REVIEW ARTICLE

Metabolic Diseases Enhance the Severity of Coronavirus Disease

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ABSTRACT

Unprecedented pandemic of coronavirus has infected 250 million individuals, and killed 5 million people worldwide, since it was discovered in Wuhan, China, in 2019. Clinical studies conducted at several geographic locations, have observed that people with underlying health conditions experience, severe illness compared to those with no underlying health conditions. Studies done at several clinics have shown that metabolic diseases such as hypertension, excess weight, diabetes, and vascular diseases contribute significantly to the severity of the coronavirus disease. Despite these observations, the exact mechanism by which these diseases increase the severity of this coronavirus disease is not clear at the time of this writing. Metabolic risk factors such as oxidative stress, chronic inflammation, altered blood sugar, insulin, and lipids, favor the development of endothelial dysfunction and platelet hyperfunction, suggesting predisposal to a thrombotic state. However, limited number of clinical trials done with antithrombotic therapies, have not provided encouraging results to promote these therapies. In the absence of an effective therapeutic protocol for the management of COVID-19 patients, we are left with very few choices for the management of this disease. Vaccination seems to be a preferred choice at the population level. However, the availability, acceptability, and economic factors, limit the use of this approach. Apart from the vaccines, use of monoclonal antibodies seem to work, in reducing the viral load in high-risk individuals. Some injectable monoclonal antibody cocktails are in use in India and other countries. Other attractive alternatives includethe development of drugs that can prevent or kill the virus at the site of infection. Several nasal sprays are currently in use for this purpose. Yet another approach is to develop or repurpose antivirals drugs for the management of coronavirus disease. At least two FDA approved oral antiviral drugs, repurposed for use, are under clinical testing, in various countries, for preventing COVID-19 related acute complications.

Key words: SARS-CoV-2, Coronavirus, Metabolic diseases, mRNA vaccines, Endothelial dysfunction.

INTRODUCTION

Metabolic diseases such as hypertension, excess weight, obesity, type-2 diabetes contribute significantly to the development of vascular diseases. Each of these metabolic diseases, act as independent risk factor for cardiovascular disease, and in combination elevate the severity of the vascular disease (1-2). These diseases have increased rapidly during the last four decades, to epidemic proportions worldwide (3-9). When we use the term metabolic disease, we are not using it to describe a cluster of metabolic risks (referred to as Metabolic Syndrome), but in the broadest term of metabolic alterations, leading to the development of metabolic risk factors. We and others have described the rapid increase in these diseases as epidemic, pandemic, or even as Tsunami in our earlier publications (4,6,8,9). It is estimated, that 31% of the adults (approx. 1.9 billion) have hypertension. Globally, 39% (more than 2 billion) of the adults aged 18 are older are overweight or obese. The number of individuals with type-2 diabetes, rose from 108 million (1980) to 462

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million (2017) in the last four decades. In 2019, according to the World Health Organization, estimated 1.5 million deaths were due to diabetes, and another 2.5 million deaths were due to high blood glucose levels. There are more prediabetics, than diabetics worldwide. Since these diseases are syndemic in nature, deaths due to vascular diseases rank number one, and are the leading causes of premature mortality, taking an estimated 17.9 million lives each year. Coronavirus disease is an unprecedented pandemic, that has taken advantage of an already existing pandemic of metabolic diseases and caused great public health and economic crisis. We and other investigators have described the syndemic nature of COVID-19 with the metabolic diseases (10). In this overview, we discuss the specific roles of vascular endothelium, and circulating platelets, in enhancing the severity of coronavirus disease.

CORONAVIRUS DISEASE-2019 (COVID-19)

Coronavirus 2019 (SARS-CoV-2) has caused an unprecedented healthcare and economic crisis worldwide. Of the six strains of coronavirus (229E, NL63, OC43, HKU1, MERS-CoV and the SARS-CoV) that have infected humans, four of them have been responsible for one-third of common colds. According to the Johns Hopkins Coronavirus Tracker, as of this writing, globally, 243 million individuals have been infected, and the virus has caused 5 million deaths. The ranking of top five countries with the highest infectionis as follows: the USA (45 million), India (34 million), Brazil (21.8million), the UK (8.7 million), and Russia (8.0 million). It is rather hard to believe that in the most advanced country, the USA. Number of individuals infected as well as number of patients succumbed to COVID-19 remains the highest. Less than 5% of COVID-positive individuals needed hospitalization. The experts have estimated that more than 900, 000 infections occurred in the first nine months of the Covid pandemic. According to them 30% of these hospitalizations were attributable to obesity, 26% to hypertension, 21% to diabetes, and 12% to heart conditions (NIH RESEARCH MATTERS March 9, 2021). Ongoing monitoring of hospitalization rates is critical to understanding the evolving epidemiology of the disease. Having said that, population-based rates of laboratory confirmed, coronavirus disease-associated hospitalization data are lacking. In a report generated in the first three months of 2020, the overall laboratory confirmed COVID-19-associated rate was 4.6% per 100,000 population in the US. Of the individuals admitted to hospital, 89.3% had one or more underlying conditions. The most common underlying condition was hypertension (49.7%), obesity (48.3%), chronic lung disease (34.6%), Diabetes (28.3%), and cardiovascular disease (27.8%) (11).

SARS-CoV-2 is a beta coronavirus with a single-stranded RNA. The virion contains four structural proteins, spike (S), envelope (E), membrane (M), and nucleocapsid (N). The viral RNA genome contains 29,903 base pairs, much larger than other RNA viruses. SARS-CoV-2 virions attach to human cells with their densely glycosylated (receptor binding domain; RBD) spike proteins. This has been the target of many medical interventions, including the successful mRNA vaccines. The spike protein has two functional domains (S1, S2), S1 for receptor binding and S2 responsible for cell membrane fusion. Receptor binding domain of the virus as high affinity for the angiotensin (Ang)-converting enzymes-11(ACE2) on the human cells. The renin-angiotensin system plays a crucial role in blood pressure management and fluid dynamics.This enzyme is present on most of the cells including circulating blood platelets. Though this protein is abundantly expressed on endothelium, enzymatic cleavage results in a circulating form in the plasma. The virus entry into the host cells is mediated by the transmembrane spike (S) protein that forms homotrimers protruding from the viral surface. The S unit is further cleaved by host proteases, at the S2 site of the fusion peptide. Because of this method of transmission, the virus entry to the host cell is quite complex, and requires both the receptor binding protein, and proteolytic processing of the S protein, to promote virus-cell fusion (12).

ROLE OF ENDOTHELIAL CELLS AND PLATELETS IN THE SEVERITY OF CORONA VIRUS DISEASE

Accumulating evidence indicates that the coronavirus infection exerts adverse effects on the vascular and capillary endothelium. Altering the integrity of the vessel barrier, promoting coagulation state, inducing endothelial inflammation, mediating leukocyte infiltration, and activating circulating platelets (13-15). ACE2 is the primary receptor for the virus entry to the host cells. As the viral load increases, the amount of functional ACE2 on the endothelial cells decrease and thereby, creates an imbalance in the ability of the ACE 2 to catalyze the conversion of Ang-11 to Ang, resulting in the accumulation of Ang-11 and vascular damage. Vascular endothelium is the largest organ system of the human body. A monolayer of endothelial cells, strategically interface between the tissue components and circulating blood. These cells and their normal function are pivotal for vascular integrity, protection against vascular injury, and maintaining of normal hemostasis. The normal endothelium releases vasoactive molecules, such as prostacyclin and nitric oxide, potent inhibitors of platelet activation as well as vasodilators. Healthy endothelial cells express, antiplatelet and anticoagulant agents that prevent platelet activation, aggregation, and fibrin formation. Damage to the endothelium will deplete the

availability of these vasoactive

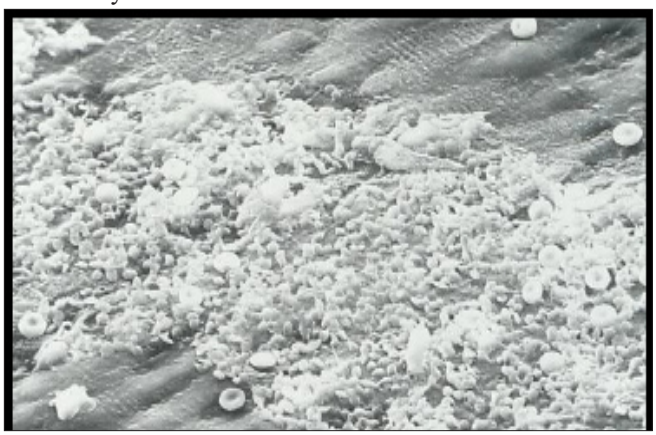

Figure1. Electron photomicrograph showing platelet interaction with damaged endothelium (Courtesy: Professor (Late) James G. White, University of Minnesota).

molecules. An example of what will happen, if the endothelial function is compromised, is illustrated in Fig.1 In the figure above, one can see healthy endothelial cells devoid of any activated platelets. The damaged subendothelial surface with cell matrix components is covered by platelets in various stages of activation. Direct infection of endothelial cells may lead to damage of the endothelial lining by apoptosis or pyroptosis. Compromised endothelium, could trigger platelets, and activate the expression epitopes on platelet GP 11b/111a, which now can recognize the RDG motif on COVID spike proteins and bind to them (16, 17). This may explain the platelet microaggregates observed by clinicians, in regional microvascular and macrovascular beds.

Studies from the University of Minnesota half a century ago, demonstrated that platelets interact with the invading bacteria and viruses. In these studies, we demonstrated the ability of bacteria to activate and induce release of the granule contents (18). Our associates in the School of Dentistry at the University of Minnesota, in a series of elegant studies demonstrated, that platelet aggregation-inducing strains of bacteria, contain collagen like interactive domains (pro-gly-glu-gln-gly-pro-lys) and induce platelet activation, by interacting with transmembrane signal-transducing receptor complexes, known as integrins (19). Researchers from Northeastern University Boston, MA, have demonstrated the emergence of a tripeptide, arginine-glycine-aspartate (RGD) motif, in the spike proteins of SARS-CoV-2, and speculate that that viral binding to cell-surface integrins, may contribute to the high infectivity and widespread extra-pulmonary impacts of the spike protein. RGD is a motif, commonly used by viruses, to bind cell-surface integrins. Therefore, it is no surprise that activated platelets are attracted to the viruses as they can recognize this tri-peptide arginine-glycine-aspartic acid on viral spike proteins (20).

It is well known in the thrombosis research that activation of glycoprotein 11b/111a on platelets, leads to the recognition of RGD tripeptide on fibrinogen, leading to aggregation. During infection with respiratory viruses, the integrity of infected endothelial cells become compromised, leading to increased permeability that allows virus to crossover into the circulation. Platelets are the frontline of COVID-19 pathogenesis, as they release various bioactive molecules,during different stages of the disease. They may have the potential to contribute overwhelming thrombo-inflammation in COVID19, and therefore it is speculated that, inhibition of pathways related to platelet activation, may improve the outcomes during COVID-19 (20).A recent study showed that ACE2, a host cell receptor for SARS-CoV-2, and TMPRSS2, a serine protease for protein priming, are expressed in platelets, and that SARS-CoV-2 virus directly activates platelets and potentiates, their prothrombotic function and inflammatory response, via SPIKE/ACE2 interactions (21). Due to their abundance, platelets may be the first blood components to internalize viral particles and induce response once the pathogen reaches circulation. By this way, the virus also gets access to the entire vascular system, and the tissues and organs that depend upon this system for their growth and survival.

How do the metabolic diseases enhance the severity of coronavirus disease? Why do individuals with underlying conditions, more susceptible for this disease? These are questions, which can only be partially answered at this time. Having said that, it is possible to develop some working hypothesis. All the metabolic diseases have a dysfunctional endothelium and probably hyperfictional platelets. Since both endothelium and platelets have abundant ACE2 receptor, it is reasonable to assume that the virions prefer these cells for their entry, replication, and spreading. Since spike proteins also have RGD binding sites, activated platelets adhere and get into the circulation carrying with them the virions. Dysfunctional endothelium with compromised ACE2 function will induce alteration in the blood pressure as well as blood fluidity, all favoring development of prothrombotic state. Swiss Scientists and the US scientists, claim that Coronavirus disease may not be a typical respiratory disease. They provide evidence to support, that coronavirus disease may indeed be a vascular disease. Just to distinguish the term 'vascular disease' from the vascular damage and pathology observed in the severely ill Covid-19 patients, we refer to this condition as a 'disease of the blood vessels' (15, 17). Global COVID-19 Thrombosis Collaborative Group, endorsed by professional societies such as ISTH, NATF, ESVM. And the IUA led by Professor Bikdeli of Columbia University Medical Center concludes, "Thrombotic disease may be

precedent factors or incident complications in patients with COVID-19. Important considerations for the preventive and therapeutic use of antithrombotic agents should be kept in mind to mitigate the thrombotic and hemorrhagic events in the high-risk patients (22)".

Despite these observations, the exact role of metabolic disease, in enhancing the severity of coronavirus disease is elusive. Let us just discuss some studies, which followed the advice of the Global COVID-19 Thrombosis Collaborative Group and tested antithrombotic therapy. Professor Chow and associates from the George Washington University, Washington DC, studied the effect of aspirin on hospitalized COVID-patients. They found a crude association with less mechanical ventilation and ICU admission, but no crude association with in-hospital mortality (23). However, they suggested the need for a sufficiently powered randomized controlled trial, to assess whether a causal relationship exists, between aspirin use and reduced lung injury and mortality in COVID-19 patients. Maldonado and associates of the Oregon Health and Science University, based on the new evidence on thromboembolism in COVID-19 patients, did not find any need for a change in the current guidance, on the thromboprophylaxis among hospitalized patients (24). Of course, they too suggested the need for prospective clinical trials of antithrombotic treatment strategies. In a State-of-the-art review by Iranian researchers and the members of the global COVID-19 thrombosis group, authors concluded that 'Optimal antithrombotic therapy in patients with COVID-19 has yet to be determined (25). Professor Berwanger of Hospital Israelita Albert Einstein, Sao Paulo, Brazil in an editorial in JAMA concluded that, "Given the null results for major cardiovascular and pulmonary events, currently, the use of aspirin or apixaban for symptomatic but stable ambulatory patients with Covid-19, does not seem justifiable. Having said that, we must inform the readers, that at least 10 randomized clinical trials are underway, to test interventions such as antiplatelet agents, direct oral anticoagulants, and standard prophylactic doses of low-molecular-weight heparins.

CORONAVIRUS DISEASE INTERVENTIONS

We are amid a therapeutic revolution, the likes of which have not been seen, since the advent of recombinant protein technology, almost half a century ago in Silicon Valley or for that matter, since the time James Watson and Francis Crick elucidated the molecular structure of the DNA (26, 27). Unprecedented coronavirus pandemic accelerated the development of emerging technologies. Advances in the generation, purification, modification of the base pairs, to suit the purpose and packing for targeted delivery of mRNA, have enabled the development of mRNA-based therapies for a broad array of therapeutic applications (28). Scientists at Moderna, a biotech company specializing in messenger RNA, -therapeutic applications, were able to design a customized 'mRNA' on paper in less than 48 hours after the COVID-19 genome information was announced, according to a report by Antonio Regalado in MIT Technology Review (124(2),2021). Extensive studies done at the Perlman School of Medicine, University of Pennsylvania, by Professor Drew Weismann, and associates, helped to the success of mRNA vaccine development, by providing a suitable targeted delivery system using lipid nanoparticles (29). Currently, Pfizer BioNTech (BNT162b2), Moderna (mRNA-1273), Oxford/AstraZeneca, The Jansen Ad26, the Sinovac-CoronaVac, and the Sinopharm COVID-19 have been in use across the globe. However, the distribution of vaccine is not on an equitable basis (30). Majority of the resource poor countries, have no access to these vaccines. Even where it is available, there are large number of individuals who refuse to get vaccinated.

Treatment for COVID-19 patients, is classified into several categories: antibody therapies, which use laboratory engineered antibodies, to help stop viral replication, develop new antivirals, or explore repurposing of available drugs, which specifically target, prevent infection, or kill viral particles, -corticosteroids, which reduce body's inflammatory response to the infection. REGEN-CoV antibody combination trial investigators reported that COVID-19-related hospitalization or death was reduced,in antibody infused individuals compared to placebo control (31). In India Cipla and Roche Pharma companies, have made available 1200 mg injectable antibody (Casirivima and Imdevimab) cocktails, for use in COVID-19 patients to minimize hospitalization and severity of the disease. British drug maker GlaxoSmithKline with Zydus Cadilla, India, is trying to introduce a recently US-FDA approved cocktail (Covimabs), for COVID-19 positive individuals. This cocktail has been shown, to provide 85% reduction in the risk for hospitalization or death in high-risk adult outpatients. There is great opportunity for the development of new antiviral drugs or screen existing drugs for repurposing. Drug repurposing is considered as an emerging strategy of computational approach; to identify new therapeutic agents within a short period of time for effective treatment of COVId-19 (32). The structural and molecular basis of interactions, suggest that the FDA approved drugs can be repurposed, towards multiple targets of SARS-CoV-2 (33). The use of computational tools has revolutionized this approach, by predicting the association of ligands (34). A novel drug developed by computational biology strategy, inhibits endothelial apoptosis, by inhibiting iron-sulfur biogenesis gene glutathionylation and rescuing oxidative metabolism, decreasing endothelial apoptosis, and improving pulmonary hypertension (35). These studies

revealed a key role for pulmonary hypertension gene cluster encompassing galectiv-8 (LGALS8) as modulator of endothelial pathophysiology. Pharma industries are developing newer state-of-the-art technologies, for structure-activity based drug development (36, 37).

PREVENTION STRATEGIES: NEED OF THE HOUR AND CALL FOR ACTION

Globally, more than 3 billion individuals are 'at-risk' for severe coronavirus disease, due to underlying health conditions. We and others have noted that metabolic diseases are the major contributors, for this increased risk for coronavirus related morbidity and mortality (8, 9.10,15). Metabolic diseases have increased to epidemic proportions, worldwide in the last four decades. No country has reduced, reversed, or prevented the increase in the incidence of metabolic diseases. Unprecedented pandemic of coronavirus has taken advantage of this existing pandemic and used these individuals with compromised vascular function to its advantage for infection and replication. The novel virus has engineered its spike proteins for a greater efficiency, and transmissibility by selecting ACE2 as the primary receptor for cell entry. Just like the metabolic diseases which have continued to plague us, the coronavirus will also linger on and undergo mutations to evolve into better strains. Despite our knowledge about the fact, that most of the individuals with severe COVID-19 end up with thromboembolic events, we do not have any approved treatment protocol to prevent these complications. Moreover, when we consider prevention strategies, we should aim at the primary prevention, rather than management of the risks associated with the disease. The best and the 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.

Other alternatives include ways and means 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% Astodrimer sodium SPL7013) is already in the market today and it is registered for distribution in India and Europe (36). 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 lauoryl 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 (37).

Merck has reported recently, that its oral antiviral drug molnupiravir is effective against known variants of the coronavirus, including the dominant, highly transmissible Delta. Molnupiravir, like Remedesivir, is a nucleoside analogue, which mimics the building blocks of RNA. Remedesivir is a chain terminator, whereas Molnupiravir gets incorporated to viral RNA strands and wreaks havoc. There seems to be some concern, as the drug mutates RNA, - whether it can do the same on patient's own genetic material. Pfizer recently announced that its oral antiviral pill (Paxlovid) slashed hospitalization by 89% among those covid patients treated within three days of appearance of symptoms. Pfizer drug therapy consists of two distinct medications, the SARS-CoV-2 protease inhibitor (PF-07321332) and a generic HIV drug (Ritonavir) that boosts the effectiveness of protease inhibitors. Since these drugs do not target the spike protein of the virus, the target of some of the current COVID-19 vaccines, -drugs should be equally effective on any continuously evolving mutants. The Merck drug has been approved by the UK government for use in the treatment of moderate to severe COVID patients. Five out of the eight Indian Pharma companies, -Dr Reddy's, Cipla, Sun Pharma, Torrent, and Emcure are conducting a joint trail for the antiviral drug only in mild to moderate COVID-19 patients in an outpatient setting.

Fluvoxamine, a common serotonin uptake inhibitor at doses of 100 mg three times daily, has been shown to reduce the need for hospitalization of COVID-19 positive individuals (38, 39). "The antidepressant FDA approved drug Fluvoxamine could be one of our most powerful weapons against the virus and its effectiveness is one of the most important discoveries made since the pandemic began," says Edward Mills, a co-principal investigator of the TOGETHER trial. Our call for action for the pharma companies' is to focus on developing new safe and effective oral antivirals or find FDA approved drugs for repurposing as therapeutics for managing COVID-positive individuals in out-patient settings. Ofcourse, we already have two very effective antiviral oral pills in clinical trials at various global sites. If safe and effective antivirals could be developed, it could have enormous benefit for reducing severe illness, for both unvaccinated and breakthrough vaccinated individuals. Pharma companies are developing

some state-of-the-art approaches for the development of newer drugs or for repurposing already approved drugs (40-42). There are already speculations, that introduction of highly effective treatment options, may reduce some global demand for COVID-19 vaccines. Emerging supportive digital care technologies include design, and implementation of automated algorithm driven COVID-19 triage tool, for screening severe acute respiratory syndrome like symptoms (43).

CONCLUSION

A novel, killer, severe acute respiratory syndrome (SARS) coronavirus evolved in Wuhan, China, and spread rapidly in December of 2019 like a wildfire worldwide. SARS-CoV-2 virus caused globally, an unprecedented healthcare and economic crisis. The original animal virus evolved and engineered itself for high infectivity and transmissibility in humans. The spike protein receptor- binding is the critical determinant of a viral infectivity and transmissibility. Spike proteins undergo conformational transition from prefusion to post fusion with the help of proteases like furin, TMPRSS2, and cathepsins. SARS-CoV-2 has higher binding affinity than the other SARS viruses. Unlike other SARS viruses, cell entry of SARS-CoV-2 is preactivated by proprotein convertase furin, reducing its dependence on target cell proteases for entry. The selection of ACE2 as the primary cell entry receptor makes it easy for this virus to get into the circulation and spread to all the organ systems. Endothelium and platelets express ACE2 and serve as conduits for distribution of the virus in the human system. Furthermore, revelations that an RGD (arginine-glycine-aspartate) sequence exists in the receptor binding domain of the spike protein, enhances the ability of the virus to interact with surface membrane integrins of other circulating cells including blood platelets. Clinical consequences of Integrin-RGD motif interaction of virions, can lead to the modulation of a variety of cell signaling mechanisms.

Metabolic diseases like hypertension, excess weight, type-2 diabetes, and vascular diseases have increased rapidly in the last four decades to epidemic proportions worldwide. Coronavirus has taken advantage of this existing metabolic disease pandemic. Clinicians have noticed that the severity of the coronavirus disease is greater in individuals with underlying health conditions. Globally, there are more than 3 billion people with one or more of the metabolic diseases and hence, are at-risk for severe coronavirus diseases. The overall proportion of comorbidities in hospitalized covid patients have been, hypertension (17.1%), cardio-cerbrovascular disease (16.4%), and diabetes (9.7%), respectively. 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. Those with comorbidities seem to have compromised immune function. Furthermore, they also seem to have dysfunctional endothelium and hyperfunctional platelets. We and others have described coronavirus disease as a 'disease of the blood vessels.' Despite our knowledge about the fact that most of the individuals with severe COVID-19 end up with thromboembolic events, we do not have any approved treatment protocol to prevent these complications. Moreover, when we consider prevention strategies, we should aim at the primary prevention, rather than management of the risks associated with the disease.

Epidemic of metabolic diseases have been in progress for decades. No country has reduced, reversed, are prevented these diseases. Coronavirus disease also will remain with us for some time to come. Many effective and safe vaccines are available. However, vaccinating every individual globally is a herculean task. For the near future, population at large should be advised to follow the best public health safety practices to avoid contacting the virus. There is an immediate need to find ways, to kill the virus or reduce the load of the virus before it becomes established. There are number of nasal sprays available in the market undergoing evaluation. Since the time HIV/AIDS became a public health menace, there is a race for developing antiviral drugs. Covid pandemic has been 'a wake-up-call' for the development of newer antiviral drugs. Antivirals for coronaviruses are "task number one", says NIH director Francis Collins. There are great opportunities for drug discovery, computational biology, and drug repurposing to come up with newer biologics, as well as small molecules, for the primary prevention of this devastating viral disease.

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