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HOW CO-MORBIDITIES MAKE COVID SEVERE

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Medical students are taught to classify diseases as either congenital or acquired. Acquired diseases are infectious or inflammatory, nutritional or metabolic, vascular or neoplastic (tumours, benign or malignant). COVID-19 is acquired, infectious/inflammatory. The microbe is SARS-CoV-2.

What are co-morbidities and why do they make COVID-19 severe and life-threatening? Chronic nutritional/metabolic diseases start as diabetes, hypertension, metabolic syndrome or obesity. They in turn lead to chronic heart, brain and kidney diseases because of damage to the lining cells of the blood vessels, the ‘endothelium’. For someone with an acute disease, a pre-existing chronic disease is now a co-morbidity.

The immune system is highly conserved even in undernourished people; the impact of co-morbidities on the immune system is mild. Exceptions occur: TB is more common in undernourished adults and uncontrolled diabetes; metabolic syndrome, however, is associated with over-nutrition. If someone with a co-morbidity gets COVID-19, the disease severity is increased out of proportion to any subtle or mild effect of the co-morbidity on the immune system.

There are four ubiquitous coronaviruses, highly adapted to human hosts, causing only common cold. Three coronaviruses — SARS-CoV-1, MERS-CoV and SARS-CoV-2 — have recently jumped the host species, presumably bats or dromedary camels, and caused severe disease in humans, primarily pneumonia. SARS-CoV-1 and SARS-CoV-2 latch on to a human cell surface protein called ‘angiotensin converting enzyme 2’ (ACE2), mediated through the viral surface spike protein, a key that opens the lock to gain entry. Once inside, the virus hijacks cell functions for its own multiplication. There is no precedent of viruses using ACE2 as cell receptors.

ACE1 and ACE2 are widely distributed on the lining ‘endothelial’ cells of all arterial, venous and capillary blood vessels and on smooth muscles that surround them. They also abound on the lining epithelial cells of the respiratory tract, kidneys and gut. Blood carries oxygen and nutrition to all organs; anything that affects the blood vessels affects the organs as well. Contrast this with influenza virus receptors that are present only on epithelial cells of the respiratory tract – the virus cannot invade and infect inner organs and tissues. COVID-19 may invade and infect any tissue or organ from the head to the toes and cause damage through reduced blood supply.

Physiologically ACE1 and ACE2 play critical roles in regulating blood pressure, and blood flow to organs. They act on angiotensin-1 and convert it to active peptides. ACE1 converts angiotensin-1 to angiotensin-2, a potent constrictor of blood vessels. ACE2, on the other hand, converts angiotensin-1 and angiotensin-2 to peptides that dilate blood vessels. Through their balanced and contrasting effects on blood vessels, these peptides regulate regional blood flow in organs and tissues. In chronic diseases there is widespread dysfunction of these activities.

By occupying ACE2, COVID-19 interferes with angiotensin conversion to vaso-dilatory peptides; the balance tilts in favour of vaso-constriction resulting in decreased oxygen and nutrient supply to organs. If the person’s blood sugar level is very high, the blood becomes viscous. Damaged endothelial cells hasten blood clotting and further reduce blood supply. If someone has, say, diabetes, SARS-CoV-2 can further severely reduce oxygen supply to tissues. This synergy could be fatal. Well-controlled diabetes carries less risk as damage to the endothelial cells is minimal.

COVID-19 is an infectious disease and especially affects the lungs. The immune system responds as best as it can. Within 2-3 weeks of infection, when immunity is at its peak, the immune system may clear the virus from the organs, but the damages to the organs take time to repair. In the absence of co-morbidities, the body physiology can bounce back to normalcy quickly, but in those with co-morbidities, the ailing organs may not recover in time to avert death due to damage to the lungs, heart, kidney or brain. The borders between infectious pathology and metabolic/vascular pathology are blurred or breached.

The poor response to convalescent plasma that rapidly reduces virus load in the body surprised experts. Once the vascular and clotting cascade sets in, even if you remove the virus, the downhill course continues. If you want prevention of disease progression in those at high risk of death, either the coronaviruses must be neutralised very early, even before or early after onset of symptoms, or you must be vaccinated. This illustrates the need for vaccine emergency use authorisation for the elderly and those with co-morbidities. Vaccination will confer some protection to those at high risk of death through the sinister synergy of COVID-19 and co-morbidities. The elderly are vulnerable due to senile degeneration, decline of immune functions and elements of co-morbidities.

There is another sinister association: the insulin-secreting Beta cells in the pancreas are studded with ACE2 and are easy targets for COVID-19. In COVID-19, insulin secretion is decreased. Non-diabetics sometimes develop diabetes for the first time after COVID-19 and those with diabetes may develop very high blood sugar levels.

Those who recover from COVID-19 are prone to develop chronic diseases. Those with obesity, diabetes and hypertension who recover from COVID-19 are at increased risk of heart attack and stroke because of severe blood vessel narrowing during COVID-19. Some people develop chronic sequelae, called chronic or ‘long’ COVID-19 — some of them due to damage to blood vessels in the lungs, kidneys, heart and brain. COVID-19 also seems to trigger auto-immunity, that is, one’s immune system turns against one’s own tissues/organs. These conditions may lead to severe muscle or joint pain, severe fatigue, memory loss and mental depression.

The damage to the lungs in COVID-19 starts as infection, but quickly becomes massive inflammation with outpouring of plasma into the air sacs, sludging of blood flow in capillaries and clotting. The reason for these is what is called a ‘cytokine storm’: a reaction of blood vessels to substances called cytokines that are excessively secreted by immune cells. This cascade leads to further decreased oxygen in blood. The widespread narrowing of blood vessels and hypoxia serve as twin triggers to damage vital body organs.

Physicians are confronted with a complex problem that involves multiple organ systems. For the elderly and those with co-morbidities, prevention is better than cure. COVID-19 vaccines should induce protective immunity in youngsters, adults and the elderly, except in those with diseases or treatments that directly suppress the immune system (such as those with cancers and organ transplants). As the immune system is only modestly affected by co-morbidities, we expect vaccine-induced immunity sufficient to avert severe disease. Yet, there may be disappointing surprises. Therefore, people with obesity, diabetes and hypertension should ensure that they are diligent in the practices of mask wearing, physical distancing, hand hygiene and avoiding crowds. Until we know more details, vaccination, good control of co-morbidity parameters and good infection control practices together will save lives.

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