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STUDY ON THE IMMUNITY INTERVENTIONS A DETERRENT EFFECT AGAINST PATHOGENS

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ABSTRACT

The year 2020 is exceptional year in human history and normal activities have almost stopped. That indicates human life will face greater consequences of Pandemics (COVID-19) in future. Few decades back man was not highly dependent on science and technology as today and has become ease oriented that pushing us toward non-healthy lifestyle. Economic challenges, social pressures, and health issues are some of things that might negatively affect our immune system. The cytokine storm was decreased by a large dosage of vitamin C, which also lowered chances of ICU admission and moderate or mild lymphopenia recovery in people who slept well by enhancing immunity mechanisms. Weak immune system is a big threat and life can be miserable if we failed to improve, revive and replenish our immune system. Healthy and active life style can increase immunity which will give us hope to fight with these types of catastrophic conditions.

1. INTRODUCTION

It should be considered that viral diseases are a huge threat on the basis of their retrospective effects in terms of epidemics and pandemics which have left indelible imprints on humanity. One of the best solutions to overcome these conditions is to improve and maintain the immune system (Lindsay, 2016). All the pathogenic organisms i.e., fungi, bacteria, viruses, and parasites are seized and destroyed by the immune system which consists of a chain of effectors mechanisms (Williams, 2011). An immune system is further divided on the basis of two types of responses: an innate or non-specific immune response (natural) and an acquired immune response (antigen-specific), that distinguish the PAMPs (pathogen-associated molecular patterns) (Aderem & Ulevitch, 2000). PAMPs are perceived by PRRs (pattern recognition receptors) mostly symbolized in innate immunity cells, these PPRs are also able to distinguish DAMPs (damage-associated molecular patterns) molecules that are unleashed from gangrene cells infected by assaulted microorganisms (Lamb, 2012).

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The natural immune system principally consists of two types of barriers the first one is physical barriers, like skin and mucous covering. The second one is chemical barriers which include antimicrobial peptides and reactive oxygen species (ROS) (Williams, 2011), natural immune cells, complement cascade, innate antibodies, and associated cytokines (Aderem & Ulevitch, 2000). The most important function of an inherent immune system is: (1) to use the physical and chemical barriers to stop the entrance of pathogens into the body (Williams, 2011) (2) to prevent the outbreak of infection by using the complement system and other humoral factors inside the body; (3) to get rid the body from pathogens by phagocytosis and cytotoxicity mechanism (Tosi, 2005) and (4) to stimulate the acquired immune response through synthesizing the several cytokines and antigen presentation to T and B cells which are natural killing source for body in its defense mechanism.

During skin infection, swelling and redness are the most common host response and it varies depending upon the strain and type of infection caused by the pathogen. Viruses in the absence of cytopathologic damage at the

early stages of infection inhibit the induction of acute-phase protein response because early monocytes are not activated. However, the NK cells take part in host protection and play a significant role in the host's protection; they distinguish virus-infected cells in an antigen-independent manner and exert a toxic effect on infected cells. NK cells rapidly produce IFN-γ in a large amount that takes part in the activation of the adaptive immune cell enhancing the antigen presentation during body encounter with viruses (Tosi, 2005). Type I interferons are recognized as the most important cytokines that defend the host against the viral infection. It is documented that interferons have antiviral properties and they do not exert their antiviral effects by acting directly on viruses.

However, they stimulate the production of antiviral proteins by gene activation. These proteins inhibit viral replication and mediate the effects of suppressor T cells (Thimme et al., 2006). The acquired immune response is mainly composed of the humoral immune response that is mediated by antibody production intended for viral antigens. Though cellular immunity is essential for viral pathogen elimination, T CD4+ cells recognize antigens presented by MHC-II (major histocompatibility complex) molecules on the surface of APCs (antigen-presenting cells) (Koziel, 2005). Afterward, CD4+ helper cells have multiple functions including direct activation of antigen-specific macrophages and B cells, as well as cytokine-dependent activation of T CD8+ cells. T CD8+ killer cells disintegrate the virus-containing cells and emit cytokines such i.e. TNF-α and IFN-γ, which are also involved in the inhibition of viral replication. Therefore, in most cases, the involvement of both immunological responses i.e. innate and adaptive immune responses eradicates viral infections through a humoral and cellular immune system. Nevertheless, certain viruses can develop a system for immune dodging to survive longer and so be able to replicate without any problem until causing serious infection and its symptoms to the host (Accapezzato et al., 2005). Previous studies have shown that T cell response to different proteins (S protein, M, and N proteins) is long-term, constant and it is used for forming new drugs and vaccines for SARS-CoV-2 made up of viral structural proteins. These vaccines can induce dominant, efficient, and long -term memory cell responses in body memory cells against the virus. Though, former studies have also shown an important role of both CD8+ killer cells and CD4+ helper T cells in SARS-CoV2 clearance from the host body (Chen et al., 2010), whereas also documented that the formation of definite neutralizing antibodies for SARS -CoV needs CD4+ T helper cells (Janice et al., 2012).

In this review article, we will discuss features that can affect our immune system.

Nutrition and Immunity

Undernourishment comes up due to numerous variations in daily lifestyle that includes poverty, intellectual condition, societal position, and a host with other problems (Volkert et al., 2020). Regularly, there are dietary deficiencies of calcium, vitamin C and Figure 1 represented the role of vitamin C in recovery of COVID-19 patient (Liu et al., 2020), vitamin D, folate, and zinc among the victim and aged people (Power et al., 2014). Malnourishment can lead to a weak immune system in the old people and making them more vulnerable to infections as compared to the others. Diet and immunity are closely associated, as when we compare its volume with other systems of body, the maximum energy is consumed by protection system of the body and thus it is mainly influenced by nutrient deficiency. One important component of this system is adipose tissue, which play a significant intermediate role between nutrient availability and immune cell functioning. Adipocytes control tissue homeostasis and prevent swelling in people who have a healthy body weight. In 1993, the discovery of the expression of inflammatory cytosine tumor necrosis factor alpha (TNFα) was linked with the insulin resistance and obesity. The genetically engineered obese mice and rat, the TNFα mRNA persistence have expressions than the wild type in adipose tissue in control experiment, thus providing link between inflammatory response and obesity (Hotamisligil et al., 1993). Though, the prolonged and excess taking of nutrients resulted in obesity and the increase in lipocytes has a negative impact on the immune function and host defense (Milner & Beck, 2012).

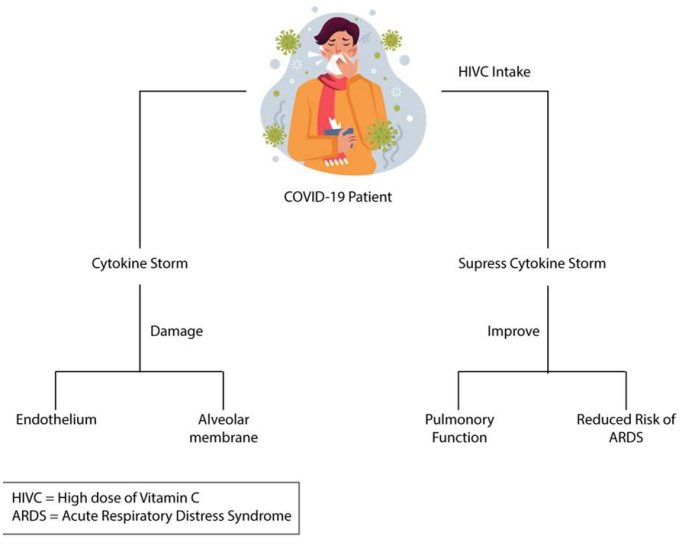

Figure 1. Role of vitamin C in recovery of COVID- 19 patient (after Liu et al., 2020).

Under homeostatic state, regulatory and alternatively activated (type 2) immune cells are persistence in the adipose immune system. The cells include invariant natural killer cell functionally regulatory, Delta Gamma T cell, some lymphoid cell like type 2 innate (LC), adipose Macrophages and Bregs abbreviated as B regulatory cells. The cells functions as inflammation reduction and involved in normal adipose remodeling (secretion of factor like interleukins 10, IL 4 etc). White adipose serving as energy reservoir, store free fatty acids, glucose and other nutrients, provide the nutrient of demand. In system metabolism, healthy adipose tissue plays a pivotal role. In the case of obesity, hypertrophic and dysregulation leads to the accumulation of triglycerides with cells of non-adipose (Ectopic lipid deposition) and inflammation due to excessive release of the INF gamma and TNF aplha. Disturbance in the immune repertoire and inflammatory immunity cells, specifically adipose tissue macrophages and metabolically stimulated ATMs promote pathogen remodeling through fibrosis and abnormal angiogenesis. The metabolic failure of normal adipose tissue leads to the hyperglycemia, resulting in resistance of insulin and systemic inflammation as (Kane & Lynch, 2019). Comparison between the immunity of a lean and obese person (Figure 2).

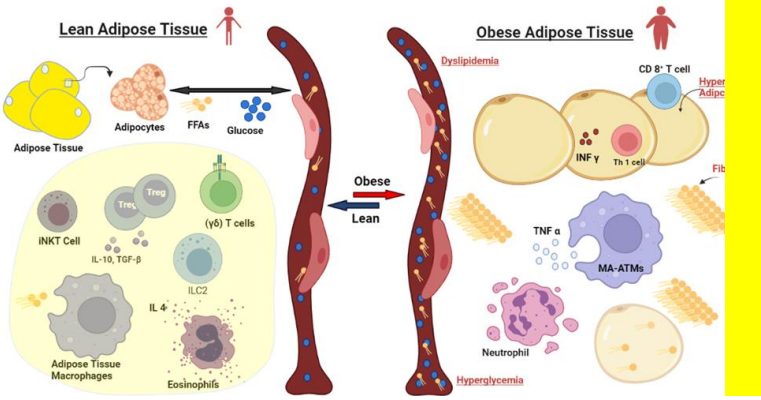

Figure 2. Comparison between the immunity of a lean and obese person

Nutritional status influences the both inborn and the acquired immune systems (Weisberg et al., 2003). The number of T lymphocytes (T cells) and B lymphocytes (B cells) are changed due to dietetic condition (Gerriets & MacIver, 2014; Winer et al., 2014). Severe starvation has been found to change T-cell count by effecting the T-cell survival and propagation. Such as, mice starved for 48-hours contain extensively decreased thymocyte and splenocyte counts compared to ad libitum-fed control mice (Howard et al., 1999; Procaccini et al., 2012; Saucillo et al., 2014). Similar results were also noted in skinny human. As, both CD4+ helper and CD8+ killer T-cell counts were decreased in blood samples collected from starved children in contrast to T-cell counts from healthy children as controls samples (Nájera et al., 2004). It was also noted that the weak children were found to have decrease level of cytokines which endorse discrimination of CD4+ T helper cells into pro-inflammatory Th1 cells: IL 12, IL 18, and IL 21. The decreased level of cytokines formed by Th1 cells: IFN and IL-2; in addition to impaired Th1-cell production (González-Martínez et al., 2008; González-Torres et al., 2013). The similar group also noted that starved children showed an increase in the relative expression of the Type 2 T helper cell (Th2) cytokine IL-4 and the anti-inflammatory cytokine IL-10 (González-Martínez et al., 2008).

Current mice studies have compared the consequence of fasting on effectors CD4+ helper T cells and regulatory T cells and found that fasted mice had a more significant decrease in T effectors cell number (particularly Th17) than in T regulatory cells (Gerriets et al., 2016). T cells of the acquired immune response have a dominant role against viruses by balancing the encounter with pathogens and the danger of devastating inflammation or increasing autoimmunity (Cecere et al., 2012). Helper T cells (CD4+) endorse the manufacturing of virus-related antibodies by stimulating the T-dependent B cells, whereas another T cells for example the CD8+ are cytotoxic and can destroy virus infected cells (Li et al., 2020). As well, the helper cells (T cells) make pro inflammatory cytokines and chemokines by the NF-kB signaling pathway, which, in order, move the lymphocytes and leukocytes, for example monocytes and neutrophils, to the location of disease, with a successive discharge of large amount of chemokines and cytokines from all these immune cells to increase the inflammatory reaction to the virus illness (Julkunen et al., 2000; Li et al., 2020).

Dietetic composition can have a pronounced effect on an individual's whole health, the decrease of NCDs, and a less vulnerability to having a disease. In this part, the advantageous effects of a nutritious diet are discussed in accordance to the present epidemic conditions (WHO, 2020). Yet, from the preceding study in relation to other viral infections it is concluded that nutritional state has an important role in patient recovery (Beck et al., 2004). At the moment it is significant to maintain good diet, because the fight against viral diseases both pandemic as well as epidemic like COVID-19 will possibly end longer than what was at first expected (Melaku et al., 2019), and to keep up a healthy invulnerable system, unusual notice must be taken to retain a healthy diet, routine work out management, and least stress as much as securely possible at this hard time (Mattioli & Puviani, 2020). A healthy and balanced diet contain all the essential macro- and micronutrients that can restore and keep up immune cell function, thus rising defense against chronic inflammation-related NCDs, on the one hand, and possible

infections and associated inflammatory appearance on the other hand (Tsoupras et al., 2018).

Sleep and Immunity

According to current study, those who suffer from sleep problems such as inadequate sleep, insomnia, or restlessness have a weakened immune system. (Bancroft, 1993; Burgos et al., 2006). People with sleep agitation suffer from depression and stress which as a result decrease cell activity (as NK cell activity), the strong immune system plays a vital role against viral infection (Cover & Irwin, 1994; Haack et al., 2007). Effects of sleep disturbance undermine the immune system in two ways which are intrinsic as well as adaptable causing a disturbance in circadian rhythms that intensify infections in cytokines (Fondell et al., 2011; Irwin, 2015). Studies demonstrate that the poor sleep pattern can alter the aspects of acquired immunity in animals and human are at the higher risk of getting infection (Opp, 2009). An anecdotal narrative put a theory that the insufficient sleepless makes the individual vulnerable to the risk of getting cold (Prather & Leung, 2016). Moreover, there is potential evidence of self-reported sleep of short duration (≤5 h per night) and prolonged duration (≥9 h per night) people on physician diagnosis had increased chances of pneumonia infection than in the person with normal sleeping pattern (Patel, 2012).

In addition to these, the nocturnal increase of the natural killer cells increases during the normal sleep pattern and decrease during the period of sleep lose at the night, Natural killer cell toxicity and sleep is reciprocally related as in the people with impaired sleep (i.e. deprived from sleep between 3 am – 7 am) from the people with the undisturbed sleep (Irwin et al., 1994). The innate and adaptive immunity is regulated by the two primary effector system the hypothalamus-pituitary-adrenal axis and the sympathetic nervous system on which sleep has a direct influence. The literature report that blood level of cortisol, norepinephrine and epinephrine impaired during the night, however mediator like growth hormone, prolactin and melatonin (the pineal hormone) show a steep increase in the blood during the sleep (Besedovsky et al., 2019). The activation of HPA axis and SNS pathways relate to the chronic sleep disturbance contributing to the increase in pro-inflammatory and basal transcriptome. Virtually the gene of every cell of the body is regulated by the hypothalamus-pituitary-adrenal axis with the assistance of hormone glucocorticoid circulating in blood (Vgontzas et al., 2013).

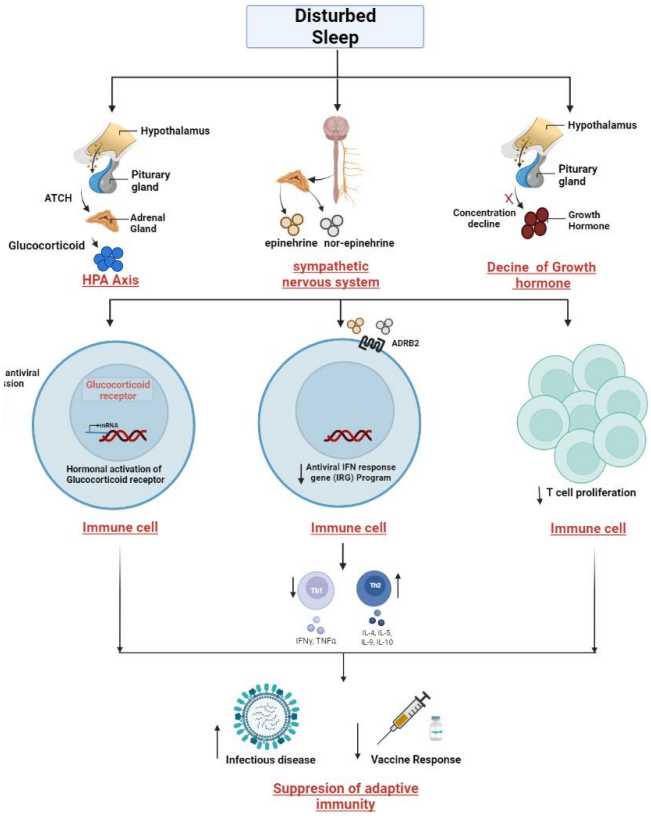

Figure 3. Overview of disturbed sleep and its effect on immunity

The suppression of antiviral programs (Such as the IFN Alpha and IFN Beta) is linked to the disturbance on the sleep as it results into the hormonal activation of glucocorticoid hormone receptor in the leukocytes. Sleep disturbance is credited as it also plays an important role in the stimulation of never fiber from sympathetic nervous system (SNS) that result in the release of neurotransmitter (epinephrines and nor-nepnephrines) into the primary and secondary lymph organs. SNS activates the adrenal gland, causing a rise in the quantity of these neurotransmitters in the bloodstream, as well as a strong effect on leukocytes androgenic receptors, suppressing the antiviral IFN response gene program (IRG). Sleep also affects growth hormone levels in the early hours of the night, causing T cells to proliferate and differentiate. The type 1 cytokine and growth hormone have reciprocal relation with each other in their activity. Deprived and disturbed sleep decrease the release of the growth hormone as IRG also imbalance the concentration of Th1 (Helper cells 1) and Th2 (Helper Cell 2), effecting the concentration of interferon and interleukins in the circulation results in the depression of adaptive immunity, make the individual more vulnerable to infection (Irwin, 2015). Overview of disturbed sleep and its effect on immunity (Figure 3).

A short period of sleep indigence is directly related to NK (natural killer) cell activity in the blood. Common

problems with sleep such as poor-quality sleep, short time sleep, and sleeplessness can bring infection in the respiratory system due to interruption in the circadian rhythm (Prather et al., 2015). A higher mortality rate is determined in patients with disturbed sleep. ACE-2 (Angiotensin Converting Enzyme) has been found as a receptor of the SARS-COV-2 spike. Recently published review predicates that because of indirect impacts in ACE-2 may evince ACE-2 and effects renin-angiotensin system, may provide a possible connection of circadian rhythm to SARS-COV-2 liability (Cruz et al., 2020). Moreover, when we explored SARS-COV-2 infection, an active chain of pro-inflammatory cytokines was found which ultimately may result as a storm of cytokine (Zhang et al., 2020).

Sleep is an important factor for cytokines especially in the formation process of secretions and synthesis, along with INF-a (tumor necrosis factor) and (IL-6) detrimental interleukin, these two INF-a and IL-6 are firmly associated with cytokines storm while disorganized circadian rhythm can effect on cytokine peaks that are dislodged from night to day (Besedovsky et al., 2019). Sleep associated hormone (Melatonin) is directly connected to decrease cytokine though the effect of Melatonin is anti-inflammatory and ability to increase the cell activity that is proposed a contributory remedy for SARS-COV-2 (Zhang et al., 2020). Role of good sleep quality in recovery of COVID- 19 patient (Figure 4).

Increasing sleep has a great effect on infected ones as drosophila (defensive host) plays important role in recovery and survival against infection as well as the ability to develop sleep in anti-infective cure (Toda et al., 2019). Patients with covid-19 are more likely to be sleepy due to illness, an unpleasant environment, and physical and psychological factors. Anyhow, no reports of covid-19 patients have been studied yet that there are any impacts of sleep in the recovery process and any progress in the immune system during treatment (Chen et al., 2020; Guo et al., 2020). Strong opinion can that good sleeping hours that are enough, has contributed to the positive impacts regarding the recovery of Covid-19 patients. In addition to this, we recommend that medical professionals should give awareness to the public on the importance of sleep and how can good sleeping habits and methods have practiced for good health and especially revival against pandemics (Chen et al., 2020).

Stress and immunity

Long-term stress is frequently associated with the loss of valuable things. According to one concept, tension occurs when demands drain or exceed existing resources. (Lazarus & Folkman, 1984). Another one conceptualizes the stress as any resource loss, whether or not it is necessary or not (Hobfoll, 1988). It is significant for health to reduce losses in supportive assets like property or income sources such as social incorporation that are strongly linked with human survival (House et al., 1988).

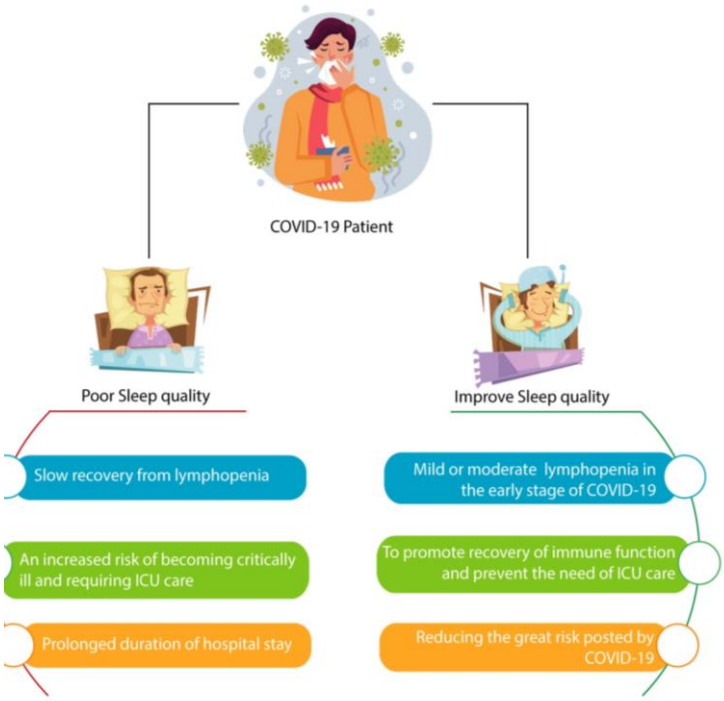

Figure 4. Role of good sleep quality in recovery of COVID- 19 patient (after Zhang et al., 2020).

When any few of the above-mentioned disciplines are in danger, it might be adaptive for organisms to direct him to pay more concerns about the fiscal resources and deviating the victim to look after its physical health. As a result, victim gradually loses its high immunity level. Where might such energy drain? One option is that resource safety involves physical action (e.g., fighting), so the muscles would require extra glucose. Though, in recent days, humans are more likely to utilize intellectual and motivational means for example planning and persistence to manage with stressors; such approach also utilizes glucose by the brain then through the muscles (Fairclough & Houston, 2004). Stressors can increase the possibility of causing transmittable infection, and they can also extend the contagious disease incident (Konstantinos & Sheridan, 2001). Such as, men and women who were constantly tensed through caring for a spouse with dementia showed apparent shortage in both their cellular and humoral immune responses to an influenza-virus vaccine in contrast with well-coordinated control individuals who were not careers (Kiecolt-Glaser et al., 1996; Vedhara et al., 1999). The defensive capability of antiviral vaccines depends on their capacity to stimulate both humoral and cell mediated immune responses (Deng et al., 2004).

These both were weak in the stressed persons as compared with control individuals. Stress-associated impairments in antibody reaction after immunization with influenza virus have also been recorded in adults of younger age (Miller et al., 2004).

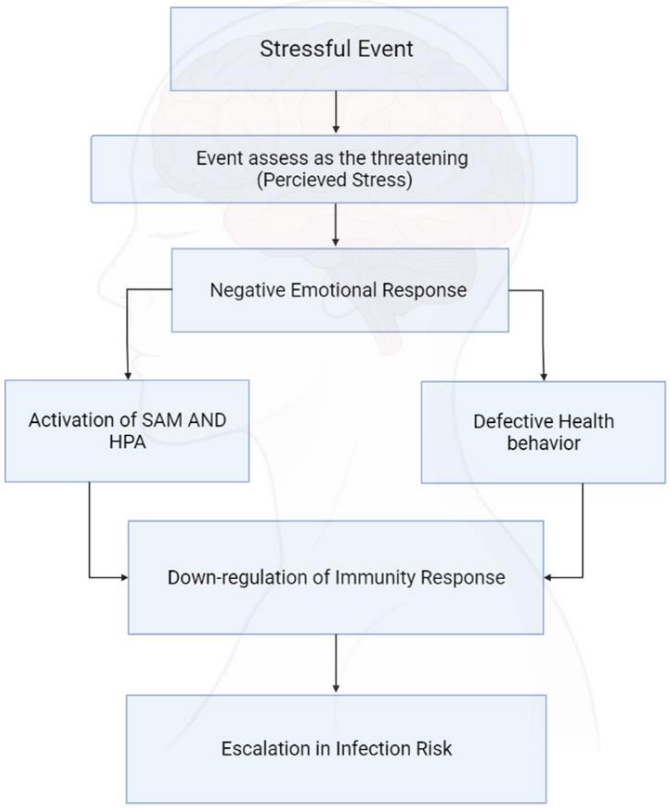

Figure 5. Relationship of stress and risk of increase in infection.

Behavioral response harmful to health (like smoking, drug abuse, drinking alcohol, sleep loss) and activation of physiological response both influence by stress and have direct and indirect effect on human health. The system that copes this stressor are sympathetic nervous system also known as sympathetic adreno-medullary system (SAM) and HPA (hypothalamic-pituitary-adrenal) system (Cohen et al., 1995; McEwen, 1998). The person may develop psychiatric disorder and physical disorder (i.e., immune, cardiovascular) due to the repeated activation of SAM and HPA system and results in the immunity down-regulation and higher risk of getting infections (Cohen et al., 2016). Relationship of stress and risk of increase in infection (Figure 5)

For example, persons who were documented more depressive signs showed raise in serum IL-6 level after 2 weeks of vaccination in opposition to influenza-virus disease while there was a slight alteration in IL-6 level of individuals having few or no symptoms (Glaser et al., 2003). This is balanced with other proof of cross-sensitization between cytokines and stressors in human and animal studies (Johnson et al., 2002; Maes et al., 2001). All the stress linked changes have a wide impact on health and the increased level of pro-inflammatory cytokines (IL-6) have been linked to various age-associated diseases and conditions (including cardiovascular disease, osteoporosis, arthritis, frailty, and functional decline) and certain cancers (such as chronic lymphocytic leukemia) (Harris et al., 1999). Hence, the improvement of the immune system could be the one connection between unreliable claims of the association between positive emotional situations and curing. More to the study of comedy it is acknowledged by researchers that hopefulness may be considered as a buffer beside stress correlated changes in the immune system. The new study documented that when facing contradictory goals, optimists are more likely to remain engaged with both goals and to experience higher short-term stress as a consequence (Segerstrom, 2001). Certainly, optimism is linked with higher numbers of CD4+ cells (helper cells) among students which were less likely to contain academic and social conflict, and with lower numbers of CD4+ cells among students that were more probably to have conflict. Results are also replicated by late-type hypersensitivity testing. The optimist may be subjected to short-term physiological costs in their determination to gain long-term rewards. It is also noted that optimism is linked with good mood, larger numbers of helper T cells, and natural killer cells (CD8) cytotoxicity. Among the immunological measures, the hopefulness and helper T cell association were only partially explained by the frame of mind, and the hopefulness and cytotoxicity link were only partially explained by perceived stress (Segerstrom et al., 1998). Figure 6 represented the overview of the factors that affecting COVID-19 patients (Mazza, 2022).

2. CONCLUSION

It is concluded that the world has not fully recovered from recent pandemic, already under threat from new clusters. The study shows ambitious aim that healthy lifestyle and strong immunity to be the last resort for humanity to fight against the catastrophic condition.

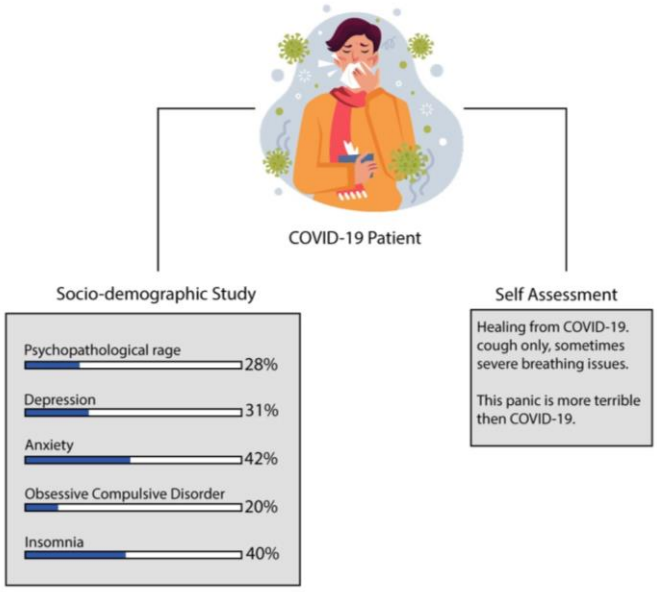

Figure 6. An overview of the factors that affecting COVID-19 patients (after Mazza, 2022).

3. ACKNOWLEDGMENTS

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4. CONFLICT OF INTEREST

All authors have declared that there is no conflict of interests regarding the publication of this article.

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