



Coronavirus Disease: An Additional Risk Factor for Acute Vascular Events

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Abstract

Unprecedented spread of a killer coronavirus from Wuhan, China, has caused a catastrophic public health and economic crisis worldwide. Since its initial discovery in late 2019, the virus has spread to all the countries, infected 237 million individuals, and caused death of 4.8 million individuals. No country was prepared to face such a devastating infectious disease pandemic. Global Pharma industries responded rapidly to the call of 'Operation Warp Speed' and developed effective vaccines, faster than at any other time in our history. Despite the availability of safe and effective vaccines, large sections of global population, do not have access to these COVID-vaccines. Coronavirus which is highly contagious is transmitted by the respiratory particles and enters the cell by interacting with the angiotensin-converting enzyme-11- receptor (ACE2), which is present on a variety of cells in the human body. Since ACE2 receptors are abundantly expressed on vascular endothelium, upon entry, this virus replicates and spreads to all the vital organs of the body, which are served by the vasculature. Several studies have reported that the severity of the coronavirus disease increases in individuals with underlying health conditions such as hypertension, excess weight, obesity, diabetes, and vascular diseases. These metabolic diseases have increased in the last four decades to epidemic proportions. Individuals with metabolic diseases are at risk for severe coronavirus disease. In view of these observations, those 'at risk' population, should take extra precaution from getting infected with this virus. If infected, all attempts should be made to neutralize the virus, reduce the viral load, or initiate appropriate therapies, -to prevent known clinical complications associated with coronavirus disease.

Keywords: Coronavirus Disease; Hypertension; COVID-Vaccines

Abbreviations: ACE: Angiotensin Converting Enzyme; TMPRSS: Transmembrane Protease Serine Enzyme; BMI: Body Mass Index; vWF: von Willebrand Factor; ELAH: Ethyl Lauoryl Arginate Hydrochloride; FDA: Food and Drug Administrator; CDC: Centers for Disease Control and Prevention; NIH: National Institutes of Health; BARDA: Biomedical Advanced Research and Development Authority.

Introduction

No one realized, as to what impact it will have,-when on December 31, 2019, China informed the World Health Organization (WHO), that a cluster of pneumonia of an

unknown cause occurred in Wuhan City in Hubei province [1-3]. By January 9th, 2020, Chinese researchers had analyzed the genome of this virus and determined this virus as a novel coronavirus- 2019 [4-6]. On January 23, Wuhan was locked down and the WHO declared a "public health emergency of international concern." Since then, this killer virus has spread worldwide, mutated to more potent strains, infected 235 million individuals, and caused estimated 4.8 million deaths. In the US alone, 44 million individuals have been infected, and a staggering 700,000 individuals have succumbed to this disease (coronavirus.jhu.edu/map.html). The pandemic of coronavirus disease (COVID-19) has caused unprecedented healthcare crisis worldwide. Nothing

about this killer virus is predictable accurately, including its geographical distribution, infection rates, case fatality rates, the number of waves of infection, or for that matter, the time and duration of the surge, and the frequency of these surges. COVID positive cases have been reported from more than 180 countries. Oldest democratic country the USA, and the largest democratic country, India, have been in the list of top five countries with the highest number of COVID positive cases. India, Brazil, Iran, France, Turkey, Russia, and the UK, follow the USA as among the countries leading in COVID infection rates.

Coronavirus (SARS-CoV-2) is easily transmissible both by symptomatic individuals and asymptomatic individuals [7,8]. In earlier reports, it was claimed that it usually gets transmitted through respiratory particles and now there are indications, that it may spread airborne as well. However, it is known to spread by so-called super spreader events. Having said that, we must inform the readers, that in recent observations even this speculation seems to be debatable, as these days, you can watch a football game with over 100,000 cheering fans, without a major break-through infection. Yet, you also hear infection of players, who have been under training in 'bubbles' -adhering to the best public health safety practices. These observations suggest, that some individuals probably shed more virus than others or shedding of virus at a particular stage is more contagious than other phases. It is also possible, that some individuals have better immune response when infected with this virus, and as a result generate enough antibodies to neutralize the invading virus. Several studies have indicated that underlying health conditions increase the severity of the coronavirus disease [9-14]. We are of the opinion, that cardiometabolic diseases like hypertension, excess weight, obesity, diabetes, and vascular diseases with compromised vascular function are the major contributors for the severity of coronavirus disease [15-25]. In this overview, we present our views, supporting the concept that metabolic diseases are the number one cause for the severity of morbidity and mortality of COVID positive individuals. We further emphasize that the compromised vascular function (endothelial dysfunction) is the underlying cause for the damage and destruction of the cells, tissues, and organs.

SARS-CoV-2 and the Pandemic of Coronavirus Disease

Coronaviruses contain a single stranded 5'-capped, positive RNA-sense molecule, that ranges from 26-32 kilobases and contains six open reading frames (conserved proteins). These conserved proteins are the polyproteins (PP) pp1a, and pp1b, which encompass multiple protein domains involved in viral genome replication. They include transmembrane glycoprotein (M), the Spike glycoprotein (S),

the envelope protein (E), and are surrounded by a helical nucleocapsid (N) [8,26,27]. The spike protein is a type-1 transmembrane protein, comprising 1255 amino acids, and seems to be the key determinant of evolution, transmission, and virulence of SARS-CoV-2 [28,29]. Coronavirus entry into the host cell is a complex process, that requires receptor binding, and proteolytic processing of the S protein, to promote the virus-cell fusion. SARS-CoV-2 entry into a cell involves the interaction of its spike protein with the cell's membrane bound angiotensin converting enzyme-11(ACE2), which is cleaved by the transmembrane protease serine enzyme-2 (TMPRSS2), suggesting that co-expression of both genes is required for infection [30]. According to the experts, the biological processing and activation of coronavirus S-protein to expose the reactive domain also explains partially, the phenomenon of COVID-19 with severe cardiovascular damage. Key cell entry mechanism includes higher ACE2 (hACE2) binding affinity of the spike to the receptor binding domain, reduced dependence on target cell protease for entry, due to pre-activation by endogenous convertase furin [31]. Recent findings show that following the injury to lung tissue, the virus gets into the vascular endothelium, and thereby spreads to the main blood supply route of all the tissues and organs [32,33]. Endothelial dysfunction and impaired microcirculatory function contribute markedly to life threatening complications of COVID-19, such as venous thromboembolic disease and multiple organ involvement (<http://bit.ly/3cZMjKV>).

Cardiometabolic Diseases Pandemic

Metabolic diseases that contribute to the initiation and progress of vascular disease includes, hypertension, excess weight, obesity, and type-2 diabetes. These diseases have rapidly increased in the last four decades, to epidemic proportions worldwide. Hypertension is the leading cause of cardiovascular disease and premature death [34]. It is estimated that 31% of adults (1.9 billion) have hypertension. In its 2003 report on medication adherence, the WHO quoted the statement by Hanes et al, that "increasing the effectiveness of adherence of interventions, may have a far greater impact on the health of the population, than any improvement in specific medical treatments. Globally, 39% (more than 2 billion) of the adults aged 18 and older are overweight or obese in 2016, and if the current trends continue, it is estimated that 2.7 billion adults will be overweight by 2025. As to the third metabolic disease of public health importance, -type-2 diabetes, the number of people rose from 108 million (1980) to 462 million (2017). The prevalence of diabetes is rising more rapidly in low-and middle-income countries. In 2019, according to the WHO, an estimated 1.5 million deaths were directly caused by diabetes, and another 2.5 million deaths were due to high blood glucose. There are more prediabetics than diabetics, therefore, at-risk population

in this category also runs into billions of individuals. Of all the metabolic diseases, vascular diseases rank very high in causing premature mortality [35]. Cardiovascular diseases are the leading cause of death globally, taking an estimated 17.9 million lives each year. Although COVID-19 has been declared the greatest pandemic of the century, the pandemic of metabolic diseases eclipses, the covid pandemic in terms of its overall impact on health and economies of the nations [36].

Clinical Complications of Coronavirus Disease

A meta-analysis of five studies by cardiologists of Shandong University China, reported the presence of comorbidities in COVID-19 patients admitted to hospitals. The overall proportion of comorbidities were, hypertension (17.1%), cardio-cerebrovascular disease (16.4%), and diabetes (9.7%), respectively [37]. Severity and fatality seem to increase with comorbidities such as hypertension, obesity, and diabetes. In a large study of 72,314 patients from China, the authors reported that those who needed hospitalization had underlying conditions, especially hypertension, diabetes, and cardiovascular disease [25]. According to a meta-analysis published by researchers from the University of Dhaka, the most prevalent comorbidity was hypertension (20%), cardiovascular disease (11-9%) and diabetes (9.8%) [38]. Data from 6916 patient records from Kaiser Permanente reported, compared to normal body mass index (BMI) of 18-24 Kg/m², the risk of death more than doubled for patients with 40-44 Kg/m² and nearly doubled again, for those with a BMI of 45 Kg/m² or more [21]. In the first of a kind meta-analysis published by the international team of experts, capturing data of 399,000 patients, they found that people with obesity who contracted SARS-CoV-2 were 113% more likely to land in hospital, 74% more likely to be admitted to ICU, and 48% more likely to die [39]. Both arterial and venous thromboembolism are common among patients with severe COVID-19. The incidence of thromboembolic events range from 20-30% in patients admitted to intensive care units. Deep venous thrombosis has been identified in 70-100% of patients who died from COVID-19 [40].

Coronavirus Disease is a Major Disruptor of Endothelial Function

Under normal physiological conditions, vascular structure, vessel wall physiology and blood flow dynamics are maintained, by a variety of cell matrix components and endogenous vasoactive molecules. Metabolic risk factors such as oxidative stress, inflammation, and altered flow dynamics, introduce stress on the vessel wall and induce vascular dysfunction. Studies from our laboratory at the University of Minnesota, using an animal model for diabetes,

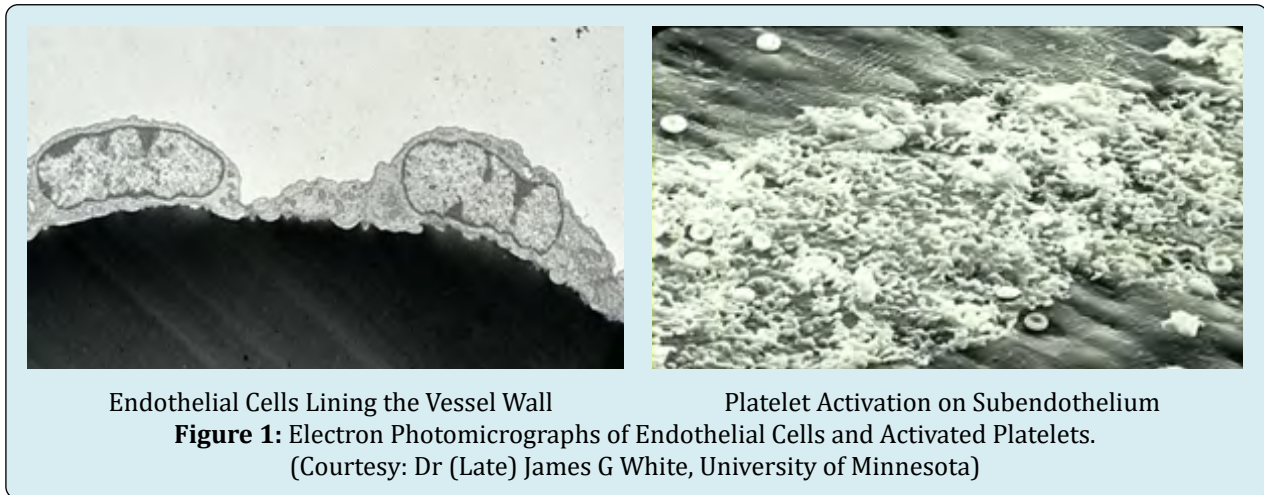
demonstrated the effect of hyperglycemia on arachidonic acid metabolism. In drug induced diabetes, the ratio of vasoactive prostanoids is changed to favor a prothrombotic status. In these studies, we demonstrated, that pancreatic islet cell transplantation restores the balance in platelet and vessel wall prostanoids and normalizes the vascular function [41]. Lowenstein and associates of Division of Cardiology, Johns Hopkins University propose, that the coronavirus triggers a unique endothelial response, -endothelial exocytosis, and microvascular thrombosis, ultimately leading to hyperinflammation and diffuse thrombosis, release of adhesion molecule (P-selectin), and von Willebrand Factor (vWF). In support of their proposed mechanism, they mention that the CRITICAL trial (Crizanilzumab in COVID-19 Vasculopathy; NCT04435184) is testing the hypothesis, that this drug may reduce the mediators of thrombosis and inflammation in patients with moderate COVID-19. A University of Maryland study by Dr. Jonathan Chow and associates has demonstrated that Aspirin use is associated with decreased mechanical ventilation, intensive care unit admission, and in-hospital mortality.

The pathophysiology of hypertension involves the complex interaction of multiple vascular effectors, including activation of the sympathetic nervous system, of the renin angiotensin system, and the inflammatory mediators. Coronavirus takes advantage of the dysfunctional endothelium in patients with metabolic diseases. Since it uses the ACE2 as its primary receptor for entry and replication, the virus has access to the entire vascular system. In this article when we say coronavirus disease is an additional risk factor for acute vascular events, we are not referring primarily to the acute events like heart attacks and stroke, -but all vessel wall dysfunction, that may lead to deterioration of the vascular function leading to ischemia, tissue damage, and ultimately organ failure.

Endothelium is the largest organ of the body, covering a large surface area, reaching out to every tissue and organ (Figure 1). As such, the injury to the endothelium could introduce a cascade of events, leading to platelet activation, thrombin generation, and promotion of both thrombotic and thrombolytic events. Just to distinguish the term 'vascular disease' from the vascular damage and pathology observed in the severely ill Covid-19 patients, we have referred to this condition in our earlier articles, as a 'disease of the blood vessels' [19]. In majority of cases, the severity of the coronavirus disease has been found to be associated with pre-existing comorbidities, which includes metabolic diseases such as hypertension, obesity, diabetes, and vascular diseases. Those with such diseases, or with elevated risk factors for such diseases, -will have a compromised endothelium, favoring vascular dysfunction. The infection of endothelium by SARS-CoV-2 seems to add to this problem,

by further damaging the endothelium, causing dysfunction, disruption of vascular integrity, and endothelial cell death

[42-44].



In a recent article, Guo and associates from China conclude, “Our data support the notion that diabetes should be considered as a risk factor for a rapid progression and bad prognosis of COVID-19” [45]. In this point of view article, we propose that for people with underlying conditions such as hypertension, excess weight, obesity, type-2 diabetes and vascular diseases, coronavirus infection poses an added risk and if intensive attentions are not paid, severity of coronavirus may cause irreversible damage to the tissues, vital organs, and result in organ failure and death.

Coronavirus Disease Prevention Strategies

In the absence of any cure for COVID-19, we are left with very few choices for the management of this virus disease. We are facing two different pandemics at the time of this writing, -pandemic of metabolic diseases and an unprecedented pandemic of coronavirus disease. Both are going to be with us for the near future. Both are syndemic in nature. Despite the knowledge that metabolic diseases have increased in incidence and prevalence to epidemic proportions in the last four decades, no country has been able to reduce, reverse, or prevent these diseases. In view of these observations, the best option we have is to protect the individuals with metabolic diseases from getting infected with this virus in the first place. The best and most widely used option for prevention is to adhere to the best public health safety practices, safe distancing, use of face masks, frequent washing of hand with soap, and tracking the spread of the virus and quarantining infected individuals.

Next best alternative is to find ways to prevent the entry of the virus, or if already present, -find ways to kill or reduce the viral load. A new nasal spray by Melbourne

Biotechnology firm, Starpharma reports the effectiveness against SARS-CoV-2 infection in animal trials. VIRALEZE (1% Astodimer sodium SPL7013) is already in the market today and it is registered for distribution in India and Europe [46]. According to Amcyte Pharma, its Nasitrol (Carrageenan) nasal spray has been shown to be effective in reducing COVID-19 infection, among intensive care unit staff in an independent clinical trial (NCT04590365). New Jersey based medical devices company Salvacion in partnership with the National Cancer Institute, is developing a nasal spray technology (COVIXYL-V), which contains ethyl lauryl arginate hydrochloride (ELAH), which creates a physical barrier, that prevents the virus from attaching itself to the surface in the nasopharynx. Since viral shedding from the nasal cavity and upper respiratory tract is the primary mode of infection, transmission, early therapeutic intervention of SARS-CoV-2 seems to be a great prevention strategy. A team of international scientists are studying the efficacy of PVP-1 complex of polyvinylpyrrolidone and iodine (Nasodine) in preventing COVID infection [47].

Yet another promising technology is in the process of development, which uses virus neutralizing nanobodies for the prevention of SARS-CoV-2 infection. Because of their small size and ease in manufacture, single domain antibodies (nanobodies) are gaining importance in emerging SARS-CoV-2 therapies. Hou and associates from the UK, report the neutralizing effect of four nanobodies (C5, H3, C1, F2) engineered as homotrimers with affinity for the receptor binding domain of the SARS-CoV-2 spike protein [48]. Advantage of this method over other neutralizing antibodies is that these nanobodies can be used as nasal aerosols. When the US President Donald Trump came down with COVID-19, an experimental monoclonal antibody

cocktail developed by Regeneron was used successfully to fight the coronavirus. At that time the recommended dose was infusion of 8 grams of REGEN-COV2, which was still undergoing clinical trial. Currently, India has given emergency use authorization for a COVID-19 antibody cocktail developed by Roche (ROG.S) and Regeneron (REGN.O) to battle a massive second wave of infections. According to Cipla, India partner of Roche, the decision was taken based on the US regulators scientific opinion and the European regulatory panel recommendations. It has been shown to reduce hospitalization in COVID-19 patients, who are at a high risk (patients with comorbidities) of developing severe illness. In India, yet another antibody cocktail therapy, -Eli Lilly's bamlanivimab and etesevimab has received emergency use approval.

A much smaller pharmaceutical company Natco Pharma (NATP.NS) has received emergency use authorization for baricitinib, developed by Eli Lilly (LLY.N) to be used with remdesivir to treat COVID-19. Merck reported recently, that its oral antiviral drug molnupiravir is effective against known variants of the coronavirus, including the dominant, highly transmissible Delta. Since this drug does not target the spike protein of the virus, the target of some of the current COVID-19 vaccines, -the drug should be equally effective on any continuously evolving mutants. Merck has approached federal regulators for emergency use authorization for its first of a kind COVID-19 pill. The former US Food and Drug Administrator (FDA) Chief, Dr. Scott Gottlieb told CNBC recently, that the drug was "a profound game changer" – since the interim clinical trial results show, that the drug may slash the risk for hospitalization or death by 50% in those with mild-to-moderate COVID. Five out of the eight Indian Pharma companies, -Dr Reddy's, Cipla, Sun Pharma, Torrent, and Emcure are conducting a joint trial for the antiviral drug only in mild to moderate COVID-19 patients in an outpatient setting. Singapore has already inked a supply and purchase agreement for antiviral drug pill to treat COVID-19. Australia has ordered 300,000 doses. The drug maker has agreed to make 1.2 billion supply deal with the US government, under which it would provide 1.7 million courses of the treatment, once the drug gains emergency use authorization by the US-FDA.

At the population level, according to public health experts, the vaccines are the safest and most effective preventive agents. Availability and acceptability are the limiting factors for achieving total global vaccination. Despite, rich countries just represent 14% of the world's population, they have bought up 53% of the most promising vaccines. But unless something drastically changes, billions of people around the world, especially the people in resource poor countries, will not receive any vaccines (98% not vaccinated) for COVID-19 for years to come. Furthermore, these resource poor countries

have the greatest burden of metabolic diseases. According to experts, excess weight and obesity are the greatest contributors for the observed severity in COVID-19 positive, hospitalized individuals. Globally, obesity has doubled in 73 countries around the world. Health problems resulting from being overweight or obese now affect more than 2 billion individuals worldwide [49,50]. These individuals are at risk for severe coronavirus disease as well. If we look at the increase in the prevalence and incidence of metabolic disease over the last four decades all of them have reached epidemic proportions. Therefore, it is time we recognize that these individuals are at risk for the severity of an unprecedented virus disease. Public health workers, critical care workers, clinicians should be made aware of the vulnerability of this 'at risk' population, so that they take needed precautions and develop appropriate prevention strategies, and treatment protocols for management of acute vascular dysfunctions [51-54]. At a time when all attention is focused on COVID-19 pandemic, it is critical to consider how to optimize the early diagnostic technologies and treatment protocols for patients with COVID, who also have underlying conditions such as hypertension, excess weight, obesity, diabetes, and vascular diseases [16-20].

Conclusion

Unprecedented pandemic of coronavirus disease has caused great economic and healthcare crisis worldwide. No country was prepared with appropriate public health measures, to contain this unprecedented contagious disease. In the USA, Operation Warp Speed, a public-private partnership was initiated to facilitate and accelerate the development of therapeutics and diagnostics for the management of COVID-19 crisis. Collaborating Health and Human Services components included the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH) and the Biomedical Advanced Research and Development Authority (BARDA). Early studies from several countries also revealed the syndemic nature of this disease with underlying health conditions such as hypertension, excess weight, diabetes, and vascular disease. Despite availability of safe and effective vaccines, there exists a great disparity in the availability of this vaccine for most of the individuals in resource poor countries. In addition, according to Global Disease Burden collaborators, metabolic diseases pose a greater burden in the low- and middle-income countries. Currently, we are facing two different pandemics, - coronavirus pandemic and metabolic disease pandemic, which are syndemic. Globally, more than two billion individuals with metabolic diseases are at risk for severe coronavirus disease.

Even though public health workers are aware of the increasing health care burden of the metabolic disease

burden worldwide, no country has been able to reduce, reverse, or prevent these metabolic diseases. Pandemic of coronavirus disease as well as metabolic diseases are going to be with us for some time. In the meantime, we need to protect the 'at risk' population with metabolic diseases from the killer virus. In the absence of any cure, prevention seems to be the most optimum choice. In addition to the safe public health practices, vaccination would be a wise option. Having said that we must inform the readers that vaccination of the global population is not an easy choice. Therefore, it is time that greater awareness is created among healthcare providers about the syndemic nature of the two pandemics, so that they develop appropriate preventive protocols to prevent infection in the first place, -neutralize or reduce the viral load, initiate antiviral therapies, anti-inflammatory therapies, and antithrombotic therapies, as needed depending upon the manifested clinical symptoms.

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