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The Correlation between COVID-19 and Cytokine Storms 'The Treacherous Immune Response'

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Abstract

SARS-CoV-2, or COVID-19, is a quickly spreading global virus that has been reported as a pandemic by the World Health Organisation (WHO). COVID-19 is spread by droplets or direct contact and, in most cases, infects the respiratory tract leading to pneumonia and, in around 15% of cases, to acute respiratory distress syndrome (ARDS). Mortality in COVID-19 patients has also been linked to the existence of the virus-induced cytokine storm. Excessive pro-inflammatory cytokine production contributes to the aggravation of ARDS and significant damage to tissues, leading to multi-organ failure and death. The cytokine storm's pathogenesis is very complex. Much data suggests that the extreme worsening in several patients was directly linked to the cytokine storm in their bodies during the COVID-19 epidemic. This article discusses the cause of incidence and management methods of the inflammatory storm caused by the COVID-19 virus to offer useful clinical treatment advice without using drugs.

Key words: COVID-19, Cytokine Storm, D3, Vitamin C, Curcumin, Zinc.

Introduction

A pneumonia epidemic due to unknown cause occurred in Wuhan, China in December 2019 and spread rapidly across the world within one month. The virus of this disease was confirmed as a novel coronavirus by molecular methods and was originally referred to as a novel coronavirus in 2019: nCoV-2019. However, on 11 February 2020 the World Health Organisation (WHO) released a new name for the epidemic: coronavirus disease (COVID-19). Until now, in more than 28 countries/regions, COVID-19 has impacted people and has become a global threat [1]. Before that, on 30 January 2020, the WHO announced the COVID-19 outbreak as the sixth international public health emergency. This epidemic presents a risk to public health by international disease transmission, which demands a coordinated international response [2]. The literature review focused on the immunological characteristics and clinical effects of COVID-19, including asymptomatic carrier status, acute respiratory disease (ARD), pneumonia and

management methods of the inflammatory storm caused by the COVID-19 virus to offer useful clinical treatment advice without using drugs.

Influenza Virus Attack

Influenza viruses primarily attack the air passages and lung tissues. The site being infected varies according to the virus strain. The highest risk is from deep lung infections. The epithelial cells that form the respiratory and lung passages are where the body first comes into contact with an influenza virus. When the virus invades the cells of lung tissues, these cells respond by releasing high concentrations of interaction chemicals, which are called cytokines, and stimulating the immune response. Not only can the inflammatory cytokines, including IL-2, IL-8, IL-1ß, TNF-α, and IFN-α, play a part in killing viruses, they also cause major destruction to the lung tissues [3].

Cytokines mainly induce immune cells such as macrophages, neutrophils, and lymphocytes to the site of the infection – which are the lungs and breathing passages in the case of influenza [4]. There are specific immune cells called macrophages within the lung tissue (especially around air sacs called alveoli), which provide the next level of viral resistance. Such essential cells develop antiviral immune compounds, but they can induce the formation of serious lung damage seen in lethal influenza cases if overactivated. Both the macrophage and the epithelial cells release cytokines that attract an array of immune cells to the lungs to fight the virus. All of this happens very quickly, within hours of the infection. The inflammatory cytokines cause the blood vessels to leak in the lungs and permit immune cells to penetrate the lung tissues where viruses have accumulated. When the leakiness occurs, or becomes extreme, the lungs can fill with fluid, interfering with breathing capacity. When an individual's immune system functions as planned, the virus will be destroyed, and the lungs will sustain minor damage. That damage can be repaired quickly, putting the person back in good health. In other cases, the immune response becomes traitorous to the body. In other words, the immune system becomes the enemy [5].

Pathogenicity of Influenza Virus

In the past, viruses were thought either to be deadly (killer viruses) or to be moderate depending on the virus' ability to harm the body. The Spanish influenza virus (1918 H1N1), for example, infected more than 50 million people worldwide, while the bulk of seasonal influenza epidemics kill several hundred to several thousand. What is now known is that a virus' ability to do significant harm, or even destroy, is dependent on its capacity to overreact – that is, it does damage to the immune system [6]. Killer viruses cause an extreme inflammatory response by activating different sets of genes that regulate an inflammatory response [6]. As a result, immune cells release large amounts of inflammatory cytokines that cause serious damage to the lungs and other tissues. Importantly, the inflammatory genes triggered by the mild H1N1 seasonal influenza virus varies from those triggered by the severe 1918 H1N1 virus, H5N1 influenza virus, or COVID-19 [7]. additionally, the stimulated genes release chemokines to attract other cells from bone marrow and lymph nodes to recruit more immune cells. This makes the immune response much more powerful. Dense protein-filled fluids are often pumped into the lungs from leaky blood

vessels and mix with a large number of immune system cells. This sticky material covers the air sacs of the lungs, preventing oxygen from reaching the capillaries. As a consequence, a person can literally drown in they own secretions.In severe cases, these immune factors propagate across the circulatory system and cause a much greater immune overreaction in the body. This may cause other organs to malfunction, including the kidneys, heart, and liver. In deadly cases, we can see a loss in multiple organs. Death comes too. This intense immune overreaction is called a cytokine storm. In certain cases, blocking extreme inflammation will decrease lung injury, even though the number of viruses remains constant or increases [8]. See Figure 1.

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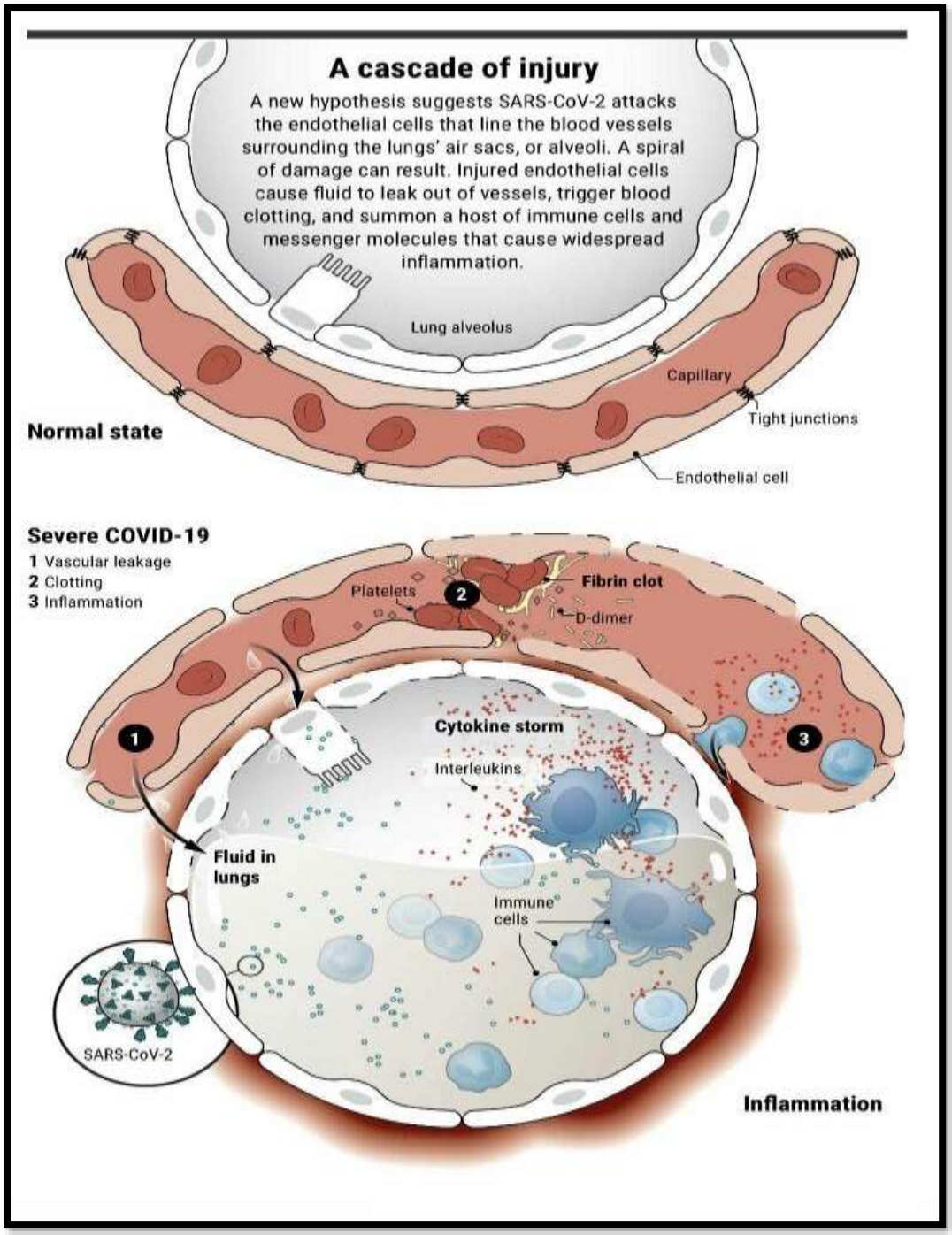

Figure 1: Imagery of a cytokine storm. (Teuwen *et al.*, 2020) [53].

Epidemiology

As of 21 February 2020, the data showed 76,769 cases of COVID-19 in total [9]. Thirty-two countries or regions registered confirmed cases, including China, Japan, Singapore, Hong Kong, Thailand, Taiwan, South Korea, Australia, Malaysia, Germany, Vietnam, USA, Macao SAR, UAE, France, Canada, the Philippines, UK, Italy, Russia, India, Finland, Sweden, Sri Lanka, Cambodia, Nepal, Spain, Iran, Egypt, and Lebanon. China has the highest number of COVID-19 patients (n = 75,543). However, asymptomatic patients or patients with moderate COVID-19 symptoms cannot seek treatment, nor be detected, leading to underestimation of COVID-19's burden.

Age and Sex:

Most cases of COVID-19 were identified in adult patients in Wuhan city; all of these cases were therefore pneumonia [10, 11]. Their mean age was (49.0–55.5). A similar result was found in two recent studies: one study of 1,099 patients from 552 hospitals in China where the study showed that 55.1% of patients were aged 15–49 years. A second study containing 4,021 confirmed cases in 30 provinces of China, with a mean age of 49 years and 50.7% of patients between the ages of 20–50 years [12, 13]. The study by Ryu *et al*. in Korea considered 15 cases to be between the ages of 25 and 62 [14]. Regarding elderly patients afflicted with SARS-CoV-2, one study found that 14.6% (6 in 41) of patients were 65 years of age [15]. Furthermore, two non-peer-reviewed reports found that only 153 patients (15.1%) were elderly patients aged ≥ 65 years [12]. And 407 patients (10.1%) were > 70 years old. Concerning children, in one study only nine (0.9%) patients aged 0–14 years were found to have COVID-19 [16]. The latest research in China found that 0.9% of patients (n = 416) were < 10 years of age. The study by [17] confirmed that, in China, nine babies below the age of one year were infected with SARS-CoV-2. Concerning the patient sex ratio, in most COVID-19 reports males accounted for more than half of the cases, and the proportion of males varied from 51.4% to 73.2% [18].

Incubation Period

It is important to recognise the duration of incubation: the interval between the interval that an infectious agent is released and the signs and symptoms of the disease appearing. The study by [19] used the exposure results from 10 reported cases in Wuhan to approximate the mean five-day incubation time (95% confidence interval). An assessment based on 125 patients with clearly specified exposure times in China revealed that the median incubation duration was 4.75 days (interquartile range 3.0–7.2) [20]. However, the study by Guan *et al.* indicated that the median incubation time was just three days, using a large sample for evaluation, but maybe as long as 24 days [21]. Detailed epidemiological information based on a wider sample of patients infected with COVID-19 is required to determine the SARS-CoV-2 infectious duration, as well as to decide if the asymptomatic individual transmission can occur during the incubation.

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Clinical Symptoms

Previous study reported that SARS-CoV-2 infected patients are asymptomatic [22]. These patients can spread the infection and can represent an easily minimal population in epidemic prevention. Therefore, the detection of asymptomatic patients with COVID-19 is critical. Because these patients are asymptomatic, they can only be detected by close observation of the disease's normal course and communication history. Depending on the latest data, we do not know whether these patients are initially only asymptomatic after contracting the disease, or whether they are asymptomatic throughout the disease course.

According to the study, which described the clinical features of the disease [23], males composed 60% of patients and the mean age was 53 years. One-fifth of the patients reported a history of smoking. The most prevalent underlying condition was hypertension (20%), followed by diabetes (14%). (67.3%) of patients have a fever and 70.5% of patients had a cough. In addition, the development of dyspnea and sputum was found in around one-third of patients. In addition, 6–8% of patients had diarrhoea or vomiting. Overall, 80% of patients needed oxygen treatment, and 28.8% required mechanical ventilation. Overall mortality was 8.2%, but 66.9% remained in hospital. In comparison, patients with pneumonia were older, with a greater incidence of smoking history. Finally, cases with pneumonia have a higher white blood cell count and neutrophil count [24].

When Does COVID-19 Become Deadly?

One of the major questions facing us is why some people, especially young, otherwise healthy people, are dying from the influenza virus (SARS-Cov-2). We know that they die as a result of a cytokine storm, but why does that only happen to certain people? It seems that these unlucky individuals have a genetic mutation that stimulates viral receptors in their epithelial tissues and macrophages called pattern recognition receptors or PRRs, which are more sensitive than normal. This activates an effective immune response that induces hypertensive inflammation in the lungs [25].

This inflammatory response does influenza not kill the flu virus any better than the normal response. These genetic mutations were named (Single Nucleotide Polymorphisms). Generally, the reaction to viruses is a closely regulated release of inflammatory chemicals. But with SNPs, we see a high amount of inflammatory chemicals released. Studies have found individuals with this group of gene defects are far more likely to die from the cytokine storm while they are sick [26]. Vaccinating those individuals cannot shield them from cytokine attacks, since viral reactions with over-responsive receptors would always occur. Interestingly, we do not know what adverse consequences these individuals could have after they are vaccinated. They may overreact to the vaccine as well. It is known that certain people have a mutation in the gene regulating the immune receptor that may cause a cytokine storm when it comes into contact with some components of the vaccine [27]. Nobody has observed this significant impact in the general population, and we just do not know how many individuals have this gene mutation. But it helps clarify why certain young, otherwise healthy people die when they are exposed to the influenza virus, especially if it is a virulent type like COVID-19.

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Regulation of Immune Response without Drugs

You would assume that the solution to this issue would be to suppress inflammation, and that is when much of the lung damage is done – not the virus itself. However, reports have shown that whether you absolutely or significantly block inflammation, the body would not be protected [28]. People need a controlled immune response to get rid of the virus and heal. Usually, when the immune system is stimulated, specific anti-inflammatory molecules are also triggered at the same time. These compounds help control the immune attack and prevent undue damage to the lungs. This system is disrupted in the case of a cytokine storm. Current therapies for people afflicted by cytokine storms are, at best, inadequate and can potentially exacerbate the problem [29]. In most treatments, patients are given high doses of corticosteroids on the grounds that the anti-inflammatory activity would reduce the harm caused by the overreaction of the immune system. Unfortunately, these steroids suppress not only damaging cytokines but also those needed to destroy the virus. As a consequence, the elevated viral load overrides the anti-inflammatory effect of the drug, and the situation becomes worse. Several other clinical studies suggest that corticosteroid therapy can probably increase long-term mortality in these situations [30].

Newer therapies are intended to selectively suppress damaging cytokines without compromising the immune system's ability to kill the virus. One therapy uses a drug that activates a special immune receptor called S1P1, sphingosine-1 phosphate. It has been shown to activate the receptor to stop cytokine storms. What we have learned is that the best protection for people from serious viral infections is to control, but not block, the immune response. The most important thing is to selectively dampen the immune-induced inflammation components that cause the damage to the lungs' cytokine storm.

Vitamin D3

It has been suggested that the reason we notice increasing viral infections in the winter months is that this is when humans have the lowest levels of vitamin D, which is produced in the skin during sun exposure [31]. Studies demonstrated that deficiency of vitamin D3 correlates with the incidence of multiple viral infections such as influenza [32]. It should be highlighted that a strong inflammatory response to the influenza virus does not necessarily imply direct control of the virus. That is also essential since influenza vaccine producers base their claims on efficacy of antibody responses, not actual viral clearance. In reality, their claims are merely smoke and mirrors.

All immune cells have vitamin D3 receptors, which are the first important line of defence against infectious agents [33]. One of the main lymphocytes needed to clear influenza viruses are T-lymphocytes, or T-cells. During the summer, these cells increase in number due to increased exposure to sunlight, consequently helping to protect against viral infection [34]. Many studies have shown beneficial effects of vitamin D3 on infection control resistance, cancer, and inflammation. These benefits include:

- Enhancing the presentation of antigens.
- Balancing the function of the immune system.
- Regulatory T-cells enhancement.

- Enhancing the production of antimicrobial proteins.
- Macrophage/monocyte activation regulation.
- Reducing excess proliferation of T-cells.

However, the most important thing vitamin D3 does is to reduce the inflammation. Vitamin D3 continues to produce peptides in epithelial cells and macrophages [35]. These peptides are considered to be the first line of defence against pathogens.

Macrophages are considered a major source of LL-37 protein, which is critically important for shielding the body from serious exposure to cytokine storms. Macrophages and LL-37 not only help kill a virus but also clear up the waste that forms after those infections in the air sacs of the lungs [36]. Vitamin D3 reduces the chemicals involved with cytokine storms, namely IL2, IL21, IL17, TNF-α, and INF, and increases the simultaneous killing of viruses [37].

Doses:

Taking 1000 IU or less of vitamin D3 a day will not help increase blood levels. It takes 2000–5000 IU a day to achieve an acceptable concentration of vitamin D3 in the blood. One study suggested that everyone should have their blood screened for vitamin D3. The standard value for optimum safety is between 65–75ng/ml) [39].

Vitamin C:

Vitamin C reaches the endothelial cells and can affect the inflammation-control genes. It also inhibits an enzyme that creates a potent form of free radical. Another essential way in which vitamin C controls a cytokine storm is to reduce leakage of body fluids from blood vessels, which is the main cause of lung suffocation [40]. Experiments in animals have also shown that vitamin C can inhibit sepsis death. Researchers injected faecal content into animals, causing severe sepsis. About 91% of animals who did not receive extra vitamin C died, whereas just 35% of those who received vitamin C died [41].

Vitamin C also prevents deaths from viral infections. In some regions of Africa, the measles mortality rate is about 15%. Researchers who gave vitamin C to children cut the mortality rate by half. When zinc was also applied, the mortality rate decreased by 80% [42].

Doses

Individuals can only absorb a small amount of vitamin C when administered orally, about 200–500mg/day, although that is a very low dose to cure a cytokine storm. Vitamin C in high doses, from 10g to 100g a day, can be delivered intravenously for high protection. The consequences of a cytokine storm, which can be stopped or reversed at that dosage, include:

- High levels of free radicals.
- Raised inflammatory cytokines TNF-α and IL-6.
- Leakage of blood vessels [43].

In one experiment, the physicians supplied 10g (10,000mg) of intravenous vitamin C to patients for five days. They observed that the inflammatory cytokines TNF-α, IL-8, and IL-6 were

greatly decreased by treatment. Even at lower doses, vitamin C significantly enhances the immune system's ability to kill infectious viruses and bacteria, which is critical in avoiding a cytokine storm [44].

Curcumin

Curcumin, a yellow compound isolated from the spice turmeric, has been shown to actively inhibit the compounds most correlated with cytokine storms: cytokines TNF, IL-6, IFN, and IL-8; and chemokines MCP1 and MIP1-α [45]. Curcumin decreases the inflammatory reaction of the acute respiratory distress syndrome caused by the virus in mouse experiments. In one study, the researchers administered curcumin to animals both prior to exposure to the virus and throughout the course of the disease. Animals treated with curcumin showed a decrease of pro-inflammatory cytokines associated with lung injury and a decrease in the level of fibrosis in the lungs after healing [46]. Curcumin is known to inhibit a variety of other virus infections: hepatitis B and C viruses, herpes simplex virus, human papillomavirus, and Japanese encephalitis [47]. Considerably, curcumin activates the production of the Suppressors of cytokine signaling (SOCS) peptide, which, as mentioned, plays a key role in the suppression of the cytokine storm [48]. Thus, this simple plant extract suppresses the cytokine storm response in several ways. If taken daily, curcumin carries considerable promise to avoid serious lung disease caused by viruses and bacteria until an infection happens, which significantly decreases the chance of death in patients. Taking it may also avoid a cytokine storm after an infection [49].

Zinc

Zinc plays a critical role in the immune response. Deficiency in animals causes a reduced size of the thymus gland, gradual depletion of T-cells and macrophages, reduced role of T and B-cells, diminished memory of antibodies, and other immune deficiencies. Zinc is not stored in tissues, so it must be regularly replaced by a diet or supplement. Zinc can decrease the severity and duration of coughs and colds, but only if it is ionised [50].

Other Compounds Suppressing Inflammatory Response

A variety of other compounds can also decrease the risk of cytokine storms, such as magnesium, green and white teas, grape seed extract, and the most impressive are apigenin and luteolin [51]. It is important to avoid omega-6 oils (peanut, safflower, corn, soybean, and sunflower oils) because they enhance inflammation as well. Omega-3 oils minimise and protect the lungs and other tissues from inflammation. The study by [51] showed that low magnesium greatly increases inflammation in the body. A diet with low carbohydrates and high in fruit and vegetables would also dramatically reduce the risk of a cytokine storm. There are very strong natural compounds that can shield people from toxic cytokine storms, which are the main cause for severe injury and deaths associated with influenza virus. After this risk has been eliminated, influenza outbreaks may be much milder, and forced vaccinations would not be needed – especially with current dangerous vaccines.

Conclusions

This review includes new information on COVID-19, and the role of the immune system in resisting viral infection, in addition to the treacherous immune response that develops the cytokine storm. Finally, we can see the powerful naturally occurring compounds that can protect people against deadly cytokine storms without the need for medical treatment.

Conflict of Interests.
There are non-conflicts of interest

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