

COVID-19 and Cardiometabolic Diseases

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Communicable diseases (CDs) as well as noncommunicable diseases (NCDs), are great public health problems, which create catastrophic economic damage, cause loss of precious lives and are preventable. According to Harvard Gazette (August 08, 2018), "eight million largely preventable deaths from various diseases, costed six trillion dollars in lost income". Researchers working on topics related to cardiometabolic diseases (CMDs), have borrowed the word 'Pandemic' from the epidemiologists who early on, described worldwide outbreaks of infectious diseases as pandemics. Like earthquakes and other natural disasters, pandemics are unpredictable. Current debate about the COVID-19 pandemic describes the dilemma very well. To the extent, the US administration has threatened, to cut off its financial aid to the World Health Organization (WHO) for colluding with China, in keeping the facts about Covid-19 infection hidden from the rest of the world. COVID-19 or SARS Cov2 virus has spread to all the countries (177 countries) across the globe, but the severity of the infection and number of deaths is not the same everywhere. The US is leading in the number of infected cases as well as in the number of deaths. Next comes the major European countries including Italy, Spain, Germany, France, Belgium and the UK. Some outliers for this spread of the virus include, Iran and Turkey. India, Bangladesh, Pakistan, Brazil, Mexico and vast majority of the countries in Africa, with poor healthcare infrastructure have much lower infection rates and deaths due to COVID-19. All generalizations, speculations, working models, to a large extent have failed to explain the symptoms, infectious stages, immunogenicity, herd-immunity, pathogenesis, risk factors and the severity of the disease with respect to gender, age, ethnicity and comorbidities.

Cardiometabolic diseases such as hypertension, excess weight, obesity, diabetes and vascular diseases have increased in prevalence and incidence worldwide, to epidemic proportions and these diseases have also been described as pandemics, syndemic or even Tsunami's in the epidemiology literature [1]. Currently, there are more than 2.2 billion individuals with excess weight worldwide. In the last three decades, obesity has increased two-fold and diabetes four-fold in the world. During the same period in China, diabetes has increased by 17-fold, giving it the dubious title, 'Diabetes Capital of the World'. Hypertension, known as the silent killer, is most common disease worldwide. Metabolic risk factors that promote the development of metabolic disease and contribute to their progress include, oxidative stress, chronic inflammation, excess weight, obesity, endothelial dysfunction, insulin resistance, altered lipid and glucose metabolism, subclinical atherosclerosis, diabetes and vascular disease. Vascular diseases have remained the number one killer and have retained this status for over a century. Spanish Flu of 1918 (H1N1), infested quarter of the global population, 500 million individuals and killed approximately 50 million people during the two-year cycle. Whereas, vascular diseases killed 18 million individuals worldwide in 2016. Modern medicine has failed to prevent or reduce the ravage of either infectious or noninfectious diseases. By focusing exclusively on intervention, we have barely managed to survive these catastrophic events.

The Nobel prize winning (1958) microbiologist, Joshua Lederberg of Yale University conceded the fact, that we have not been able to 'conquer' the infectious microbes, because of their amazing ability to change and evolve just to survive. There seem to be no other specific purpose for the existence of these viruses, other than just survival. Dr. Lederberg is known to say, "Pitted against microbial genes,

we have mainly our wits". Michael Osterholm, an infectious-disease epidemiologist at the University of Minnesota says, that the only viable endgame is to play 'whack-a mole' with coronavirus, suppressing it until a vaccine can be produced. With luck, it will take 18 to 24 months. As simple as the saying goes, if the virus cannot find you, it cannot infect you. Life as we knew is gone, at least temporarily, as the COVID2019 virus has terrorized the world. This pandemic has opened up great challenges and opportunities for the preventive medicine discipline. While facing the ravage of this disease, one can hear leaders describing that the cure may be worse than the disease, meaning the economic shut down may cause more harm than keeping the markets open and taking the losses as it has happened in earlier pandemics. Global losses amount to trillions of dollars. This is true of the global health care losses due to the cardiometabolic diseases also.

Of the total hospitalized COVID-19 patients, 89% had at least one of the pre-existing chronic conditions. About half, had high blood pressure and obesity, according to the Centers for Disease Control (CDC), USA. And about a third, had diabetes and a third had cardiovascular (CVD) disease. According to the Chinese researchers, clinical manifestation of COVID-19 are heterogenous [2]. During the time of admission COVID-19 patients reported as having at least one comorbidity, diabetes (10 - 20%), hypertension (10 - 15%), or other cardiovascular diseases and cerebrovascular diseases (7 - 40%). Analysis of 1590 hospitalized patients in China, revealed that mean average age was 49 years. The most prevalent comorbidity was hypertension (16.9%), followed by diabetes (8.2%). They found that circulatory and endocrine comorbidities, were common among patients with COVID-19 patients, leading to their conclusion, that circulatory diseases remained the most common category of comorbidities [3]. Swiss researchers on the other hand, reported that patients with hypertension (23.7%), diabetes (22%) and cerebrovascular disease (22%) were the most distinctive comorbidities [4]. ACE-2 receptor has been shown to be the entry receptor for SARS-Cov-2, the novel coronavirus responsible for COVID2019 pandemic. Studies have shown that the counter regulatory enzyme ACE2 that degrades angiotensin 11 to angiotensin, seems to facilitate SARS CoV-2 entry and virus replication [5]. There is considerable evidence, that activation of the renin-angiotensin system (RAS) and the down regulation of ACE2 expression, are involved in the pathological process of lung injury after the SARS-CoV-2 infection [5].

As with SARS, patients with COVID-19 also show potential cardiac injuries [6]. It is worth noting, that in a study done in New York, all 18 patients had elevated D-dimer levels. In contrast to this findings, in a previous study involving patients who presented with ST-segment elevation myocardial infarction, 64% had normal D-dimer levels write, -Dr Bangalore and associates from New York University Grossman School of Medicine, NY [7]. Myocardial injury in patients with Covid-19 could be due to plaque rupture, cytokine storm, hypoxic injury, coronary spasm, microthrombi, or direct endothelial or vascular injury. The ways in which the novel coronavirus provokes cardiac injury are neither new nor surprising, according to the Harvard researchers, Prof. Peter Libby and Prof. Paul Ridker [8]. The most common pattern of coagulopathy observed in patients with COVID-19 is characterized by elevations in fibrinogen and D-dimer levels. Anticoagulant therapies with either low molecular weight heparins (LMWH) or tissue plasminogen activator (tPA) appears to be associated with better prognosis in severe COVID-19 patients meeting sepsis-induced coagulopathy (SEC) [9]. According to some reputed US researchers, a hallmark of severe COVID-19 is coagulopathy, with 71.4% of patients who die of CIVD-19 meeting ISTH criteria for disseminated intravascular coagulation (DIC).

This observed increased coagulopathy, seems to be not due to a bleeding diathesis, but rather a predominantly pro-thrombotic DIC, with high venous thromboembolism rates and pulmonary congestion and microvascular thrombosis and occlusion, with high rates of central line thrombosis and vascular occlusive events (ischemic limbs, strokes). Neurologists around the world say, that a small subset of patients with Covid-19 are developing serious impairments of the brain. Similar observations have been made in Italy of COVID-19 patients having stroke, seizures, encephalitis-like symptoms and blood clots, as well as tingling or numbness in the extremities [10]. Researchers have begun enrolling some of the Covid-19 patients with ARDS like symptoms to monitor 'biomarkers' such as blood levels of clotting factors, D-dimers, fibrinogen etc., which will help identify patients who are most likely to benefit from antithrombotic or

thrombolytic therapies. In view of these observations, treatment with LMWH or with tPA seems to be a better option than antiplatelet therapies. If effective and safe, these therapies could save lives by reducing the recovery time and freeing up more ventilators for other patients in need. The American Hospital Association predicts that 96 million people in the US will eventually get COVID-19. Should this occur, it would mean that a total of 960,000 people would need mechanical ventilation.

Apart from the cardiovascular and cerebrovascular (Circulatory disorders) disorders, metabolic disease like hypertension, type-2 diabetes, and obesity also seem to play in the Covid-19 mediated acute events. American Association of Clinical Endocrinologists (AACE) Position Statement on COVID-19 and Diabetes states, "Recent studies have shown, that of those hospitalized for severe COVID-19 disease, 22.2% to 26.9% reported living with diabetes. Diabetes and high glucose levels are associated with increased complications, respiratory failure and mortality in hospitalized patients with COVID-19 [11]". Because people with diabetes may also have other comorbidities, they recommend that individuals with diabetes follow Centers of Disease Control and Prevention guidelines. National Health Service (NHS) of UK reported, that age and diabetes are the two most common risk factors in COVID-19-related severe cases. One of the diabetes related clinical complication is renal disease. Over 2 million people worldwide receive treatment with dialysis. Approximately half a million people in the US receive maintenance dialysis and they are at 'high risk' for contracting Covid-19 infections. American Society of Nephrology (ASN) and the CDC, have put together best practices for in-center dialysis [12].

Obesity may be one of the most important metabolic risk predictors for coronavirus illness. The United States has one of the highest obesity rates in the world. Some 42 percent of the adults- nearly 80 million people live with obesity. The new finding about obesity risks are bad for all Americans especially for the minorities. Abdominal obesity can cause compression of the diaphragm, lungs and chest capacity. May also induce proinflammatory cytokines, which may play a role in the severity of the COVID-19 infection. A 6-fold increase in the rate of death for African Americans living in the USA, due to a now ubiquitous virus should be deemed unconscionable, writes an African American Cardiologist in a recent tissue of *JAMA* (April 15, 2020). What is currently known about these differences in disease risk and fatality rates? In Chicago, more than 50% of COVID-19 cases and nearly 70% of COVID-19 deaths involve African American individuals, although they make up only 30% of the population. Moreover, these deaths are concentrated mostly in just 5 neighbourhoods on the city's South Side. In Louisiana, 70.5% of deaths have occurred among African Americans, who represent 32.2% of the state's population.⁷ In Michigan, 33% of COVID-19 cases and 40% of deaths have occurred among African American individuals, who represent 14% of the population [13].

In the previous paragraph, we referred to the enormity of the COVID-19 problem in the US, because of the increased rate of obesity. However, what is less known is that there are equal number of prediabetics in the USA. If we look at the worldwide incidence and prevalence of metabolic diseases, hypertension, obesity and diabetes rank very high. Nearly half of all adults in the United States, have some type of cardiovascular disease (CVD)-defined as coronary artery disease, heart failure, stroke or high blood pressure, according to the American Heart Association's annual report. In summary the US has a very great number of 'high-risk' individuals for COVID-19 infection. China and India, have large populations of hypertensives, prediabetics and diabetic individuals. If we look at the current ranking for the number of individuals infected with COVID-19, China ranks 6th or 7th, with the US leading the western world. Chinese researchers and some of the Public Health experts of South East Asian Countries, claim that relatively low number of infection is due to the excellent mitigation, contact tracing, and containment procedures, that were implemented in time. Thanks to Dr Anthony Fauci, the Director, National Institute of Allergy and Infectious Diseases (NIAID), who has been advocating these measures as the major components of a preventive strategy. Some of the US States are strictly following his suggestions, while others are not adhering to these measures. This disparity is true for various countries as well. Sweden for instance, has not recommended a lockdown at all. They are gambling on the possibilities of developing herd immunity by exposing their large population for infection.

What about India, Bangladesh, Pakistan and Nepal? A study conducted by the International Centre for Genetic Engineering and Biotechnology (ICGEB; Headquarters, Trieste, Italy: icgeb.org), New Delhi, India, claims that the severity of the Covid-19 is less in India,

because of the unique micro RNA, called has-miR-27b, which successfully mutates the coronavirus responsible for Covid-19 (The Preprint of this article is saved on biorxiv.org). Host antiviral miRNA seems to play a crucial role in the regulation of immune response to virus infection. Many known human miRNAs appear to be able to target viral genes and their functions like interfering with replication, translation and expression. The authors concluded that the presence of country-specific mutation spectrum may explain the severity of illness in other countries compared to India. Whether or not this observation is the reason for low incidence of Covid-19 infection in India and its neighbouring countries, need to be watched carefully to draw any definite conclusions. The role microRNAs needs to be further investigated. It is possible, using this approach, some very potent therapeutic applications can be developed for interfering with the viral RNAs.

When it comes to Covid-19 prevention strategies, major preventive measures seems to behavioural, -social distancing and good hygiene practices. How about preventive strategies for the CMDs? These diseases are basically life style disorders. Therefore, a healthy lifestyle, healthy diet, and improved physical activity will go a longways in preventing metabolic diseases. Making comprehensive behavioural changes can effectively treat, and in some cases fully reverse cardiometabolic diseases [14].

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