

Syndemic of Coronavirus Disease and Metabolic Disorders

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Severe Acute Respiratory Syndrome-2019 (SARS-CoV-2) has caused an unprecedented public health crisis worldwide [1-6]. This potent killer virus, which sneaked out of Wuhan, China, in December of 2019, has spread across the globe and has mutated into more aggressive, infectious, and lethal pathogen. Globally according to the Johns Hopkins coronavirus tracker more than 100 million (mil) individuals have been infected with 2.2 million deaths. As of 26th January 2021, (coronavirus.jhu.edu.map.htm), the top five countries for number of individuals found positive to COVID-19 include, the USA (25 mil), India (10.6 mil), Brazil (8.8 mil), Russia (3.7 mil), and the UK (3.6 mil). For the Covid-related deaths the ranking are as follows: the USA (420,000), Brazil (217,037), India (153, 470), Mexico (149, 614) and the UK (98,131). According to the number of Covid related deaths (case fatality rate; CFR), the top five countries are ranked as follows: Mexico (8.5%), Peru (3.5%), Italy (3.5%), South Africa (2.9%) and Indonesia (2.8%). The USA and India with the most infected individuals rank 16th and 19th respectively. According to a report of Center for Disease Control (CDC), USA, published in the Journal of Emergency Medical Services (August 31, 2020), 94 percent of the COVID 19 deaths in the United States also have contributing pre-existing conditions. Just six percent of coronavirus deaths have "COVID-19" as the only cause mentioned, revealing that 94 percent of patients who died from coronavirus also had other "health conditions, comorbidities and contributing causes".

In mid-June 2020, CDC released data on more than 1.7 million coronavirus cases and 103, 700 deaths from covid-19. The data is consistent with the earlier reports, showing the disproportionate impact of the pandemic on people with underlying medical conditions. Among nearly 600,000 people who were sickened, 33 percent of patients were Hispanic, although they make up 18 percent of the U.S. Population, 22 percent African Americans, while they constitute 13 percent of the population and 1.3 percent were Native Americans, nearly double their overall population. Researchers from the department of Statistics, University of Dhaka (Bangladesh), published a Meta-Analysis, on the prevalence of clinical manifestations and comorbidities of coronavirus infection [14]. The most prevalent comorbidity was hypertension (20%), cardiovascular disease (11.9%), and diabetes (9.8%). Other less know comorbidities include, excess weight, obesity, chronic kidney disease, chronic liver disease, chronic pulmonary disease, and cerebrovascular disease [8-13]. In a recent article in Science, Jeffrey Brainard reports, on how researchers face hurdles to evaluate, synthesize COVID-19 evidence at top speed [14]. The team analyzed more than 35,000 papers and reprints about COVID-19 in a database called Epistemonikos. According to these investigators, high percentage of COVID-19 reviews were found, to be incomplete or irrelevant only months after publication, and this observation is unprecedented, and demonstrates the complexities of this pandemic.

A recent Comment (September 26, 2020), published in the journal Lancet, says that COVID-19 is not a pandemic, it is a syndemic. Syndemics involve the clustering of two or more diseases within a population; the biological, social, and psychological interaction of those diseases; and the large-scale social forces that precipitate disease clustering in the first place [15]. Of the 1590 hospitalized patients with Covid-19 in China, the most prevalent comorbidity was hypertension (16.9%) followed by diabetes (8.2%). Of these 8.2% of patients had

two or more comorbidities. The authors concluded that a greater number of comorbidities, yielded poorer clinical outcomes than those without [16]. In a larger study of patients with COVID-19 admitted to 12 hospitals in New York City, Long Island, and Westchester County, a total of 5700 were included [13]. The most common comorbidities were hypertension (56.6%), Obesity (41.7%), and diabetes (33.8%). Of the patients who died, those with diabetes were more likely to have received invasive mechanical ventilation or care in the ICU, compared with those who did not have diabetes. Of the patients who died, those with hypertension were likely to have received invasive mechanical ventilation or care in the ICU compared to those without hypertension. On the other hand, in a Science report in September of 2020, Meredith Wadman quotes, “We didn’t understand early on what a major risk factor obesity was, it’s not until more recently that we’ve realized the devastating impact of obesity, particularly in younger people,” says Anne Dixon, a physician-scientist, who studies obesity and lung disease at the University of Vermont [17]. That “may be one reason for the devastating impact of COVID-19 in the United States, where 40% of adults are obese”.

We mentioned earlier Jeffrey Brainard’s observation about COVID-19 literature, which is incomplete and at times confusing for even scientists. Professor Young Duncan of Intensive Care Unit, University of Oxford, comments about work of Anne Dixon, to a study looking at obesity being linked with higher risk for COVID-19 complications. -a study published in ‘Obesity Reviews’, which looked at possible link between obesity and risk for COVID-19 complications. Professor Duncan Young says, “this is a rather unusual paper, as it combines a narrative of obesity in the context of COVID-19 disease, with a meta-analysis of observational data on the association with the likelihood of a positive test and hospital ICU admission. The two large studies of millions of patients passed on by General Practitioners and other records have not been included. According to the data from UK hospitals, almost 75 per cent of COVID-19 patients in intensive care are overweight. A National Health Service (NHS) data recently revealed obesity raises the risk of dying from coronavirus in hospital by 40 per cent. Scientific evidence mostly from the US, is beginning to show that someone who is obese, may be at more risk of severe complications than people with high blood pressure, respiratory disease, or asthma. A research team at New York University found, that those with a Body Mass Index (BMI) between 30 and 34 were twice likely to be admitted to critical care (ICU) than those with a BMI under 30. Frederik Karpe, professor of metabolic medicine at Oxford University says, “If you have a big belly, this can be problematic for breathing when lying down”. Obese people also may have immune dysfunction, vascular damage, and vascular dysfunction.

According to the number of Covid related deaths (case fatality rate; CFR), the top five countries are ranked as follows: Mexico (8.5%), Peru (3.5%), Italy (3.5%), South Africa (2.9%), and Indonesia (2.8%). The USA, India, and Brazil with highest number of COVID-19 patients have the lowest CFR compared to Mexico, Peru, and South Africa, which have the highest covid-related CFR. Mariam Shuchman in a news feature on 21 May 2020, writes that, “Exposure to the SARS-CoV-2 will be higher in the densely packed slums of megacities such as Karachi (Pakistan), Dhaka (Bangladesh), and Mumbai (India) and Lagos (Nigeria), where social distancing is impossible.” She further elaborates, “Low-and middle-income countries’ high rates of chronic health problems linked to COVID-19 complications such as diabetes, are going to cause severe cases, on top of that, the countries’ healthcare systems lack the critical-care resources to respond to the sort of surge in intensive-care systems seen in New York and Italy”. On the contrary, the USA as well as Italy, had a much high rates of infection and CFR, compared to the low-and middle-income countries, Shuchman refers to in her article [18].

In another article in Nature Reviews, Kontis and associates from the Medical Research Council (MRC) of the UK have reported on the magnitude, demographics, and dynamics of the effect of the first wave of the COVID-19 pandemic on all-cause mortality in 21 industrialized countries [19]. The review brings out two very different variables, that influenced the rate of infection, clinical manifestations, and the severity of the disease. Number one variable is how extensively the countries conducted community testing, contact tracing and isolation of cases and their contacts at each stage of the pandemic, with Austria, Denmark, Finland, New Zealand, and Norway introducing effective systems and Belgium, Spain, France, and the UK being more limited, with some like the UK, Spain, and France not having a system that is able to respond to the unprecedented nature of the epidemic. Second major variable was, how their healthcare system continued to

provide life-saving services; those countries that had less capacity and were less able to rapidly enhance capacity, partly related to uneven health and social care spending, responded less effectively to healthcare needs. What these reports indicate is that it is hard to generalize the observations on Covid-19, its impact on demographic and various ethnic groups, and the public health efforts to contain or prevent the spreading on this epidemic. Expert opinions have been wrong, confusing, and controversial at times, and only time will tell the real story of this unprecedented pandemic.

Since our interest is metabolic diseases, let us discuss as to how coronavirus takes advantage of the metabolic risks and metabolic diseases to its advantage for transmission and replication. These viruses enter the nasal epithelial cells using the surface spike (S) proteins, to bind a metalloprotease called, angiotensin enzyme 2 (ACE2). Following infection and viral replication, down regulation of ACE2 enzyme occurs, resulting in the dysfunction of the angiotensin system. High ACE2 (hACE2) expression has been identified in type 11 alveolar cells of lung, esophagus, enterocytes of ileum and colon, cholangiocytes, myocardial cells, kidney proximal tubule cells, bladder urothelial cells, fat cells, and vascular endothelial cells. Endothelium is the largest organ of the body, covering a large surface area, and reaching out to every tissue and organ. 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 refer to this condition as a disease of the blood vessels. Metabolic diseases such as hypertension, excess weight, obesity, and vascular diseases have a common metabolic defect, damaged endothelium or dysfunctional endothelium, which we and others have described as endothelial dysfunction [12].

Common metabolic risks such as oxidative stress, chronic inflammation, excess weight, altered flow dynamics, hardening of the arteries as well as endothelial dysfunction play an important role in the progression of the coronavirus disease. These metabolic risks are the common promoters of metabolic disease like hypertension, obesity, type-2 diabetes and vascular diseases. The mechanisms by which these metabolic risks induce vascular damage, dysfunction and vascular remodeling remains poorly understood. Suffice it to say, that individuals with metabolic disorders have dysfunctional vascular system or a compromised vascular system. Researchers from Harvard report that, "Our data showed significantly greater number of ACE2-positive cells in the lungs from Covid-19 patients than in uninfected control subjects. They found greater number of ACE 2 positive endothelial cells in vascular phase of Covid-19. The presence of SARS-CoV-2 virus within the endothelial cells, suggests that direct viral effects as well as perivascular inflammation that may contribute to the endothelial injury" [21]. The virus uses the angiotensin converting enzyme 2 receptor for internalization and then downregulates this enzyme, thereby diminishing anti-inflammatory role [22]. In a recent article Shivakumar and associates from India describe, Neutrophil-to-lymphocyte-to-monocyte, and platelet-to-lymphocyte ratios as prognostic significance in COVID-19 [23]. According to these authors, in inflammation, platelet production increases due to the increased synthesis of thrombopoietin, which is modulated by cytokines. Acute lung injury also leads to leaky blood vessels. Activated platelets enhance lymphocyte adhesion to the endothelium. These events enhance, inflammation, platelet activation, expression of tissue factor, and promote a prothrombotic condition. The elevation of D-dimer observed in some of the studies, indicate the occurrence of a prothrombotic event, followed by thrombolysis. In a normal situation, the thrombolytic system should clear thrombus formed, by endogenous thrombolytic agents. Researchers from University of North Carolina by infecting a Serpine-1- knockout mice, have shown that the urokinase pathway had a significant effect on both lung pathology and overall SARS CoV pathogenesis [24]. The dysregulation of coagulation/anti-coagulation cascades can result in worsening lung disease conditions, resulting in death.

Metabolic diseases like hypertension, excess weight, obesity, type-2 diabetes, and vascular diseases have rapidly increased to epidemic proportions worldwide. Metabolic risks such as oxidative stress, chronic inflammation, insulin resistance, altered glucose and lipid metabolism, changes in hemodynamics, endothelial dysfunction, hardening of the arteries, and subclinical atherosclerosis contribute significantly to the progress of the vascular disease and drive it eventually to acute vascular events like heart attacks and stroke. Although this situation has been noticed and discussed extensively by the global public health experts, and professional societies, the unprecedented

SARS-CoV-2 pandemic demonstrated for the first time, the interdependency or syndemic nature of a pathogenic virus with the metabolic diseases, which takes advantage of the compromised metabolic function in these diseases. For just argument's sake, COVID-19 for instance, is a pandemic over another pandemic, cardiometabolic diseases. If we were to stretch our imagination further, we will have to include all the metabolic disease risk factors also as co-existing conditions. Addressing COVID-19 management therefore means, addressing all the metabolic risk factors as well as metabolic diseases such as hypertension, excess weight, endothelial dysfunction, inflammation, obesity, diabetes, vascular diseases, and chronic respiratory diseases. SARS-CoV-2 pandemic is a public health workers nightmare, as well as that of critical care workers. Effect of this pandemic will stay with us for a long time to come.

This unprecedented pandemic of SARS-CoV-2 has taught us two lessons, firstly the importance of robust public health infrastructure, secondly the need for immediate call for action to reduce, reverse, or prevent the metabolic diseases worldwide. The recent statement from the Institute for Fiscal Studies Deaton Review on inequality (IFS Deaton Review, January 5, 2021), stressed that the opportunity cost of the pandemic for young people is potentially huge, but also that it is a "once-in-a-generation opportunity to tackle the disadvantages faced by many that this pandemic has so devastatingly exposed." In a recent editorial of the Lancet Public Health, the editor concludes that, "Adopting a broadened, equity-based approach to population health should be an essential part of building a more resilient society that is better prepared for the future pandemics [25].

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