

Protecting COVID-19 through Strengthening the Innate Immunity

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The COVID-19 pandemic is a worldwide public health problem with major socioeconomic and health consequences [1], which is likely to persist for a while. Younger people with a better immune system, are less likely to present with COVID-19 syndrome and dying from it. However, they are the largest group of silent carriers with the potential of spreading the disease, especially to the elders. As happening in Montessori schools and in kindergarten classes worldwide, smaller children frequently bring home respiratory viruses. With reference to COVID-19, viral transfections are occurring through children and young adults to elders; proactive policies and plans must be in place to prevent such happening.

COVID-19 is affecting females less than males; an approximate ratio of 1 to 1.7 [2]. The male predominance of COVID-19 in part is explained by having two alleles of angiotensin-converting enzyme-2 (ACE-2) in females (and only one allele in males), the X-linked protective mechanisms including sexual dimorphism and favourable effects of estrogen on the immune system [3]. In contrast to earlier reports, the recent data suggest that there are several strains of COVID-19 in circulation in some countries with higher replication rates [4], with high microbe reproduction numbers (R_0), infectivity [5]. These aggressive strains may have the ability to generate several-fold higher viral loads compared with the original and weaker strains [6]; this is exacerbated by uncontrolled crowd gatherings and unsafe behaviour of people. Nevertheless, the value of using R_0 for making public health decisions has failed for COVID-19 [5].

The role of asymptomatic carriers of COVID-19

Especially during the second wave of infection, the asymptomatic carriers have become an important source of the silent community spread of the COVID-19 virus. Recent data suggest that not only the overall rate of infections but also the rate of infection within the younger people, and the severity of complications and deaths are gradually increasing [7]. Rarely, children and young adults could abruptly develop unusual complications like Kawasaki syndrome, and neurological or cardiovascular complications including strokes [8-10]. It is not known whether such variations of infectivity and complications are due to, (a) changing behaviour of the virus due to mutations, (b) an increased number of older people having contracted the COVID-19 and developed antibodies against COVID-19, so the virus is progressively seeking younger hosts, (c) some communities such as the New York City are said to reaching herd immunity (unlikely) thus, while the rate of infection is decreasing among the previously known vulnerable groups (e.g., elderly), it is increasing among younger people: changing demography of infectivity.

Despite claims by the WHO, younger people continue to transmit COVID-19 to older people, sick and the disabled, vulnerable friends and co-workers, teachers, and less resilient relatives. Many countries, especially in the tropics, however, do not conduct

community PCR testing and tests are performed sparingly and unsystematically. Consequently, these countries reported spuriously low numbers of COVID-19 infected persons and extremely low numbers of deaths. With the minimal numbers of PCR testing and the lack of systematic community testing, a lesser number of COVID-19 positive cases were identified and reported, even to the WHO, misleading global misleading statistics.

Comorbid conditions and COVID-19

The most vulnerable people to COVID-19 have a common set of comorbid conditions, increasing their susceptibility to contract the disease. These include diabetes mellitus, hypertension, chronic pulmonary, cardiac, and renal diseases, chronic smoking, inactivity, and obesity, increase the risks and the severity of complications and deaths from COVID-19. Besides, there are associated conditions, such as air pollution (as in India, Iran, and China), exclusive indoor-living and/or recreation (e.g., nursing homes and disability centres), cold and dry weather conditions (temperate countries), and low ultraviolet B (UVB) irradiation index, increase the survival and the spread of COVID-19, worsen the associated complications, and increase deaths from the virus.

Next to severe vitamin D deficiency, advanced age is the most important independent risk factor for developing complications and deaths from COVID-19 [1,11,12]. Complications are especially worse (e.g., the need for ICU care for respiratory and cardiovascular complications) in the elderly with chronic diseases, mentioned above and having vitamin D deficiency. All above-mentioned groups of people also have an inherently low concentration of ACE-2, and therefore, increase vulnerable to develop complications and deaths from COVID-19.

Those with impairment of the immune system, especially having concomitant severe vitamin D deficiency, have significantly delayed responses to invading pathogens, including for COVID-19. Having feeble protective immune responses by the host, allows the virus to multiply exponentially, experiencing severe symptoms and a higher number of deaths [13].

Having a weaker innate immune system increases the vulnerability to COVID-19 and its complications

Having a poor innate immunity, the first line of defence against the invading microbes markedly increases the rate of contracting COVID-19, risk of complications, and death. These complications include cytokine storm and lung injury, endothelial damage and the associated coagulopathy, and acute respiratory distress syndrome (ARDS) [14-16]. Stimulating and the maintaining innate immunity is predominately depends on the adequate $1,25(\text{OH})_2\text{D}$ concentration within the immune cells, and its interactions with the intra-nuclear vitamin D receptors leading to activation of genes [13,17,18]. Intracellular calcitriol level is depends of serum $25(\text{OH})\text{D}$ concentration.

Hypovitaminosis D also reduces the generation of neutralizing antibodies, cellular-based immune responses of CD4+ and CD8+ T cells, B cells, NK cells, macrophages. Thus, responses are and thus, suboptimal responses to subdue inflammatory and oxidative stresses settings generated by viral infections [19,20]. These reactions are also impaired in the elderly and get worse in those with vitamin D deficiency. The current data strongly supports that having vitamin D sufficiency or consuming adequate supplements, reverse the mentioned abnormalities of the immune system [21,22].

Vitamin D adequacy strengthens the immune system via multiple mechanisms [23,24]. In addition to increasing the synthesis and release of antimicrobial peptides [25,26], as mentioned vitamin D stimulates several immune cells, increases the ACE-2 concentration, and reduces the expressions of ACE and renin genes leading to favourable clinical outcomes. It reduces the production of Ang-II, the risk of cytokine storm, lessen lung injuries as reported in experimental rat models [27,28], and complications from coronaviral illnesses, like COVID-19 [29]. 1,25(OH)2D suppresses the renin-angiotensin axis (especially Ang-II concentration), through which reduces the risks and the severity of cytokine storm and prevent ARDS in persons with COVID-19 [20,30]. Figure 1 summarizes the broader effects of vitamin D on enhancing the protective immune functions.

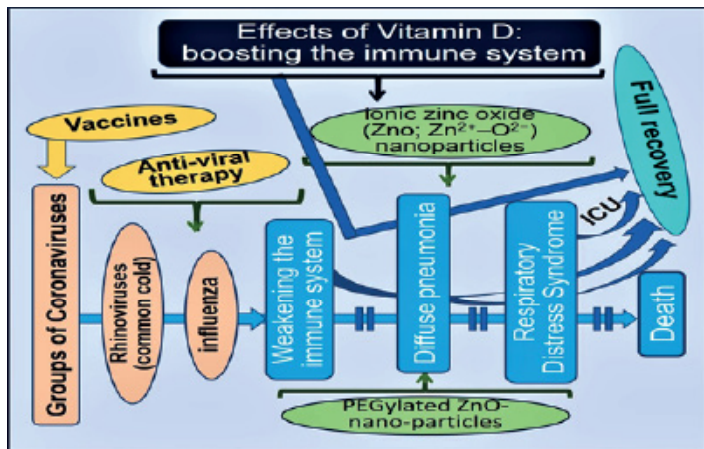


Figure 1. Vitamin D has a positive modulatory effects on all immune functions. It also subdues all respiratory viruses, including COVID-19, through stimulating the innate immune system, thus reducing the associated complications and deaths, leading to a faster recover.

Cytokine storm induced by COVID-19 infection

COVID-19 infection activates reactive oxygen species and NF-κB. Excess NF-κB activates the synthesis and release of a cascade of multiple pro-inflammatory cytokines, thus contributing to hyperinflammation and consequent cytokine storm [31]. Following the entry into human cells, COVID-19 also uses immune evasion mechanisms, including immune suppression of the host via an embedded AIDS-like RNA sequence [24] facilitating the hyper-immune reactions and cytokine storm [1]. The latter leads to the development of ARDS and systemic inflammatory response syndrome (SIRS), leading to terminal events, pulmonary oedema and death.

Having activated T-cells and specific neutralizing antibodies helps to overcome the COVID-19-induced hyperimmune reactions and autoimmunity-related lung and endothelial damage. Since the cytokine storm represents a hyperimmune state, dexamethasone could reduce the severity by dampening the diffuse inflammatory

status. This is affecting less than 4% of people infected with COVID-19. The vast majority of people needing intensive care units have such complications including, cytokine storm, thromboembolism, and ARDS. However, dexamethasone also inhibits the protective actions of T-cells, reduces antibody production from B-cells, and the effects of nosocomial activities of macrophages and thus could worsen clinical outcomes of persons with mild to moderate COVID syndrome (i.e., persons without ARDS).

The above-mentioned complications are markedly reduced by having vitamin D sufficiency. Currently, there are over 50 ongoing large, statistically powered, randomized controlled clinical studies (RCTs) using higher doses of vitamin D in COVID syndrome; results will be available in due course. Taken all data, including the experience gathered during the SARS epidemic, the most cost-effective approach in the prevention of COVID-19 is the use of vitamin D to maintain serum 25(OH)D concentration above 30 ng/mL [1,22] and the use of hydroxychloroquine at early stage of the disease. While RCTs provide answers to precise questions and hypotheses, preventative public health decisions and therapeutic clinical management require the use of data from non-RCTs, observational studies (hundreds of such had been already published), extrapolation of data, and the use of common sense approaches in using best practices to help people, especially in emergencies, like COVID-19.

The inappropriate use of prednisolone or dexamethasone, and standard chemotherapy, further impair the immunity and immune responses, allowing exponential replications of COVID-19, thus increase the viral load and prolong the survival of the virus in vivo, worsening the clinical outcome. Whereas the protection of lungs can be achieved with much less aggressive and targeted immune suppression, such as the use of nebulized triamcinolone that exposes only the lungs: can be used easily in ICU set up at a fraction of the cost of antiviral medications, without exposing the whole body to dexamethasone and its adverse effects. Therefore, the use of dexamethasone in patients with mild to moderates COVID-19 syndrome (in the absence of significant complications) can be detrimental and thus, should be discouraged.

Conclusion

The affirmative answer to the COVID-19 pandemic is not developing expensive antiviral agents, vaccines, or construct new intensive care units, hospitals, and quarantine centres, but to strengthen the weakened immune systems of people, due to poor lifestyle. The use of vitamin D and other micronutrients and positive lifestyle changes would cost less than 1% of the cost of the above-mentioned expensive therapies and healthcare expansions. To overcome this key issue needs reintroduction of healthy lifestyles to the populous. This includes, preventing anthropogenic environment pollution; assure having clean air, uncontaminated food, and water for consumption; eliminate sun avoidance behaviour; having adequate sleep and regular physical activity; engaged in programs to relax the mind; and maintain hydration, and consuming a balanced diet rich in micronutrients [13]. While vitamin D adequacy (calcitriol) is the most important in this regard, the beneficial effects of the immune system can be optimized with zinc, vitamin K₂, magnesium, omega 3 fatty acids, quercetin, and resveratrol [13].

High doses of vitamin D can strengthen the innate immune system within two to four days of its oral administration. This highly effective therapy costs less than \$8 per person per year or as an acute high-dose therapy and is expected to reduce the risks of contracting COVID-19: its severity and deaths are reduced by more

than 40%. Irrespective of the age, persons with sufficient vitamin D concentrations will have a speedy recovery, reduces the risks of developing severe COVID syndrome, and deaths. To minimize viral infections, especially the current key public health issues, such as COVID-19, HIV, and dengue, and to reduce all-cause mortality, one needs to maintain serum 25(OH)D concentration between 30 and 60 ng/mL, which is safe [22,32-34].

Once the immune system is kept strong, people will be able to get over both non-communicable and communicable diseases, that have been escalating in recent years. The latter includes overcoming infectious epidemics and pandemics relatively easily without the need for getting admitted to hospitals or succumbing to them. Mentioned negative spiteful cycles are in part created and sustained by environmental damage, persons with major conflicts of interest to satisfy their ego, power, and greed to make billions (and in the case of COVID-19, trillions of dollars through vaccines), and preventing the use of highly cost-effective therapies, at the expense and the misery of the public. Unfortunately, many governments and administrations are contributing to this negative vicious cycle for short term gains.

Conflict of interest statement

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