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REVIEW ARTICLE

COVID-19 Induced Cytokine Storm and the Impact of Obesity and Vitamin D Deficiency

Shobha Chikkavaddaragudi Ramachandra[1], Akila Prashant[1], Prashant Vishwanath[1]*

[1]Department of Biochemistry, Center of Excellence in Molecular Biology and Regenerative Medicine, JSS Medical College, JSS Academy of Higher Education & Research, Mysuru-570017 (Karnataka) India

Abstract:

Recent studies on Coronavirus Disease 2019 (COVID-19) have shown that obesity and vitamin D deficiency increase the risk of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection and its complications. The levels of cytokines are increased in SARS-CoV-2 infection, obesity, and vitamin D deficiency aggravating the complications related to COVID-19. The Angiotensin-converting Enzyme 2 (ACE2), through which SARS-CoV-2 enters the host cell, is highly expressed in adipose tissue showing the vulnerability to the infection. In this review we have explained how obese individuals are more prone and contagious than lean to COVID-19, the role of adipose tissue as a reservoir of infection, vitamin D sequestration and deficiency in obese, and its association with COVID-19 and the combined release of cytokines in obesity, vitamin D deficiency and SARS-CoV-2 infection leading to cytokine storm both locally and systemically, hence leading to multi-organ failure in elderly and younger generations.

Keywords: COVID-19, SARS-CoV-2, Obesity, Vitamin D, Cytokines, ACE2, Cytokine Storm.

Introduction:

The risk of developing Coronavirus Disease 2019 (COVID-19) and its complications are common in people with an impaired immune response or increased pro-inflammatory response. The low-grade chronic systemic inflammation is seen in people with overweight, obesity, and Vitamin D deficiency [1]. The cytokine storm leading to multiorgan failure seen in COVID-19 may get exacerbated by the pro-inflammatory cytokine seen in obesity and Vitamin D deficiency. Obese individuals are more contagious than lean leading to an increased rate of morbidity and mortality [2]. The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) enters the host cell through Angiotensin-Converting Enzyme 2 (ACE2), zinc-containing metalloenzyme, that is highly expressed in adipose tissue showing susceptibility to the infection. Calcitriol, the vitamin D agonist modulates the expression of members of Renin-Angiotensin-Aldosterone Systems (RAAS) such as ACE2 in lung tissue, protects from a lung injury, and shows that vitamin D deficiency acts as a pathogenic factor in COVID-19. Through this review, we have tried to explain how obesity and vitamin D deficiency in younger generations may act as a contributing factor in developing COVID-19 and its complications like cytokine storm leading to multiorgan failure.

COVID-19:

COVID-19 is an infectious disease caused by a newly discovered SARS-CoV-2. It was first reported in Wuhan, Hubei province of China in late December 2019, sequenced and isolated by January 2020 [3], and pandemic was declared in the mid of March 2020 by the World Health Organization (WHO) [4]. As of 15th March 2021, more than 119,220,681 cases have been reported globally, resulting in more than 2,642,826 deaths [5]. In India, 11,359,048 cases were reported positive with 158,607 deaths [6].

SARS-CoV-2 enters the host cell via ACE2 which is abundantly present in type 2 alveolar cells of the lungs. The surface glycoprotein present on the virus called spike attaches to the enzyme ACE2 and gains access to the host cell [7]. The entry into the cell may occur either by endocytosis or by proteolytic cleavage of the receptor. The coronavirus primarily spreads by close contact via small respiratory droplets produced during sneezing, coughing and talking. The virus primarily infects the upper respiratory tract leading to symptoms like cough, shortness of breath or difficulty in breathing, fever, chills, sore throat within 2-14 days after exposure and the disease may progress to pneumonia, multi-organ failure, and death in some. Elderly people and people with any underlying medical illness like lung disease, cardiovascular disease, diabetes, chronic kidney or liver disease, immunocompromised people, over-fat (overweight and obese) individuals, and vitamin D deficiency states are at increased risk of developing COVID-19 [8-9].

Burden of Obesity and COVID-19:

In 2016, as estimated by WHO, nearly 650 million adults aged 18 years and above along with 340 million children and adolescents were reported to be obese globally. In India, 3.9% of adults were reported to be obese in the same year [10]. Increased calorie intake and decreased physical activity are the major factors for increasing the prevalence of obesity. For Asians, the cut-offs of $\geqslant$ 23.0kg/m^2 and $\geqslant$ 25.0kg/m^2 are defined as overweight and obesity respectively that are lower than WHO criteria due to tendency towards abdominal obesity and associated morbidities [11-12]. An ongoing study conducted by Sir Gangaram Hospital's Institute of Minimal Access, Metabolic and Bariatric Surgery, and the Department of Internal Medicine and Infectious Disease in 1000 patients who developed COVID-19, have shown that almost half of the patients in ICU are obese with less than 50 years of age [13]. A study conducted at COVID-19 ICU, at university hospitals at Johns Hopkins, New York University, University of Cincinnati, University of Washington, Florida Health, and the University of Pennsylvania showed an inverse correlation between age and Body Mass Index (BMI). The younger individuals admitted had a median BMI of 29.3 kg/m^2, 25% of individuals had a BMI of less than 26 kg/m^2, and 25% exceeding a BMI of 34.7 kg/m^2. Hence it was concluded that not only the older generations, but COVID-19 also affects the younger population with a high prevalence of obesity [14]. Another retrospective analysis by Peng *et al.* showed that among the SARS-CoV-2 infected patients, the median BMI of the critical group was 25.5 kg/m^2 which was significantly higher than that of the general group with a median

BMI of 22.0 kg/m^2. Patients further were divided as non-survivors and survivors. 88.2% of patients among the non-survivors had a BMI > 25 kg/m^2 which was significantly higher compared to survivors (18.9%). Hence, it was concluded that obesity may be an aggravating factor for the development of complications and death from COVID-19 infection [15]. Table 1 depicts few other studies demonstrating the fact that obesity and overweight aggravate SARS-CoV-2 infection [16-24]. These studies highlighted the fact that overweight and obesity may play an important role in the prognosis of SARS-CoV-2 infection not only in the elderly but also in the younger population.

Obesity, Adipocytes and Inflammation:

Well balance between calorie consumption and energy expenditure should be maintained for healthy weight and BMI. Any imbalance leads to the storage of intracellular triglyceride in

Table 1: Global Status of Obesity and COVID 19

Study conducted in	Type of study and number of participants	Results
Italy [16]	Retrospective cohort study of 482 patients	BMI ⩾ 30 kg/m^2 & BMI ⩾ 35 kg/m^2 increase the risk of severe illness & risk of death respectively
New York [17]	Retrospective study of 200 patients	Severe obesity, higher age, and males were associated independently with mortality of COVID-19
Italy [18]	Prospective cohort study of 233 patients	Obesity, older age, and severe illness are the associated factors to increase the risk of morbidity in hospitalized COVID-19 patients
New York [19]	Retrospective study of 3,406 patients	Younger patients younger than 50 years, who were hospitalized with severe obesity, are at increased risk to die of COVID-19.
China [20]	Retrospective study of 383 patients	Obese patients are prone to progress to severe COVID-19
Chicago [21]	Retrospective study of 238 patients	Among the inpatients with COVID-19, obesity is a major predictor of mortality after adjusting for gender, age, and other comorbidities
United States [22]	Retrospective cohort of 103 patients	COVID-19 with severe obesity was associated with ICU admission, and required aggressive treatment.
Spain [23]	Retrospective cohort of 2226 patients	COVID-19 with obesity are 51% more likely to have mortality
Brazil [24]	Retrospective study of 717 patients	Obese people require hospitalization more than twice following COVID-19 development.

adipocytes increasing the fat mass which evince both hypertrophy and hyperplasia in adipocytes. Obesity is the result of increased adipogenesis and increased basal rate of lipolysis. Accumulation of visceral white adipose tissue than subcutaneous adipose tissue leads to complications of obesity like insulin resistance and metabolic syndrome. Many factors like insulin, glucocorticoid, Tumor Necrosis Factor 1-Alpha (TNF1-α), Insulin-like Growth Factor-1 (IGF-1), and transcription factors like Peroxisome Proliferator-Activated Receptor-γ (PPAR-γ), CCAAT/Enhancer-Binding Proteins (C/EBPs), Sterol-Regulatory Element-Binding Protein (SREBP) play an important role in hypertrophy and hyperplasia of the adipocytes [25].

In obesity, there exists chronic low-grade sterile inflammation or inflammation in metabolic tissues along with increased levels of circulating pro-inflammatory factors without clinical signs of inflammation. The local and systemic cytokine levels, infiltrating immune cells and neutrophils are increased in the acute phase whereas macrophages are seen in the chronic phase [1]. Adipose tissue is involved in the regulation of physiological and pathological processes like immunity and inflammation by releasing a variety of adipokines like leptin, adiponectin, and resistin, pro-inflammatory cytokines like TNF-α, Interleukin (IL)-6, anti-inflammatory cytokines like IL-4 and IL-10, and both anti-inflammatory and pro-inflammatory cytokine-like interferon (IFN)-γ [26].

In a cross-sectional study, it has been shown that SARS-CoV-2 infected patients with a similar BMI as control patients had significantly higher levels of serum leptin. Due to SARS-CoV-2 infection, ACE2- Angiotensin II disbalance occurs leading to local pulmonary inflammation which is enhanced by an increase in leptin production in visceral fat. Hence, it was concluded that visceral adipose tissue, leptin, and lung tissue have an interconnecting role in SARS-CoV-2 infection [27]. Michalakis *et al.* stated that SARS-CoV-2 and obesity (resistance to leptin and resistin) share common elements of the inflammatory process exacerbating SARS-CoV-2 infection in the obese [28]. A mild or highly acute respiratory syndrome caused by COVID-19 causes the release of pro-inflammatory cytokines like IL-6 and TNF-α. Thus, modification of the dietary regimen by adding ω-3 PUFA improves the adiponectin levels prevents the infection with COVID-19 and reduces the cytokine release [29].

Cytokines:

Cytokines are a group of proteins, glycoproteins, or peptides (~5–20 kDa), secreted by specific cells of the immune system that have a definite effect on the interactions and communications between cells. Cytokine may have autocrine action which acts on the cells from which it is secreted, endocrine action which acts on distant cells, or paracrine action which acts on nearby cells. Cytokines include lymphokine, interleukin, chemokine, and monokine. They are mainly produced by helper T cells and macrophages [30].

In case of severe immune reactions like severe infection and autoimmune diseases body responds by releasing various cytokines all at once which leads to multi-organ failure or death. This is known as a cytokine storm. Cytokine storm is a complication seen in respiratory diseases caused

by coronaviruses, SARS, and MERS, and few non-infectious diseases. There is a release of cytokines in inflammatory conditions like obesity. This along with the infections caused by coronaviruses may exacerbate cytokine storm. The cytokine storm is the systemic expression that results in the release of more than 150 inflammatory mediators including cytokines, oxygen-free radicals, and coagulation factors. In patients with severe infections, cytokine storm results in the release of both the pro-inflammatory cytokines like TNF-alpha, IL-1, and IL-6 and anti-inflammatory cytokines like IL- 10 and IL-1 receptor antagonist. Such patients present with high fever, redness and swelling, severe fatigue and nausea [31].

Cytokine Storm:

After the primary exposure, the viruses replicate within the cell at the same time infecting other cells. Inflammatory responses are triggered when infected cells die by either necrosis or apoptosis. Initially, there is an acute inflammation that is characterized by increased blood flow, enabling plasma and leukocytes to reach the extra-vascular sites of injury, elevating local temperatures, pain, and activating pro-inflammatory cytokines or chemokines. These chemokines lead to the recruitment of inflammatory cells followed by increased expression of inflammatory, antiviral and apoptotic genes, immune cell infiltration, and tissue damage. The resolution of the damage and regenerative processes will be initiated at the same time and by this reparative process, functions can be completely rebuilt in most cases. In severe inflammation associated with cytokine storm, more serious pathological changes like immuno-pathologic injury and persistent organ dysfunction occur. These severe inflammatory cytokines enter the circulation leading to systemic cytokine storms, resulting in multi-organ dysfunction [32-33].

The term Cytokine Release Syndrome (CRS) is interchanged occasionally with the term cytokine storm due to resemblance in clinical phenotype and biomarker signature [34]. The cytokines that are found to be raised in CRS include IL-6, IL-10, and IFN-γ. The activated T cell causes an enormous release of IFN-γ which triggers CRS. The released IFN-γ causes activation of macrophages, thus releasing more amounts of cytokines such as IL-6, IL-10 and TNF-α. TNF-α released is responsible for the synthesis of acute-phase proteins, watery diarrhea, vascular leakage, lung injury, and cardiomyopathy [35]. In the pathophysiology of CRS, the endothelium plays a crucial role by amplifying the inflammatory response and also as a target organ [36]. The endothelial cells of large adipose tissue, which are increased in obese individuals, secrete cell adhesion molecules, chemokines, adipokines, and inflammatory molecules playing a significant role in the promotion of both adipocyte alterations and inflammation [37].

Obesity and Vitamin D:

Vitamin D is inversely associated with overweight and obesity and it is said that for every 1 kg/m^2 increase in BMI, there is a decrease of 1.15% of 25-hydroxyvitamin D [25(OH)D] [38]. The possible mechanisms responsible for this could be: (A) decreased 25(OH)D due to negative feedback from the increased concentration of 1,25(OH)D: The increased demand in overweight and obese individuals leads to further hydroxylation of 25(OH)D to the active form,

1,25(OH)D, which further switches off the 25(OH)D production [39]. (B) The lower 25(OH)D concentration due to volumetric dilution: Vitamin D is fat-soluble, present in fat, muscle, liver, and serum, whose compartments are increased in volume in obesity. Hence, the lower vitamin D reflects the volumetric dilution effect even when the stores of vitamin D are adequate [40]. (C) Sequestration of vitamin D within adipose tissue: Vitamin D gets 'trapped' in adipose tissue because of adipose expansion due to insufficient lipolytic stimulation or tissue dysfunction/adaptation.

A study by Carrelli *et al*. showed that total body vitamin D stores measured by mass spectroscopy in subcutaneous and omental adipose tissues, were significantly greater in obese (2.3 ± 0.6 mg) than in lean (0.4 ± 0.8 mg) individuals. Hence, hypothesized that obese individuals with increased adipose tissue act as a reservoir for vitamin D and that the increased amount of vitamin D is needed to saturate this large depot, which may predispose obese individuals to low serum 25(OH)D. Thus, a high dose of vitamin D is required in overweight and obese. (D) Decreased sun exposure due to reduced outdoor activity, increased body surface area: a study has shown that regular exercise improves the function of adipocytes and mobilizes vitamin D from adipose tissue [41].

Effect of Obesity and Vitamin D Deficiency in COVID-19:

Hypertrophy of adipocytes seen in obesity triggers the release of adipokines and cytokines increasing the risk of complications related to cytokine storm (Fig 1). Obese individuals have an increased inflammatory response compared to lean. A study by Muniz *et al.* showed that increased basal leptin expression in obese individuals led to chronic low-level inflammatory response making the obese individuals more susceptible to *Francisella tularensis* infection and exacerbated immuno-pathological cytokine storm [42]. A study by Easterbrook *et al*. showed that the antigen of influenza virus was more pronounced in the alveolar regions of the lungs of diet-induced obese mice than control mice due to interferon-β and proinflammatory cytokines in circulation. This has led to increased morbidity and mortality among HINI influenza-infected obese mice than non-obese mice [43]. The immunological response of adipocytes through leptin shows that altered leptin concentration leads to altered cell-mediated immune responses and insulin resistance [42]. A study by Zhang *et al*. to assess the role of leptin-mediated pathogenesis of influenza A (H1N1) pandemic showed that preexisting higher levels of serum leptin, a pro-inflammatory cytokine, and chemokine contributes to the development of complication like severe lung injury [44]. The adipokine (adiponectin) which is inversely related to BMI released from adipocytes too plays a role in an immune response by induction of interleukin 10 and suppression of nuclear factor-kB in macrophages [45]. A study by Kuwabara *et al*. showed that the Neutrophil Toll-like receptor 4 pathway was affected in the experimental models (obese and diabetes), resulting in altered production of cytokines and chemokines, migration and myeloperoxidase activity [46].

Human ACE2 is a recognized receptor for the entry of COVID-19 into host cells. The tissue expression of ACE2 differs in different organs like in lungs,

kidneys, and heart of healthy patients and coronavirus-infected patients. The adipose tissue shows higher level of ACE2 expression than in lung tissue, which shows adipose tissue may be vulnerable to infection. And also, treatment with ACE inhibitors for hypertension and angiotensin receptor blockers increases the expression of ACE and viral entry into the host [47]. Adipose tissue acts as a reservoir for certain viruses such as adenovirus, influenza virus, HIV, cytomegalovirus, etc [48]. Similarly, adipose tissue may be attributed to act as a reservoir of infection and may act as a research model for a better understanding of the pathogenesis of COVID-19 [49].

The severe vitamin D deficiency (<25 nmol/L) is associated with disease progression and increased mortality in patients with autoimmune liver diseases [50]. Vitamin D deficiency was seen in 63% of individuals with diabetes, 58% of individuals with prediabetes, and 80% of obese individuals, who are at high risk for COVID-19 [51]. Calcitriol, the vitamin D agonist modulates the expression of members of RAAS such as ACE2 in lung tissue, thus exhibiting the protective role against acute lung injury [52]. This may lead to the conclusion that vitamin D deficiency acts as a pathogenic factor in COVID-19. A study by Ilie *et al*. who investigated the role of vitamin D in the prevention of COVID-19 stated that there is a severely low level of vitamin D in the aging population of Spain, Italy and Switzerland, who are most vulnerable to COVID-19 and vitamin D supplementation plays a significant role in reducing the mortality among them [53]. Based on the data of retrospective analysis, it was shown that vitamin D deficiency is associated with high CRP, a surrogate marker for cytokine storm, and vitamin D supplementation reduces the complications of unregulated inflammation and cytokine storm [9]. Calcitriol has a protective role against acute lung injury which modulates the expression of RAAS members like ACE2 [52]. VDRs are abundantly distributed in respiratory epithelial cells and immune cells such as B cell, T cell, macrophages, and monocytes. In the bronchial epithelium and immune cells, the dominant circulating form of vitamin D 25(OH)D is converted to 1,25-dihydroxyvitamin D, the active form of vitamin D with the help of the enzyme 1α-hydroxylase. Thus, vitamin D may improve the immune response with an adequate amount of 25(OH)D to increase levels of 1,25-dihydroxyvitamin D [54-55]. Vitamin D also plays a significant role in the production of antimicrobial peptides and reducing the inflammatory response to COVID-19, that reduces the infection, mortality, and morbidity when infected with the virus [56].

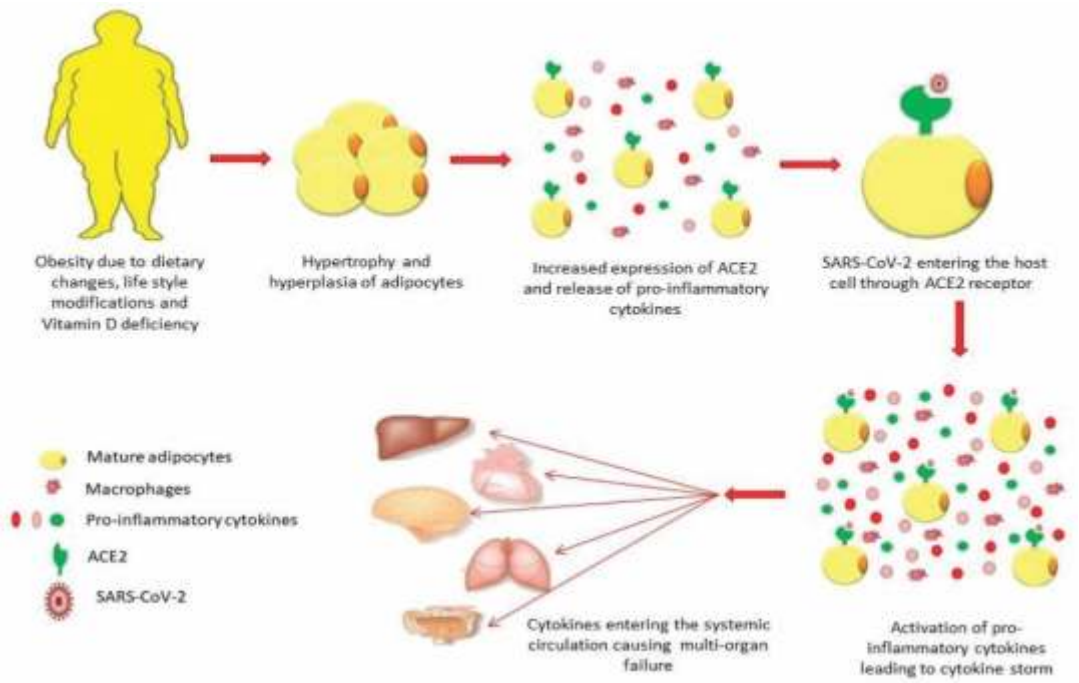

Fig. 1: Obesity, Vitamin D Deficiency, Cytokine Storm and SARS-CoV-2 Infection Leading to Multi-Organ Failure:

Overweight and obesity is a chronic low-grade inflammatory state caused by hypertrophy and hyperplasia of adipocytes and Vitamin D deficiency resulting in the release of pro-inflammatory cytokines and adipokines like leptin, adiponectin, and resistin. The SARS-CoV-2 gain entry into the host cell through ACE2 whose expression is higher in adipose tissue than compared to lungs. Once inside the host cell, the virus proliferates activating pro-inflammatory cytokines or chemokines and also infect the neighboring cells leading to overproduction of pro-inflammatory cytokines called a cytokine storm. These pro-inflammatory cytokines or chemokines enter the systemic circulation leading to multi-organ failure called systemic cytokine storms.

Vitamin D and Inflammation:

Vitamin D regulates intestinal, bone, and kidney calcium and phosphorus absorption, bone mineralization, and also plays a vital role in inflammation. There is an inverse relationship between 25(OH)D and markers of inflammation. The prolonged inflammatory microenvironment can lead to tumor production. Vitamin D influence this inflammatory microenvironment by mechanisms like: A. balancing the interaction between tumor cells and immune cells to regulate cytokines levels (inhibiting IL-6, 8,10 and TGF and activating IL-17A), B. up-regulating MAP Kinase Phosphatase 5, a calcitriol responsive gene, C. inhibiting NF-κB signaling pathway, D. inhibiting the prostaglandins pathway via reducing prostaglandins receptor, reduced COX-2 expression and increased 15-hydroxyprostaglandin dehydrogenase expression which is an antagonist of COX-2 and E. inhibiting immune cells via Vitamin D Receptor (VDR) [57]. Deficiency of vitamin D impairs the macrophages' ability to mature, to synthesize macrophage-specific surface

antigens, to synthesize the lysosomal enzyme acid phosphatase, and secretion of hydrogen peroxide which is their integral antimicrobial function [53]. The activity of matrix metalloproteinase in sputum cells during respiratory diseases like Chronic Obstructive Pulmonary Disease (COPD) is altered and also there is an increase in MMP-9 during acute exacerbations of COPD. MMP-9 is increased by TNF-α in alveolar macrophages and IL-10 reduces the ratio of MMP-9 to the MMP inhibitor. Vitamin D inhibits TNF-α and enhances IL-10 in immune cells of healthy individuals and supplementation of vitamin D in such patients may improve the condition [58]. A meta-analysis on vitamin D supplementation to prevent acute respiratory tract infections showed that vitamin D supplementation was safe and protected against acute respiratory tract infections and the patients with very low serum 25(OH)D (<25 nmol/L) concentrations, not receiving any prior vitamin D supplementation experienced the most benefit [59].

SARS-CoV-2, Inflammation, and Cytokine Storm:

Among the patients infected with SARS-CoV-2, 80% had mild disease, 14% had severe disease and 5% had critical disease as reported by the Chinese Center for Disease Control and Prevention [60]. The triggering factor which is responsible for severe disease in patients infected with SARS-CoV-2 is not only related to viral load but also because of the excessive inflammatory response which is associated with high levels of circulating cytokines, profound lymphopenia, and substantial mononuclear cell infiltration in the lungs, heart, kidney, spleen and lymph nodes [61-62].

Many studies have reported that higher the age and the existence of comorbidities are the risk factors for severity of disease in patients with COVID-19, but later it was also seen that COVID-19 can also occur in younger age group people without any pre-existing medical comorbidities [62]. The pathophysiology of SARS-CoV-2 infection closely resembles that of SARS-CoV infection, with aggressive inflammatory responses. Hence the disease severity is not only due to the viral infection but also the host response [63].

Increased inflammatory markers such as C-reactive protein, ferritin, and D-dimers, neutrophil to lymphocyte ratio, and inflammatory cytokines and chemokines are associated with severity of disease and morbidity. These profiles of systemic cytokine were found to be similar to that in cytokine release syndromes, such as macrophage activation syndrome and increased production of cytokines such as IL-6, IL-7, and TNF. There is global T cell lymphopenia in the CD8 T cell compartment which is more pronounced in patients with the severe form of the disease. Hence, it can be concluded that COVID-19 is associated with hyper-inflammation [61-62,64].

ACE2 is predominantly present in airway epithelial cells, alveolar epithelial cells, vascular endothelial cells, and macrophages in the lung. ACE2 is a zinc-containing metalloenzyme and a homolog of ACE that acts as a transmembrane protein for the entry of the coronavirus into the host cell. ACE2 by converting Angiotensin II to Angiotensin 1-7, regulates the renin-angiotensin system negatively, by declining and opposing the angiotensin II, vasoconstrictor effect. The interactions of ACE, ACE2, angiotensin II, and other RAAS are quite complex, and paradoxical. ACE2 plays a major role

in maintaining blood pressure, fluid and electrolyte balance, and enhancing inflammation and vascular permeability in the airways. The viral load decreases the function of ACE2, hence altering the RAAS. The severity of lung injury are reduced by ACE inhibitors in certain viral pneumonia, and it has been argued that they could be advantageous in COVID-19 [38]. SARS-CoV-2 infects the cells which express the surface receptors ACE2 leading to active replication and release of the virus which triggers the host cell to undergo pyroptosis and release damage-associated molecular patterns. This process is recognized by the neighboring endothelial cells, epithelial cells, and alveolar macrophages, leading to the release of pro-inflammatory cytokines and chemokines. The released proteins attract monocytes, macrophages, and T cells to the site of infection, further assisting the inflammation and initiating the pro-inflammatory feedback loop. In the normal immune response, at the early stage of inflammation, T cell which is virus specific is attracted to the site of infection and neutralizing antibodies eliminate the infected cells and hence stop the virus spread. This neutralized virus is recognized by the alveolar macrophages which are cleared by phagocytosis and hence the lung damage is reduced. In the altered immune response, overproduction of pro-inflammatory cytokines in the lung results in a cytokine storm, further this cytokine storm spreads to other organs causing multi-organ damage [31, 63, 65].

Obesity and Its Infectious Nature:

An epidemiological study to investigate the duration of influenza viral shedding in obese and non-obese by Maier *et al*. showed that obese adults infected with influenza A virus shed the virus for up to 104% longer period than non-obese adults [66]. A study by Honce *et al.* showed that an altered microenvironment in obesity contributes to the development of heterogeneous viral quasispecies due to decreased type 1 INF response in both obese mice and obesity-derived human bronchial epithelial cells implying that obesity allows the putative growth of pathogenic viral variants [67]. A study by Yan *et al*. to check the infectious seasonal influenza virus in exhaled breath of symptomatic individuals in a 30-minute breath sample and nasopharyngeal swab showed that BMI was positively associated with shedding the infectious virus in both fine and coarse aerosols with a stronger association in fine than coarse aerosols [68]. Hence, they came to the assumption that obese individuals are more contagious than lean [2].The most important cause of obesity is a sedentary lifestyle and improper diet. Reduced physical activity alters the immune response against a viral load. Evidence from epidemiological studies has shown an inverse relationship between physical activity and markers of low-grade systemic inflammation [69]. Ertek *et al*. showed that moderate physical activity has anti-inflammatory effects in healthy adults and elderly subjects and also in patients with cardiovascular risk factors such as metabolic syndrome [70]. Similarly, Warren *et al.* showed that physical activity reversed the obesity-associated alterations in host-immune defense [71]. Obesity also restricts ventilation by impeding the diaphragm which is a necessary treatment for the severely affected patients admitted in ICU [14].

Conclusion:

The burden of overweight and obesity and its comorbidities like diabetes mellitus, cardio-vascular disease, hypertension, etc. may increase the risk of acquiring the SARS-CoV-2 infection. By the information available till now it is not only elderly above the age of 60 who are at risk, even the younger generations are also at risk. This may be attributed to obesity, where there is a surge of cytokine storm and ACE2 levels. Overweight and obesity are associated with vitamin D deficiency which is a pathogenic factor involved in infections like COVID-19. Obesity may increase the risk of infection or its complications, hence increasing the mortality rate. Calcitriol modulates the expression of RAAS members such as ACE2 in lung tissue, hence vitamin D deficiency may act as a pathogenic factor in COVID-19. The combined effect of both obesity and vitamin D deficiency may exacerbate the SARS-CoV-2 infection and its related complications. It is not clear what kind of people or what percentage of affected people will develop complications or die due to cytokine storm and to date no vaccine with 100% efficacy or definite treatment is available for the SARS-CoV-2. Knowing the fact, that regular physical exercise helps in desequestration of vitamin D from adipose tissue and aid in normal levels and its function, measures should be taken to do regular exercise. And other preventive measures like regular or frequent hand wash, use of mask, sneezing and coughing etiquette, social distancing, and proper diet should be followed to fight against the infection and obesity.

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***Author for Correspondence:**

Dr. Prashant Vishwanath, Department of Biochemistry, Center of Excellence in Molecular Biology and Regenerative Medicine, JSS Medical College, JSS Academy of Higher Education & Research, Mysuru-570017, Karnataka, India

Email: prashantv@jssuni.edu.in Cell: 9740400007

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