of stress on the immune system and the gut microbiota. In addition, we can conclude that the bidirectional effect of an individual's gut microbiome arrangement and immune system may affect the subject's vulnerability and reaction to COVID-19 infection. Therefore, these aspects necessitate the presence of social and governmental support for health workers to mitigate stress. Further, due to the lack of proven therapies for COVID-19, new therapeutic approaches targeting the host biological interactions could be developed.

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Conflicts of interest

There are no conflicts of interest.

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