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Review Article

COVID-19 Infection is Associated with Worsening of the Quality of Life in Obesity, Diabetes, and Hypertension Patients: Alteration of the Immune Response May be the Underlying Mechanism

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Abstract

Obesity and diabetes are complex syndromes caused by an intricate combination of genes and environmental interactions. Higher blood glucose levels in people affected with diabetes diminishes the immune potential to tackle infections. This puts individuals with diabetes at a higher risk of developing relatively worse symptoms once they contract SARS-CoV-2. Moreover, the higher mortality rate in patients with at least one of these comorbidities ignites a major public health concern at a global level. It has been known that people with underlying disorders like hypertension, obesity, diabetes, coronary artery, respiratory disease, kidney problems, etc. are at a higher risk of developing severe illness after SARS-CoV-2 infection. As of November 22, 2020 SARS-CoV-2 infection has spread to more than 57.8 million people and has claimed 1.3 million lives. More than a quarter of these cases have been pre-diagnosed with diabetes, obesity, or hypertension. Needless to say, fatality in the normal versus obese or diabetic population. This review aims to provide an elaborate for the above-mentioned comorbidities in COVID-19.

Keywords: *Coronavirus; Inflammatory Cytokines; Coronary Artery Diseases; Respiratory Illness; Obesity; Diabetes; Cardiovascular Disease (CVD); Myocarditis; COVID-19; SARS-CoV-2*

Introduction

A pandemic is capable of impeding the functionality of a society from a household to the level of an entire country or a continent. The world is currently suffering from a zoonotic disease caused by SARS-CoV-2 which was initially observed in a cluster of patients hospitalized around late December 2019 in Wuhan, Hubei Province, China, who were suffering from respiratory illness with pneumonia-like symptoms with unknown cause [1]. A higher to be called Coronavirus disease 2019 or COVID-19 as termed by WHO [2]. The International Committee on Taxonomy of Viruses characterized this unknown etiologic agent of COVID-19 as SARS-CoV-2 that has disrupted the lives of millions of people across the globe [3,4].

The highly communicable disease [5] has spreaded in more than 57.8 million people worldwide and has managed to cause us a loss of more than 1.3 million lives (as per WHO Weekly epidemiological update - 24 November 2020). Also, an economic slowdown with a loss of billions of dollars and uncountable psychological burden. The reports from people affected in China, Italy and New York suggest

that 25 percent of these patients were already suffering from at least one of the underlying medical conditions such as diabetes, obesity, respiratory illness, hypertension or coronary artery disease. Needless to mention adding more risk and slower recovery. The most common comorbidity observed in patients tested positive for COVID-19 is hypertension with 48% of cases having this as an underlying issue followed by diabetes 31% and coronary heart diseases 24% [6,7]. The symptoms varied in different populations with a wide array of combinations of flu like symptoms but respiratory illness was common in most of the severe cases. So far it is known that the stress on lungs is caused by SARS-CoV-2 infection. The viral infection in lung epithelial cells i.e. ciliated cell, basal cell, and club cell may increase expression of angiotensin-converting enzyme 2 (ACE2) and activate these cells in order to produce proinflammatory cytokine storms eventually leading to impairment of the immune system [8]. The dysregulation of immune response can lead to alveolar damage that could be indicative of early acute respiratory distress syndrome in the COVID-19 patients or diffuse alveolar damage (DAD) [9].

Aims:

1. Analyzing the complications in the diabetic and obese population affected by COVID-19 and offering possible management and cure solutions.
2. We evaluate the possible reasons and mechanism of higher risk of SARS-CoV2 in patients with heart and lung conditions.
3. Interventions, management and resilience in patients diagnosed with SARS-CoV-2 with pre-identified comorbidity.

Diabetes and obesity

Obesity and diabetes have been one of the biggest challenges of our society, epidemiologists and scientists in the current era. With the advent of modern technology, we are able to understand the pathways and mechanisms of these complex metabolic syndromes. Obesity is one of the major population health problems that has impacted the lives of millions of children and adults worldwide. Obesity comes with an array of other related problems ranging from other epidemiological problems such as type 2 diabetes, coronary heart disease, stroke, kidney malfunctioning etc. to psychological issues like self-image, improper eating habits *etc*. It is believed that obesity is caused by a complex amalgamation of both environmental and genetic factors (G × E) [10]. Environmental factors are sedentary lifestyles, unhealthy eating habits also peer pressure and socio-economic status of the person [11,12]. In 2017-2018 there were 42.4% obese adults in US [13], and 10.5% has diabetes [14]. Obesity cases have tripled in the last four decades. During the current times of global pandemic these people are at higher risk and a large number of fatalities have at least one of the underlying diseases with obesity and diabetes being very common [15]. A study from the COVID-19 patients in New York, have found higher death rates in patients with pre-existing underlying medical conditions such as hypertension, obesity, diabetes, respiratory illness *etc.* More than 40% of the COVID-19 patients had obesity while 30% of the patients had diabetes. A similar trend was also observed in a study in China [16,17]. Clearly having a comorbidity imparts people at a higher risk of severe symptoms and fatalities. However, correlation between comorbidity and higher death rates remains unclear. "An explanation can be the high blood glucose levels in these co-morbid patients, which leads to a weaker immune system." In addition to this, activation of proinflammatory markers as noted in COVID-19 patients with diabetes compared to normal COVID-19. These proinflammatory markers are increased number of leukocytes, neutrophil, high-sensitivity C reactive protein, procalcitonin, ferritin, proinflammatory cytokines such as IL-2 receptor, IL-6, IL-8, TNFα etc [18]. furthermore, more amount of fibrinogen and D-dimer, which could be a the central cause of severity, has been observed in the diabetes compared to COVID-19 without diabetes, indicating that they are at higher risk to develop blood coagulation during the progression of SARS-CoV-2, known to be linked with occurrence of severe form of diseases [19].

Higher number of comorbidity with obesity and type 2 diabetes possibly due to use of ACEi and ARB blockers which can increased ACE2 expression on the cells in type 2 diabetes which might have a protective role, However it may lead to severe SARS-CoV-2 infection as the immunity against infections goes down due to increased blood-glucose levels [20,21]. Hence, it may possibly account for more fatalities. The pathways used by some of the medications to cure these metabolic diseases includes ACEi and ARB blocker, these in turn can increase mRNA expression of cardiac ACE2 [17] eventually paving path to become one of the factors for a higher mortality rate in

COVID-19 patients with a comorbidity. Increased levels of adiponectin are likely to play a protective role as that may block the secretion of inflammatory cytokines such as IL-6 and TNF-α and promote the secretion of anti-inflammatory cytokines IL-10 (reviewed in [22]. Adipokines is an adiponectin hormone that accounts for 0.01 percent of the total human plasma protein. There are three known isoforms of adiponectin low molecular weight (LMW), medium molecular weight (MMW), and high molecular weight (HMW) [23]. Among these HMW adiponectin is the active form, more closely associated with Homeostatic Model Assessment (HOMA) of insulin resistance in human subjects [24,25]. However, in mice, adiponectin involves sensitizing insulin [26]. Hence, treating patients with adiponectin can have a tremendous impact on obese patients [26].

Further studies are required to completely understand the role of all of the three isoforms of adiponectin. Meanwhile, managing the blood glucose level of diabetic people seems to be very important in terms of prevention of severe risks of SARS-CoV-2. For type 2 diabetes patients, metformin is currently an effective treatment to control blood glucose levels. Another alternative to controlling blood glucose level is to treat patients with INT131 (formerly T0903131, T131, AMG131) is a potent non-thiazolidinedione (TZD) selective peroxisome proliferator-activated receptor γ modulator (SPPARM) that increases adiponectin secretion for the treatment of type-2 diabetes mellitus (T2DM). INT131 is selectively and more efficient when compared to PPARγ and rosiglitazone or pioglitazone [27]. It blocks most of the effect of rosiglitazone on fat cell differentiation, reviewed in [27].

Inflammatory response and cardiac health

SARS-CoV-2 is a highly contagious and one of the rapidly spreading viruses that we have seen in recent history. It has claimed a lot of lives and has spread in a vast majority of population in a very short span of time The virus is known to have an inflammatory response, and researchers are looking for its effects on other organs besides the lungs and heart. Current data suggests that hypertension delays the recovery period and increases the chances of showing symptoms. Furthermore, it has been well-established that people with acute infections of respiratory viruses such as influenza, SARS, MERS, and bacterial pneumonia have more chances of succumbing to cardiovascular diseases (CVD) [28,29]. Moreover, underlying CVD conditions are known to cause adverse events and have simplified the severity of the infection [30]. Recent studies have found similar scenarios with COVID19 as well [31,32]. As we are still exploring SARS-CoV-2, it is very crucial to understand and analyse the research that has been undergoing in various parts of the world so that we take the knowledge collected by ingenious minds and dwell on that. The aim is to review the findings of SARS-CoV-2, SARS, MERS, and other respiratory diseases and their impact on chronic diseases. Analyzing the effects of COVID-19 on the cardiovascular system is critical for providing early comprehensive medical care for cardiac patients during this unprecedented pandemic. COVID-19 may either initiate new cardiac pathologies or exacerbate underlying CVDs. Severity and extent on short-term versus long-term cardiovascular effects, the actual cause, and interventions are under investigation. So far, more fatalities have been claimed from CVDs after COVID19 infection in comparison to pneumonia from influenza [33] that being said, we still need to carefully disassociate the fatalities primarily due to COVID19 vs pre-existing condition [34]. The burden on the heart can increase during the infection due to pneumonia leading to decrease in circulation of oxygen also, an unusual condition known as myocarditis has been observed in certain studies.

Inflammatory response of heart muscles due to COVID-19: Marked inflammation of heart muscles known as myocarditis has been observed in COVID-19 cases [35]. Increased levels of troponins were observed in blood samples of COVID patients, which is a response generated by damaged heart muscles, eventually leading to improper cardiac rhythms. The electrocardiograms of patients suffering from COVID-19 show changes indicative of a heart attack. Hence it is advisable for people suffering from CVDs to take extra precautions to protect themselves from COVID-19 (ref-circulation). Currently, it is being evaluated whether the myocarditis is caused by the presence of coronavirus in our body or by the immune response generated and the best response to tackle this. Either way, the probability of fatalities increased 10 folds from one percent chance of a fatality in normal circumstances for a CVD patient versus 10% if affected by COVID-19.

The speculated reason behind the higher mortality rate in patients with preexisting conditions of coronary artery disease (CAD) and hypertension may be the use of blood pressure medications called angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). These are the two most commonly prescribed medications. As the currently developed fact that the coronavirus attaches to the ACE2 receptor for cellular entry and henceforth infection, this receptor is found in heart and lung tissue. Therefore, taking extra precautions to avert the infection should undoubtedly prioritize people with cardiac health issues and boost the immune system.

Hypertension

Hypertension or high blood pressure is highly prevalent across the globe affecting one in every three US adults. Also, known as Silent Killer, as there is no early sign or symptoms of the disease and a huge chunk of the population gets a diagnosis at a very late stage [36]. The blood pressure is measured in mmHg as a standard unit with a systolic/diastolic value, and the usual value lies around 120/80 mmHg. Systolic blood pressure- is the blood vessels' pressure when the heart contracts or beats and diastolic blood pressure in the blood vessels when the heart goes under relaxation in between beats. Hypertension is considered when a person has repetitive blood of ≥ 140/90 mmHg.

Lungs and inflammatory response from SARS-CoV-2 infection

Lungs are the primary organs of the respiratory system that exchange O_2 and CO_2 gas between breathing air and circulating blood in tiny capillaries [37]. Inhaled air enters through the nose (mostly) or mouth (under certain circumstances) passage to the trachea through nasopharynx. Further from trachea the air moves into the right and left lungs through its tubular branches known as bronchi, which further is divided into small sub-branches known as bronchioles. The air further moves to alveoli which are tiny air sacs that look like clusters of grapes found at the end of bronchioles. Alveoli is surrounded by a dense network of the capillary and interalveolar septum that support the structural basis of O_2 and CO_2 gas exchange between the air compartment (alveolar airspace) and circulating blood compartment (capillary lumen) [38-40]. With the inhalation or the SARS-CoV-2 particles present in the air find their way to enter into the lungs by interacting with the ACE2 and TMPRSS2 present on the nasal and bronchial epithelial cells in the respiratory lining [41-43]. Coronavirus may multiply in the goblet cells at the initial stage of disease progression in an asymptomatic manner and come out from cells without damaging them (Figure 1 and 2) [41,42]. This is the initial stage in the progression of the diseases, once virus infection reaches to alveoli where it infects type I pneumocytes and type II pneumocytes as these cells express ACE2 as well and damage caused to these cells can lead to diffuse alveolar damage (DAD) [9,41,42] Gene expression study reported the ACE2 and TMPRSS2 largely expressed on the type II pneumocytes [44-46]. Post SARS-CoV-2 infection in macaques, noticed that infiltration of alveolar macrophage, few neutrophils, and lymphocytes, and diffuse alveolar damage in lungs [47] from this tissue damage site virus could leak into blood capillary.

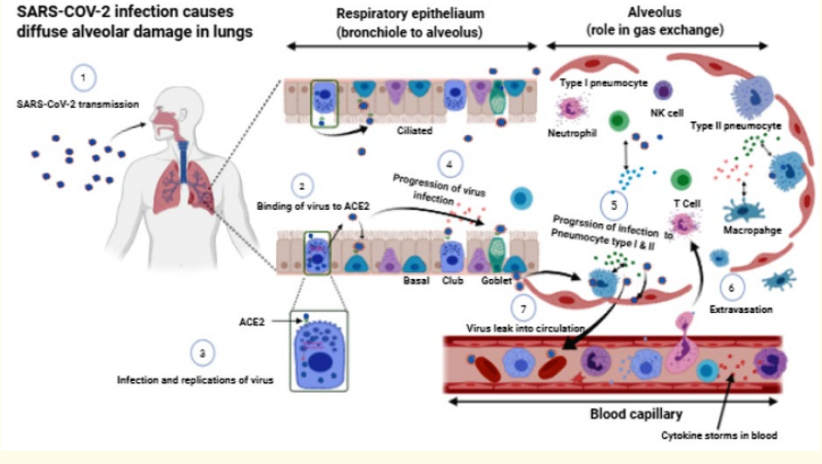

Figure 1: *Schematic of SARS-CoV-2 infection and progression of disease.*

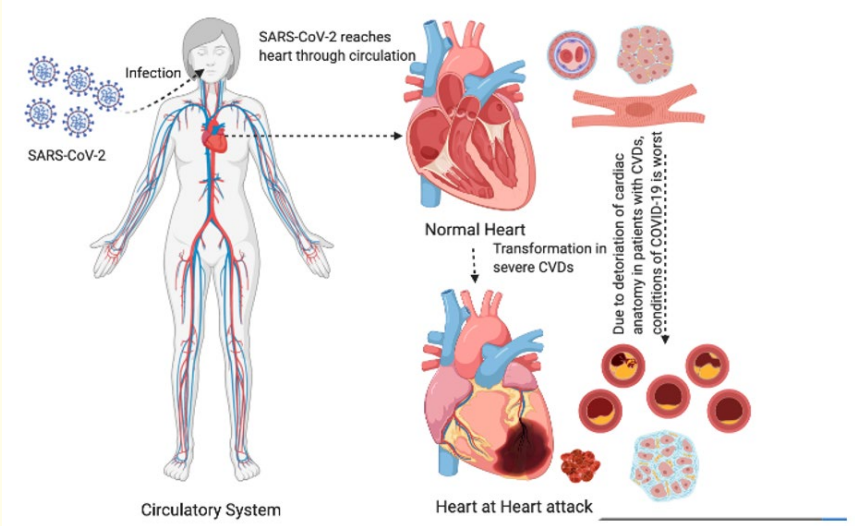

Figure 2: *Schematic of SARS-CoV-2 infection and progression of disease to the heart.*

Furthermore, leading to immune malfunction, such as a decreased number of lymphocytes and increased inflammatory cytokines levels in the blood [34,48,49]. A similar response has been observed with other respiratory viruses like SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) infections [48,49]. A recent study in post SARS-CoV-2 infection in macaques identified SARS-CoV-2 in type I pneumocytes and type II pneumocytes at the site of diffused alveolar damage and the ciliated epithelial cells of nasal, bronchial, and bronchial mucosae [47]. In the early stage of recovery from the SARS-CoV-2 infection, a reduction in the number of T cells, while an increase in the number of monocytes in peripheral blood and plasma cells is observed. Increased number of inflammatory monocytes with increased number of inflammatory gene expression may be associated with increases in IL-1β and M-CSF [50]. These genes can work as a target for inflammatory cytokines storms. Single-cell RNA seq demonstrated the expression of both ACE2 and TMPRSS2 on the same cells from the respiratory tree, esophagus, ileum, colon, gallbladder, and common bile duct [42]. So, these other organs can also be a target of SARS-CoV-2 infection and multi-organ inflammation.

Conclusion and Limitation of the Study

Ongoing pandemic across the world has drastically affected the globe, from socio-economic, financial, physiological, or mental health. With a higher risk of affecting people with underlying comorbidities in a negative way. We are still exploring things like mutation rate, how long the SARS-CoV-2 sustains in the human body, how long is the immune period after an infection, etc.

Conflict of Interest

None.

Author Contributions

KS conceived the idea. KS, AG, and DD wrote the initial draft. KS, AG, DD, AT, FD revised the draft. KS, and DD prepared the figures.

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