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Relationship between Stress, Immune System, and Pandemics of Coronaviruses' COVID19: Updates Narrative Review

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Abstract: Background: How stress impacts the immune system of the human being is one of the questions that has been answered through many conducted researches. The immune system is a host defense system comprising many biological structures and processes within an organism that protects against disease. Among recent examples presented nationally and internationally how immune system function properly to preventing the Coronavirus (COVID19) which appear at the end of 2019 and the beginning of 2020. Aim: The purpose of this review was to collect and corroborate updated information and trials related to the various effect of COVID19 on the immune system and how stress, loneliness, and lack of sleep can all weaken your immune system, making people more vulnerable to diseases such as COVID-19. Methods: To compile this review various journals, books, electronic databases, and other resources were used using keywords of immune system, Covid19, stress, and pandemics. The intent behind this review is to provide readers with an in-depth and updated knowledge about this pandemic virus to help resources available for utilization by families and communities. It is also directed towards identifying critical issues about decreasing the vulnerability to infection by improving our immune system, decreasing sources of stressors, and getting enough sleep. Conclusion: Covid-19 has been a wakeup call to us all. It made us realize how important having a strong immunity is. Therefore, people should give themselves a good fighting chance and make changes to their diet and lifestyle today. However, achieving this is not impossible since all agencies and scientists from everywhere are spending time, effort, and money to improve the understanding of the chronological features of CoV- induced inflammatory response concerning the creation of effective vaccine and therapeutic interventions.
Keywords: COVID19, Immune System, Pandemics, Stress, Updates

Introduction

How stress impacts the immune system of the human being is one of the questions that been answered through many conducted pieces of research. The immune system is a host defense system comprising many biological structures and processes within an organism that protects against disease. To work appropriately, an immune system must notice a variety of agents, known as pathogens, from viruses to parasitic worms, and distinguish them from the organism's healthy tissue. Moreover, the immune system is "the bodily system that protects the body from foreign substances, cells, and tissues by producing the immune response and that includes, the thymus, spleen, lymph nodes, special deposits of lymphoid tissue (as in the gastrointestinal tract and bone marrow), macrophages, lymphocytes including the B cells and T cells, and antibodies" [1]

Among recent examples presented nationally and internationally on how the immune system functions properly to preventing the Coronavirus (COVID19) which appeared at the end of 2019 and the beginning of 2020. Multiple human cases of novel COVID-19 infection were first identified in Wuhan

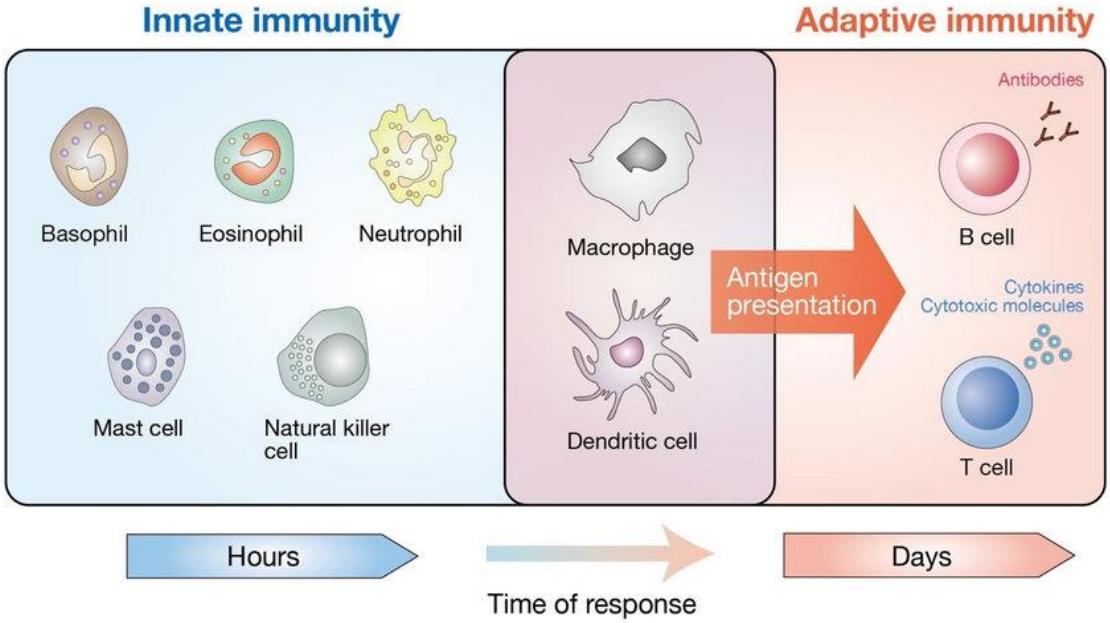
China among people who commonly visit the Huanan Seafood Wholesale Market (South China Seafood City Food Market). On 7 January 2020, the virus was identified as a novel coronavirus and officially named by the WHO as 2019- nCoV, the new coronavirus in 2019. On a very fast spread and since the discovery in December 2019, the virus spread within a month, and over 25 countries had confirmed cases. Hence on 1st February 2020, the World Health Organization declared COVID 19 a public health emergency [2]. Shortly after, Thailand, Japan, and Korea confirmed the discovery of human infection with 2019- nCoV from China. The most vulnerable groups are older adults and those with underlying medical conditions or weak immune systems [3]. Nevertheless, health authorities have advised that the elderly and people with weak immune systems not attend games or matches there in the near term [4].

In many species, there are two major subsystems of the immune system: the innate immune system and the adaptive immune system. Both subsystems use humoral immunity and cell-mediated immunity to perform their functions. In humans, the blood-brain barrier, blood-cerebrospinal fluid barrier, and similar fluid–brain barriers separate the peripheral immune system from the neuro-immune system, which protects the brain.

Innate immune system

The innate immune system is made of defenses against infection that can be activated immediately once a pathogen attacks. The innate immune system is essentially made up of barriers that aim to keep viruses, bacteria, parasites, and other foreign particles out of your body or limit their ability to spread and move throughout the body. Microorganisms or toxins that successfully enter tend to encounter the cells and mechanisms of the innate immune system. The innate response is usually triggered when microbes are identified by pattern recognition receptors, which recognize components that are conserved among broad groups of microorganisms [5] or when damaged, injured or stressed, cells send out alarm signals, many of which (but not all) are recognized by the same receptors as those that recognize pathogens [6]. Innate immune defenses are non-specific, meaning these systems generically respond to pathogens [7]. The innate immune system is always general, or nonspecific, meaning anything that is identified as foreign or non-self is a target for the innate immune response. The innate immune system is activated by the presence of antigens and their chemical properties. This system does not confer long-lasting immunity against a pathogen. The innate immune system is the dominant system of host defense in most organisms [8].

Components of the innate and adaptive immune system.



Cellular components of the mammalian immune system.

Adopted from research gate.net [9]

As it is shown in the image, the cells of the Innate Immune System are many types of white blood cells, or *leukocytes*, which work to defend and protect the human body. In order to patrol the entire body, leukocytes travel by way of the circulatory system. But how the immune system identifies or detect the pathogens? How does the body know? So as to be effective, the immune system needs to be able to identify which particles are foreign, and which are a part of your body. Self refers to particles, such as proteins and other molecules, which are a part of, or made by, your body. They can be found circulating in your blood or attached to different tissues. Something that is self should not be targeted and destroyed by the immune system. The non-reactivity of the immune system to self-particles is called tolerance. [10]

On the other hand, the particles that are not made by your body, and are recognized as potentially harmful. These are, sometimes, called foreign bodies or antigens such as bacteria, viruses, parasites, pollen, dust, and toxic chemicals, which intend to cause damage. The presence of antigens is like a name tag for each pathogen that proclaim the presence to your immune system. Some pathogens are general, whereas others are very specific. Two types of molecules which are Cytokines and Chemokine's. The Cytokines are used for cell signaling, or communication between cells. Cytokines are also used to trigger cell trafficking, or movement, to a specific area of the body. While Chemokine's is a type of cytokines that are released by infected cells. Infected host cells release chemokines in order to initiate an immune response, and to warn neighboring cells of the threat. [11]

The adaptive immune system:

The adaptive immune system relies on fewer types of cells which is a special type of leukocytes, called lymphocytes. The cells of the adaptive immune system are the B cells and T cells, which are the major types of lymphocytes and are derived from hematopoietic stem cells in the bone marrow [12] While, B cells are involved in the humoral immune response, T cells are involved in cell-mediated immune response. Killer T cells only recognize antigens coupled to Class I MHC molecules, while helper T cells and regulatory T cells only recognize antigens coupled to Class II MHC molecules. These two mechanisms of antigen presentation reflect the different roles of the two types of T cells. A third, minor subtype are the γ δ T cells that recognize intact antigens that are not bound to MHC receptors [13]. The double-positive T cells are exposed to a wide variety of self-antigens in the thymus, in which iodine is necessary for its thymus development and activity [8, 14]

In contrast, the B cell antigen-specific receptor is an antibody molecule on the B cell surface and recognizes whole pathogens without any need for antigen processing. Each lineage of B cell expresses a different antibody, so the complete set of B cell antigen receptors represent all the antibodies that the body can manufacture [15]. The adaptive immune system, or the acquired immunity, uses specific antigens to strategically mount an immune response. Unlike the innate immune system, which attacks only based on the identification of general threats, the adaptive immunity is activated by exposure to pathogens, and uses an immunological memory to learn about the threat and enhance the immune response accordingly. The adaptive immune response is much slower to respond to threats and infections than the innate immune response, which is always primed and ready to fight.

Methods:

To assemble this review various journals, books, electronic databases, and other resources were curated. The search terms used were based on three core concepts, using keywords related to the following terms: stress, immune system, and COVID19.

The main aim behind this review is to provide readers with an in-depth and updated knowledge about this pandemic virus to help resources available for utilization by families and communities. It is also directed towards identifying critical issues about decreasing the vulnerability to infection by improving our immune system, decreasing sources of stressors, and getting enough sleep

Relationship between Stress, the Immune System, and Health

A dearth of evidenced based research over the last decades has obviously recognized that psychological stress affects clinically relevant immune system outcomes, including responses to infectious agents and other immune challenges (e.g., vaccinations, autoimmunity, and cancer) inflammatory processes, and wound healing. Coping with stressors can vary among individuals with regard to their perception of stress, mood (e.g., depressive symptoms), and adverse life events, which can modify the quality of life, since stressors exert a negative influence on the human being immune system function. Individual differences exist in the extent to which people mount a physiological stress response. Individual differences in stress physiology are, among other things, related to the brain, which plays a critical role in appraising stressors, as well as in modulating immune system reactivity to physical and social threats [16]. Stress can be defined as the body's way of responding to any kind of demand or threat and the way of defending when you sense danger—whether it's real or imagined—the body's defenses kick into high gear in a rapid, automatic process known as the "fight-or-flight" reaction or the "stress response."

When it functions properly, it helps you stay focused, energetic, and alert. In urgent situations, stress can save your life—giving you extra strength to defend yourself, for example, spurring you to slam on the brakes to avoid a car accident. On the other hand, at certain point, stress stops being helpful and starts causing major damage to your health, mood, productivity, relationships, and your quality of life. Accordingly, Lazarus and Folkman [17] defined stressor as an event that exceeds an individual's perceived ability to cope and can result in an allostatic load and overload. Additionally, certain characteristics of a situation are associated with greater stress responses, including the intensity, severity, controllability, and predictability of the stressor. Physiological reactivity to stressors is commonly observed even after repeated exposure to the same stressor [18].

The conceptualizations of the nature of the relationship between stress and the immune system have changed over time. Selye's [19] finding of thymic involution led to an initial model in which stress is broadly immunosuppressive. Early human studies supported this model, reporting that chronic forms of stress were accompanied by reduced natural killer cell cytotoxicity, suppressed lymphocyte proliferative responses, and blunted humoral responses to immunization [20, 21, and 22]. Diminished immune responses of this nature were assumed to be responsible for the heightened incidence of infectious and neoplastic diseases found among chronically stressed individuals [23, 24.]

Psychopathology of stressors and effect on the immune system:

The immune system is a collection of billions of cells that travel through the bloodstream. They move in and out of tissues and organs, defending the body against foreign bodies (antigens), such as bacteria, viruses and cancerous cells. There are two types of lymphocytes: B cells- produce antibodies which are released into the fluid surrounding the body's cells to destroy the invading viruses and bacteria. T cells - if the invader gets inside a cell, these (T cells) lock on to the infected cell, multiply and destroy it. The main types of immune cells are white blood cells. There are two types of white blood cells – lymphocytes and phagocytes. [25]

When we're stressed, the immune system's ability to fight off antigens is reduced. That is why we are more susceptible to infections. The stress hormone corticosteroid can suppress the effectiveness of the immune system (e.g. lowers the number of lymphocytes). Stress can also have an indirect effect on the immune system as a person may use unhealthy behavioral coping strategies to reduce their stress, such as drinking and smoking. Stress is linked to headaches; infectious illnesses (e.g. 'flu); cardiovascular diseases; diabetes, asthma and gastric ulcers.

How does illness occur as a response to stress and decreased immunity?

Immunity is the natural or acquired resistance of an organism to bacterial or viral invaders, diseases, or infections, while having adequate tolerance to avoid allergy, and autoimmune diseases. The autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis are two major stress-signaling pathways that contribute to immune deregulation [26]. Experiencing a stressful situation,

as perceived by the brain, activates the HPA axis and the sympathetic-adrenal medullary axis (SAM), which provokes the release of hormones which modulate immune function including adrenocorticotropic hormone (ACTH), cortisol, growth hormone, prolactin, epinephrine, and norepinephrine [26]. Chronic stress can suppress or deregulate innate and adaptive immune responses by altering the type 1/type 2 cytokine balance, thereby inducing low-grade inflammation and suppressing the function of immune-protective cells [18]. A primary focus of the field of psychoneuroimmunology has been to understand the link between stress and inflammatory responses. Although acute inflammation is an adaptive response to physical injury or infection, exaggerated and/or prolonged inflammatory responses are detrimental to health [18]. Chronic inflammation secondary to long-term stress has been causally linked to risk of numerous diseases, including infectious illnesses.

Stress, Immune system and COVID19

Human coronaviruses (HCoVs) were first recorded in the late 1960s and were associated with respiratory tract illnesses but were also involved in enteric and central nervous system diseases. "They are represented by 2 prototype strains, HCoV-229E and HCoV-OC43, which belong to antigenic groups 1 and 2, respectively" [27]. In December 2019, severe acute respiratory coronavirus 2 (SARS-CoV-2) has become a worldwide pandemic [28], which caused the illness of Covid-19, which later led to a global emergency. COVID-19 is caused by a novel corona virus where its structure is related to the virus responsible for severe acute respiratory syndrome [29].

All patients presented with a form of viral pneumonia and were tested utilizing broncho alveolar lavage, whole genome sequencing, cell cultures and polymerase chain reaction. After testing, the virus was identified as a genus beta corona virus, relating to the Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome [30].

COVID-19 mode of spread is human-to-human transmission, which is the major transmission mode. According to National Health Commission of China, the sixth version of the guidance for diagnosis and treatments for COVID-19, SARS-CoV-2 being transmitted through respiratory aspirates, droplets, contacts, and feces, and aerosols transmission is highly possible [31]. All groups are considered generally susceptible to COVID-19 regardless of age or gender [32]. Corona virus can be asymptomatic. Symptoms of coronavirus appears after an incubation period of 5 days [33] and include fever and a cough that may progress to severe pneumonia causing shortness of breath and breathing difficulties. Generally, coronavirus can cause more severe symptoms in people with weakened immune systems, older people, and those with long-term conditions like diabetes, cancer and chronic lung disease [34]. Typical symptoms of COVID 19 include fever, cough, headache, sputum production, diarrhea, hemoptysis, diarrhea, dyspnea and lymphopenia. Radiological features include pneumonia, acute respiratory distress syndrome, and acute cardiac injury leading to death. The time from the onset of symptoms to death ranged from 6-41 days with average of 14 days. This time frame is relatively shorter in patients older than 70 years of age and patients with a weaker immune system [31].

The outbreak of coronavirus disease 2019 (COVID-19) may be stressful for people. Fear and anxiety about a disease can be overwhelming and can cause strong emotions in adults and children. Therefore, coping with stressors is urgently required to decrease the vulnerability for anxiety, depression and other psychological reactions. While the reaction to stressors is completely different from one person to another, it mainly depends on personal background, the things that make you different from other people, and the community you live in. Older people are among who respond more strongly to the stress of a crisis, as well as people with chronic diseases who are at higher risk for COVID-19. On the other hand, children and teens are among people who are helping with the response to COVID-19, like doctors and other health care providers, or first responders

With regard to mentally ill people or those who have mental health conditions, including problems with stress during an infectious disease outbreak can cause fear and worry about their own health, sleep or eating patterns disturbance, difficulty in attention and concentration and over consumption of alcohol and drug abuse. Furthermore, the challenges of the COVID-19 pandemic are different for various socio-demographic groups, in which this crisis has affected the more vulnerable

elderly group and those with preexisting health conditions such as diabetes, cardiovascular and respiratory disorders.

The COVID-19 disease has hit older adults harder than other age groups. Older adults are more likely to already have underlying conditions such as cardiovascular disease, diabetes, or respiratory illness — comorbidities that raise the risk of severe COVID-19 and COVID-19-related death. In addition, a likely weaker immune system makes it harder for older adults to fight off infection. Consequently, the impact on older adults is notable. According to World Health Organization (WHO) data from April 2020, more than 95% of COVID-19 deaths were among people over 60 years of age, and more than half of all deaths occurred in people of 80 years-plus [32]. In fact, older adults are at a significantly increased risk of severe disease following infection from COVID-19, because of their low immune system, therefore, supporting and protecting older people living alone in the community is everyone's business" [33]. Moreover, at least half of the older adults living in these care facilities have Alzheimer's disease or other forms of dementia, which makes it more difficult to contain possible infections with the new coronavirus. One of the specific challenges for people living with dementia and similar forms of cognitive impairment is that they may have difficulty understanding the dangers of infection. Also, they may forget to follow safety precautions, such as washing their hands or practicing physical distancing.

Care givers for people with dementia and have gotten the virus may also avoid seeking treatment or being hospitalized because they cannot afford to leave their elders alone. On the other hand, people with dementia themselves who have COVID-19 and need hospitalization may avoid it because they fear that, due to hospital triaging protocols, they may fall at the bottom of the ladder when it comes to receiving medical resources and attention.

Furthermore, people may be discouraged from seeking medical attention for dementia itself if they start to display symptoms; memory clinics are shutting, as seeing new patients is perceived to be riskier than for some people who did not to receive a dementia diagnosis. Therefore, special attention and supporting measures should be given for those highly vulnerable older adults, from the probability of developing a more severe form of COVID-19 to the risks of isolation and mental health problems. This report looks at conditions in which older adults have taken the effect of the pandemic and causing death.

Among high-risk groups who are vulnerable to infection with Covid 19 is a type of blood group. Recently, new research suggests that people with O blood type are less likely to contract the novel coronavirus. For such blood type, the risk of developing severe symptoms, including organ failure, is also reduced. On the other hand, people who have blood types A and AB are the most vulnerable to the infection [34]. These findings were reported from two separate studies aimed to reason why the virus is lethal for some, while others are not vulnerable at all. First research collected data from 4, 73,000 Danish Covid-19 positive individuals out of 2, 2 million of the general population. The results showed that there were fewer positive results among those with blood type O. While peers with blood type A and AB were the most vulnerable. Rates of infection were similar in these three groups. On the other hand, the other study collected data from 95 critically ill Covid-19 patients in a hospital in Vancouver. They found that the A and AB blood types were at higher risk of severe symptoms than those with O or B. In addition, the researchers observed that patients with these blood types are more vulnerable for lung injury so, they might require mechanical ventilation and dialysis for kidney failure. The researchers also noted that people with blood types A and AB did not have longer overall hospital stays. However, they remained in the intensive care unit (ICU) for longer on average [34].

According to Glaser and Kiecolt-Glaser [26] the stressful situation can lead to dysregulation of humoral and cellular immune responses to pathogens, which increases the risk for infectious illnesses including influenza and common cold. The relationship between psychological stress and vulnerability to the common cold has long been recognized; stress suppresses the host resistance to infection and increases rates of infection [35]. Loneliness is another well-established risk factor for poor physical health. In a study of our own, we were able to demonstrate that loneliness predicts self-reported cold symptoms after a viral challenge, suggesting that cold symptoms are more severe among those who feel lonely [36]. Therefore, the vaccination against influenza virus is expected to reduce both risk and severity of infection, thus decreasing risk for hospitalization and death. Vaccine effectiveness is of

particular importance among high-risk groups, including pregnant women and older adults. However, the protective efficacy of antiviral vaccines depends upon their ability to induce both humoral and cell-mediated immune responses [37].

Moreover, a meta-analysis of 13 studies established that the influence of stress on antibody responses to influenza virus vaccination corresponded to adequate antibody responses among 41% of stressed individuals versus 59% of less-stressed individuals with similar effects among older and younger adults [38].

The viral infections, including Coronavirus (COVID19) adopt a latent state after the initial infection [38]. After primary infection, the virus continues to reside in B lymphocytes and white blood cells for the life of the individual. Under normal health conditions, reactivation and replication of the virus is prevented by the cellular immune system, largely orchestrated through specific-memory cytotoxic T cells and natural killer (NK); thus, individuals with Corona virus infections generally remain asymptomatic for more than 14 days [39]. However, under stressful conditions, suppressive immune activity may be reduced, permitting reactivation of the virus.

Nowadays, an extensive body of literature in humans endorses that psychosocial stressors predict reactivation of latent viruses. For instance, people with good health was associated with lower reactivation of latent viruses and inflammation [40]. Meanwhile, it increases the antibody titers against viral capsid antigen (VCA) which have been observed in the context of depression, perceived stress [41, 42] childhood adversity [43] bereavement or divorce [44], exam stress [45], attachment anxiety [46], and perceived discrimination [47]. All together concluded that, these human and animal studies showed that stress can modulate the steady-state expression of latent viruses, down regulating specific T-cell responses to the virus to an extent that is sufficient to result in viral activation.

Furthermore, Coronavirus (COVID19) is similar to herpes viruses, in that the virus remains in a latent state in the body after primary infection. As individuals infected with COVID19 have increased antibody-secreting cells (ASCs), follicular helper T cells (TFH cells), activated CD4+ T cells and CD8+ T cells and immunoglobulin M (IgM) and IgG antibodies that bound the COVID-19-causing coronavirus SARS-CoV-2 were detected in blood before symptomatic recovery. These immunological changes persisted for at least 7 days following full resolution of symptoms. Interestingly, what are important to fight infections, exists in whether chronic stress and depression—that also are known to suppress the human immune system—may affect the disease progression. Indeed, there is a substantial body of evidence pointing at a relationship between stress and the rate of viral infection progression. In particular, stressful life events are considered to exert important impacts on certain biological markers of the disease: viral load and CD4 cell count [48].

Psychological Reaction to Infections with COVID19

Fear and anxiety are highly prevalent among Coronavirus-positive patients. Anxiety, and fear are associated with, among other factors, increased inflammatory markers (e.g., CRP; IL-1β; IL-6, TNF) [49] which may alter the function of lymphocytes and decrease NK activity, to respiratory distress progression and mortality in these patients [50]. These findings are confirmed by a study that investigated norepinephrine, cortisol, depression, hopelessness, coping, and life event stress as predictors of decreasing immune system and progression of viral diseases in a diverse subject sample every 6 months over a period of 4 years. The researcher reported that norepinephrine, depression, hopelessness, and coping significantly predicted a greater rate of decrease in CD4 and increase in viral load, demonstrating a robust effect of stress on attacking the immune system and progression of viral and inflammatory diseases [51].

Likewise, studies in adults and adolescence have confirmed that negative emotions, including anxiety and depression, can modulate the antibody and T-cell responses to antiviral vaccinations, resulting in suppressed immune responses [52, 53]. Attractively, a study [54] reported that post 4 weeks' intervention in students embarking on academic examinations was associated with reduced distress and enhanced antibody responses after a hepatitis B vaccine. In the same vein, a positive effects and response was reported among individuals practicing mind-body therapies, including Tai Chi, Qi Gong,

meditation, and Yoga, on the immune system and virus-specific antibody responses to vaccines have also been documented in a meta-analysis of 34 studies [55]

Why Covid19 Is Stressful to all People?

Many reasons were discussed in many literatures among these are the followings:

- Fear of unknown usually leads to anxiety.
- Accelerating rate of prevalence of infection as reported daily in T.V. and social network.
- Increased number of deaths all over the world.
- Failure of people to follow the pandemic precautions.
- Social distancing and quarantine lead to loneliness, depression, loss of jobs and anxiety.
- Stigma as a response of public to infected people.
- Treatment and less training of health care professionals and non-preparedness of health care sectors to manage infected people and protecting their families from getting infection with COVID 19.
- No declaration of successful vaccine until now despite the research efforts and financial resources allocated to find the exact one.

COVID19 is under attack and research worldwide

More recently Italian scientists today discovered that, the disease was proved not to be a pneumonia ... but rather: diffuse thrombosis inside the vessels of the veins (thrombosis). Therefore, antibiotics, antivirals, anti-inflammatories and anticoagulants are the way to fight it. Consequently, since this discovery, the procedures in Italy have been updated and useful knowledge from the Italian pathologist verified that ventilators and intensive care units were never needed worldwide. Unfortunately, COVID-19 has been wrongly attacked for its serious physiological diagnostic error. The impressive case of a Mexican family has been documented in the United States, which they claim has been cured by home treatment: Consists of three 500 mg aspirin dissolved with honey in locally boiled lemon juice, taken hot. The next day the entire Mexican family woke up as if they had no symptoms! Well the following scientific information proves that they have been absolutely right! [56]

Accordingly, this information was shared by a medical researchers from Italy:

In an analysis of 50 autopsies performed in patients who died from COVID-19, Italian pathologists have confirmed that this is not exactly pneumonia, since the virus not only kills pulmonary cells such as this one, but also uses an inflammatory storm to induce endothelial vascular thrombosis. As with diffuse thrombosis in the blood vessels, the lung is most affected because it is the most inflammatory, but there is also a heart attack, stroke, and several other thromboembolic diseases. In fact, the protocols rendered antiviral treatments useless and concentrated on anti-inflammatory and anticoagulant treatments. These procedures should also be done immediately, even at home, as the care of patients responds very well. If the Chinese club called aspirin, the standard inflammatory drug that shows spectacular results in a rise in blood thinners and is prescribed to elderly people to avoid thrombosis, they would have invested in home treatment and saved the life.

In fact, patients who are positive to Covid19 did not need to enter the intensive care unit because they are undergoing corticosteroid treatment, which is a great anti-inflammatory. This is the main reason why hospitalizations have decreased in Italy and have become a treatable disease at home. Treated well at home, hospitalization is not only avoided, but also the risk of developing a stroke. It was not easy to understand, because the signs of partial embolization have disappeared! With this important discovery, it is possible to return to normal life and return to production immediately and open closed deals due to quarantine and social isolation, not immediately, but it is time to publish this data, so that the authorities can assess individuals' 'health in each country to conduct its own analysis of this information and prevent further deaths [56].

Updates in COVID-19 Vaccines Development:

It is important to note that a vaccine fit for humans usually takes years to develop as it goes through a series of human trials to test its safety and efficiency. The World Health Organization is tracking the potential vaccines for COVID-19 in the clinical evaluation .There are currently more than 100 COVID-19 vaccine candidates under development, with a number of these in the human trial phase. The WHO works in cooperation with scientists, business and global health organizations through the ACT Accelerator to accelerate the response of the pandemic. When a safe and effective vaccine is discovered, COVAX (led by WHO, GAVI and CEPI) will promote equal access and distribution of these vaccines to protect people in all countries.

Coronavirus Vaccine Tracker

According to Corum, Wee and Zimmer [(57)] investigators are testing 54 vaccines in human clinical trials and at least 87 pre-clinical vaccines are under evaluation in animals. Research launched in January with the deciphering of the SARS-CoV-2 genome. The first safety tests of vaccines in humans began in March, and 13 have now entered the final stage of research. Some of these trials may fail, but a few vaccines may be able to stimulate the immune system to produce strong antibodies to the virus. While these vaccines may potentially prevent infection, they cannot cure the disease. On the other hand, WHO [(58)] reported that, the antibodies against COVID19 will spare millions of lives each year? Immunizations work by preparing and planning the body's common resistances, the resistant framework is to recognize and battle off the infections and microscopic organisms they target. In the event that the body is uncovered to those disease-causing germs afterward, the body is promptly prepared to crush them, avoiding sickness. Immunization right now avoids 2-3 million deaths' each year from infections like diphtheria, lockjaw, pertussis, flu and measles [(58).] Recently, there are vaccines to anticipate more than 20 life-threatening infections, and work is continuous at exceptional speed to too make COVID-19 a vaccine-preventable infection. Here is the status of all vaccines that have been evaluated in humans, along with a list of promising vaccines:

AstraZeneca reports promising in its early outcomes:

The British-Swedish company AstraZeneca and the College of Oxford created a immunization based on a chimpanzee adenovirus. On Nov. 23, they declared that a preparatory examination of their Stage 3 trial discovered the immunization was up to 90 percent convincing, depending on the measurement [(58).]

• Pfizer and BioNtech vaccine requests emergency use authorization:

Pfizer and BioNtech vaccine: US-based Pfizer pharmaceutical company and its German partner BioNtech are working together on four RNA vaccine candidates. They also began clinical trials of their vaccine candidate BNT162. Their vaccine candidate is based on specially designed messenger RNA (similar to the Moderna vaccine) and the trails for testing the vaccine are taking place in the USA and they plan to test the potential vaccine on 360 healthy volunteers. On Nov. 9, Modern York-based Pfizer and the German company BioNtech made history by displaying preparatory information demonstrating that their coronavirus immunization was over 90 percent viable. It was the primary time anybody had found such prove. A week afterward, Moderna detailed comparable discoveries with a comparable immunization. [(57)].

Additionally, an antibody by **Anhui Zhifei Longcom** and the **Chinese Institute of Restorative Sciences** moves to Stage (3) In Nov. 2020. Whereas, an antibody by **West China Clinic of Sichuan College** moves to Stage (2) at the same time [(57).]

Here's taking a look at the six potential vaccines which are leading the race:

1. The University of Oxford has developed a vaccine candidate 'ChAdOx1 nCoV-19' in under three months. The vaccine candidate uses a weakened strain of common cold virus (adenovirus) and is combined with the genetic material of the SARS-CoV-2 (the coronavirus causing COVID-19).This will enable the body to identify the spike protein of the novel coronavirus. The vaccine candidate is now in a clinical trial phase-1 and healthy volunteers have already been injected to check its safety and efficiency.

2. In the US, the Massachusetts-based biotech company Moderna is developing an RNA based vaccine in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID). The vaccine candidate mRNA-1273 has already conducted phase 1 trials and is all set to begin phase 2 trials. The RNA vaccine works by entering the human cells and carries the molecular instructions to make the viral protein. Once, this viral protein is recognized by the body, the immune system of the body is triggered.
3. Beijing-based Sinovac Biotech: Chinese scientists are claiming to have successfully tested a potential vaccine for the novel coronavirus in monkeys. To conduct this experiment, the researchers injected the monkeys with the potential vaccine PiCoVacc which is made by Sinovac Biotech, a Chinese biopharmaceutical company. The monkeys were later exposed to novel coronavirus and it was found that those injected with a dose of the potential vaccine were largely protected from the virus. The vaccine is currently undergoing human clinical trials.
4. What is the status of COVID-19 vaccine in India: As per recent reports, the Indian Council of Medical Research (ICMR) has teamed up with Bharat Biotech International Limited (BBIL) for developing COVID-19 vaccine. It is important to note that the vaccine will use the virus strain isolated at the National Institute of Virology (NIV), in Pune. The strain has been successfully transferred from NIV to BBIL. Moreover, the Serum Institute of India (SII), which is the world's largest maker of vaccines by volume, has partnered with Oxford University to produce up to 60 million doses of a potential vaccine.
5. DNA-based vaccine by Inovio Pharmaceuticals; Inovio Pharmaceuticals, a biotechnology company received 5 million dollars aid for developing a vaccine for the novel coronavirus. Located in Plymouth Meeting, Pennsylvania, the pharmaceuticals has developed a potential vaccine in its San Diego lab and is all set to begin Phase 1 trial at the University of Pennsylvania. The vaccine is named INO-4800 and each volunteer will receive two doses of the relatively novel DNA-based vaccine candidate, four weeks apart to check its efficiency and safety.
6. The BCG vaccine: The Bacillus Calmette-Guerin (BCG) live-attenuated vaccine candidate is in the phase 2/3 and is used against tuberculosis to boost the immune system. Clinical trials are being conducted to test the affectivity and safety of this vaccine candidate in protecting people against COVID-19.

Conclusion

Stress can not only increase susceptibility to illness after exposure to infectious agents but also can inhibit antibody and virus-specific T cell responses to vaccines, permit reactivation of latent herpes viruses, and influence the progression of autoimmune -related disease. Although the global immunosuppression model enjoyed long popularity and continues to be influential, the broad decreases in immune function it predicts would not have been evolutionarily adaptive in life-threatening circumstances. In a study done by Dhabhar and McEwen [59] who suggested that acute fight-or-flight stressors should instead cause redistribution of immune cells into the compartments in which they can act the most quickly and efficiently against invaders. At present there is no specific treatment for COVID-19.

The person-to-person transmission of COVID-19 infection led to the isolation of patients. At present, there is no specific vaccine or a specific antiviral drug against COVID-19 infection for potential therapy of humans. At current broad-spectrum antiviral drugs like Nucleoside analogues and HIV-protease inhibitors are used. These drugs are used as it is believed they that could attenuate virus infection until the specific antiviral becomes available [59]. Compassionate use of Remdesivir in a cohort of 53 patients revealed clinical improvement however further measurement of efficacy requires ongoing testing [60]. Moreover, Geng Li et al [61] reported that, finding the targeted immunotherapy will be a good alternative to some antivirals that have narrow treatment windows and meet with drug resistance easily. For instance, in 2003, when glucocorticoid was used in treatment of SARS to control pulmonary infection by regulating inflammatory response, they found that, the inflammatory response of the body played a crucial role in SARS- induced lung injury cases. Therefore, in COVID19 pneumonia cases, it is significant to control the cytokine production and inflammatory response, assumed that they are accountable for the accumulation of cells and fluids. This strategy is challenging as we have not yet

clearly identified any features in an immune response that can be inhibited specifically without compromising the beneficial host defense.

In addition to stress that affect negatively the immune system of the affected corona viruses' patients and these findings that, proposed a biphasic model in which acute stress enhances, and chronic stress suppresses, the immune response. At the same time scientists and researchers across the globe are racing against the time to develop a vaccine for the novel coronavirus. As if now, Pfizer and BioNtech vaccine was reported very promising and scientists request an emergency use authorization to start distribution by the beginning of 2021 to fight against COVID-19. However, achieving this, is not impossible since all agencies and scientists from everywhere spending time, effort and money to improve the understanding of the chronological features of CoV- induced inflammatory response in relation to the effectiveness of therapeutic interventions.

Recommendations;

To improve our immune system the following are recommended to control the infection with Covid19 as the followings:

- Looking for lasting lifestyle change, not quick fixes healthy lifestyle habits support a healthy immune system 'sleep is good for everything"
- Keeping stress in check also important "exercise delivers a double whammy to your immune system. It slows the release of stress hormones, while at the same time improving natural immune defense activity.
- Taking moderate exercise: anything that gets your heart pumping helps! Your immune system responds almost immediately to exercise. In addition, use deep breathing to stimulate lymph flow and exercise outdoor if it is possible.
- Loading up on vitamin C or zinc to prevent covid-19: Nutritional compounds like vitamin C, antioxidants and zinc do work with your immune system and help it function more effectively, but the truth is that if you are already eating a balanced diet, the evidence and research don't promote the need.
- Focusing on a healthy diet, sleeping well and moving more are the 3 cornerstones to a healthy immune system. But a positive mindset is equally as important. Research shows that positive thoughts reduce stress and inflammation and increase resilience to infection. Additionally, optimism, and socialization with friends and family through different social network and media are proved very helpful in decreasing stressors and increasing the immune system.

Conflict of interest statement:

The authors declare that they don't have any conflict of interest

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