

CONTROLLING COVID-19 PANDEMIC WITH CHOLECALCIFEROL

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ABSTRACT

The elderly and those with underlying chronic pulmonary, cardiovascular, metabolic, and renal diseases are at a higher risk for experiencing COVID-19 infection and more prone to serious clinical complications, such as cytokine storm and acute respiratory distress syndrome, leading to death. In addition to pulmonary cells, COVID-19 also impairs endothelial cells and could initiate intravascular haemolysis and microvascular thrombosis, and consequent pulmonary microembolization, which leads to multi-organ failure and death. Vitamin D adequacy however, can minimize the mentioned harmful outcomes. Sufficient exposure to ultraviolet B rays from sunlight and/or adequate doses of vitamin D supplements enhances the immune system. *In vitro* and *in vivo* data suggest that having adequate vitamin D, increased expression of anti-inflammatory, antioxidant, and anti-microbial related genes. These, suppress excessive inflammation and oxidative processes, and therefore, minimize the symptomatic COVID-19 infections, associated complications, and enable rapid recovery. Whereas, weaker immune systems are primarily responsible for complications and deaths from COVID-19. Administration of higher doses of vitamin D can rapidly boost the immunosystem. It is the most cost-effective way to keep the immune system at high alert and prevent complications and deaths from COVID-19. Therefore, one should proactively consider using a combination of safe sun exposure and oral vitamin D supplements to prevent and manage COVID-19. In addition, ivermectin and hydroxychloroquine could also use cost-effectively in those who had been exposed to a person with COVID-19, immediately after become PCR positive, and in early stage of the disease.

KEYWORDS: Angiotensin-converting enzyme-2; 25(OH)D; Coronavirus; Endocrine system; Renin-angiotensin; Hypovitaminosis D; Innate immune system; SARS.Cov-2.

INTRODUCTION

COVID-19, the novel coronavirus that emerged in late 2019 is a highly infectious disease that causes acute, lower respiratory tract infection that can be associated with severe complications.^[1] Following recovery from the infection, some may develop residual complications that could last for years. Those who are older than 70 years; with pre-existing chronic pulmonary, cardiac, or renal diseases, hypertension, diabetes, or obesity; and those who are immune-suppressed have higher vulnerability to contract COVID-19 and experiencing complications and death.^[2,3]

COVID-19 is a predominantly, world that respiratory virus spreads through airborne droplets as virus-containing aerosol particles. Besides, it can spread through personal contacts, touch from contaminated surfaces via fingers through mucous membranes.^[1] Following the initial outbreak from in Wuhan, China, and disrupted global supply chain, affecting all industries. COVID -19 rapidly progress into a pandemic.

Commenced in Hubei Province of China, COVID-19, it spread across the world.^[1,4]

The global community had a chance to learn from the experience derived from the first wave of COVID-19, during the first half of 2020. One must use such knowledge to enact the right policies and actions to avoid mistakes. These include but not limited to, mandating face masks to reduce the viral load, adhering to personal hygiene, taking precautions such as keeping distance between people, avoid collective institutionalisation (as with group quarantining and in cruise and naval ships), prisons and other enclosed institutions. Nonadherence to these could lead to community outbreaks. Moreover, spread must minimise through asymptomatic carriers, especially transmitting to the elderly and the sick.

Progress of managing COVID-19

The current situation with the COVID-19 pandemic is unprecedented. However, it is heartening that some pharmaceutical companies working with academic

research groups to develop broader armamentaria against COVID-19, including diagnosis and testing procedures, anti-viral agents, and vaccines.^[1]

The United States Food and Drug Administration (FDA) and other regulatory bodies have continued to approve diagnostic polymerase chain reaction (PCR) test kits with a shorter duration, and anti-viral agents, and vaccines against COVID-19. Besides, nasopharyngeal swabs, procedures should be developed to use samples such as saliva for PCR and other rapid antigen testing procedure.

Immune-stimulating effects of Vitamin D

1,25-dihydroxycholecalciferol [1,25(OH)₂D; calciferol] is a potent immune modulator essential for combating invading pathogens. It activates the vitamin D receptors (VDRs) located in the nucleus. Vitamin D exerts immunomodulatory effects by activating VDR pathways by various mechanisms. These include the down-regulation of oxidative stress and inflammation through cytokines; activation of immune cells such as T and B cells and macrophage and dendritic cells; and enhanced production of several antimicrobial peptides.^[5]

In the absence of vitamin D supplements, most people experience vitamin D deficiency some time of the year, especially during the winter months, when the occurrences of respiratory viral diseases peak. While hypovitaminosis D is common among those who are admitted with severe acute illnesses,^[6] 25(OH)D concentration is low in those with a viral illness,^[7-9] especially in those with COVID-19.^[10-12] Moreover, severe vitamin D deficiency significantly increases people's vulnerability to viral illnesses, including COVID-19, dengue etc.^[13]

Serum 25(OH)D concentrations were reported to be significantly lower ($p=0.004$) in those who are PCR-positive for SARS-CoV-2 (mean concentration of 11.1 ng/mL) compared with those with negative results (24.6 ng/mL).^[14] Besides, there is a strong correlation between severe vitamin D deficiency and cytokine storm,^[15,16] which is a hyperinflammatory condition caused by an uncontrolled, overactive immune status.^[17] Vitamin are infected, D may not prevent a person from contracting COVID-19 but it will reduce complications and deaths in those who.^[18]

Vitamin D and its broader health-related benefits

Vitamin D is a secosteroid hormone with broad physiological functions,^[19,20] including anti-inflammatory and anti-oxidant actions, membrane stability, reproductive biology, immune modulation, and enhancement of favourable gene transcription.^[20-23] Besides, vitamin D is involved in bone formation and mineralisation, controlling cell proliferation and maturity, cancer growth, brain development, mitochondrial energy generation, and respiratory functions.^[1,20,24,25] Several of the mentioned functions are relevant to controlling COVID-19 infection. As

discussed below, emerging data support that vitamin D should use as an adjunct therapy in those with COVID-19 infection.^[26-29]

1,25(OH)₂D works in conjunction with controlling inflammation, in part through suppressing the expression of inflammatory cytokines and increasing anti-inflammatory cytokines.^[28,30] Its antimicrobial actions are mediated through multiple mechanisms, including the production of antimicrobial peptides, cathelicidin and defensin that stimulate white blood cells, natural killer cells,^[31] and stimulating macrophages and pulmonary epithelial cells. Calcitriol stabilises tight junctions of epithelial cells, preventing virus intrusion, especially in the respiratory tract and endothelium, thus protecting from viral entry.^[32,33]

The role of vitamin D in immunity and immune disorders

The active form of vitamin D, calcitriol, is an important hormone that affects every tissue in the body. In, vertebrates, it is generated in the skin following exposure to solar, UVB rays.^[34,35] Calcitriol is derived from the main circulatory form, 25(OH)D deficiency is associated with a high incidence of viral infections and many chronic diseases, including coronaviruses affecting humans.^[13,29,36]

Taking small daily doses (between 400 and 1,000 IU as advised by some physicians, likely to take more than a year to build up the necessary physiological blood concentrations of 25(OH)D concentrations in a person deficient in vitamin D, for a meaningful impact on enhancing the immunity. Whereas taking a larger dose of oral vitamin D can rapidly build the serum 25(OH)D concentration and hence the immunity, preventing viral respiratory illnesses, such as COVID-19.^[37]

Respiratory tract illnesses, such as cold, influenza, and COVID-19, occur most commonly during the winter months. There are specific reasons countries located far north and south of the equator experiencing this increase in viral illnesses during respective wintertime.^[38-40] In these countries during the winter periods, sunlight does not carry effective UVB rays, people have significantly lower serum (25(OH)D concentrations. Besides, most respiratory viruses live longer outside human bodies in cold and dry climatic conditions when sunlight and temperature are low.^[37,41,42]

Vitamin D deficiency markedly impairs immunity and thus increases the risk of illness, especially from microbes.^[43,44] Waken innate immunity increased the vulnerability, especially to viral respiratory illnesses,^[27,28,45-48] including coronaviruses.^[49-51] It has been estimated that vitamin D adequacy—having blood levels greater than 30 ng/mL,^[52] during a viral epidemic—reduces the risk of infections by more than 30%.^[27,53,54] Figure 1 summarises the immunomodulatory functions of vitamin D.

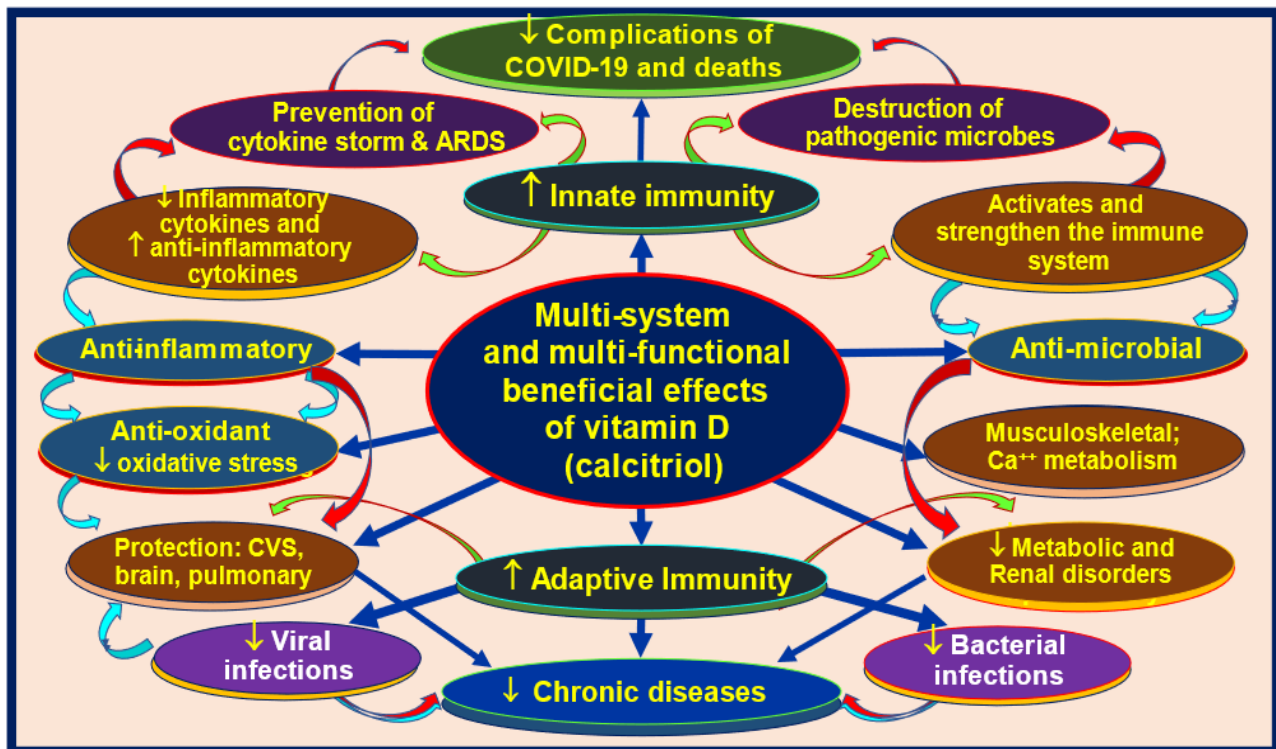


Figure 1: Illustrates a summary of mechanisms that stimulate the innate and adaptive immune system by the hormone, calcitriol [1,25(OH)₂D]. It also highlights the key functions of vitamin D: anti-inflammatory, anti-oxidant, and effects on viral growth and control (red ovals), leading to the destruction and removal of pathogens, reducing the risk of cytokine storm, acute respiratory distress syndrome (ARDS), and deaths (purple ovals). Mechanism of the mentioned actions are illustrated in brown ovals [ACE-2 = angiotensin-converting enzyme-2 = COVID-19 = SARS.Cov-2; RAS = renin–angiotensin system].

Children have a stronger innate immunity and cell-mediated acquired immune (the second line of defence) systems. This combination makes their immune systems robust, enabling them to negate coronaviral infections. Consequently, they are less likely to be infected with COVID-19, do not develop severe complications, or die of it. However, occasionally children with COVID-19 experience a hyperimmune reaction Kawasaki-like syndrome that can be lethal.^[55]

Ambient temperature, sunny weather, and COVID-19 spread

When the mean ambient temperature is less than 14° C, it significantly enhances the growth of COVID-19 than in warmer locations ($p = 0.0001$); death rates follow a similar pattern ($p < 0.02$).^[56] Besides less ventilation in indoor setups, less sunlight leads to low serum 25(OH)D concentrations and more COVID-19 transmission. Therefore, people should spend time outdoors when possible.^[56] Whereas the spread and survival of coronaviruses are less in equatorial countries with abundant sunlight, higher temperature, and humidity. Besides, because of inevitable sunlight exposure, virtually no severe vitamin D deficiency cases are present in those living in tropical countries. Mentioned conditions not only reduces the symptomatic disease but also the spread, complications, and death from COVID-19.^[57,58]

On a per-capita basis, the same countries have significantly less international travel, fewer large gatherings in confined spaces, such as sports and musical arenas, and a higher percentage of younger people and a smaller proportion of older people.^[59,60] These conditions make the prevalence, complications, and death rates associated with COVID-19 lower than those experienced in temperate countries.^[61,62]

Moreover, Blacks and Asians living in temperate countries are dying of COVID-19 at a higher rate than are whites.^[63,64] Socioeconomic factors, such as gaps in healthcare access, may also play a role. However, the common denominator is severe vitamin D deficiency among these groups living in colder countries. To date, severe vitamin D deficiency that weakens the immune system has overlooked by many researchers.^[65,66]

Efficacy of vitamin D on respiratory viral diseases

Worldwide, respiratory illnesses such as influenza and COVID-19, most commonly occur during the winter months.^[67,68] During the winter months, sunlight does not carry adequate or effective UVB rays, and rays arrive at a broader angle that prevents skin penetration. Also, most viruses live longer outside human bodies in cold climatic conditions, and people have significantly lower serum 25(OH)D concentrations.^[39,40,69,70] during the winter months.

While the data related to COVID-19 are still emerging, these suggest that the rate of infections and the mortality associated with COVID-19 are inversely related to population serum 25(OH)D concentrations.^[27] Data from previous coronaviral epidemics suggest that infection rates,^[53] complications, and death rates are highest among those with the lowest serum 25(OH)D concentrations; worst in those having serum 25(OH)D concentrations less than 10 ng/mL (25 nmol/L)—severe vitamin D deficiency.^[53,71,72] Such a person with severe hypovitaminosis D, when get infected with respiratory tract infections, COPD,^[73] bronchitis,^[74] or COVID-19,^[73,74] will have a higher risk for complications and deaths (Figure 1).

Mechanisms of action of calcitriol respiratory viral diseases

Calcitriol stimulates the body’s immune/defence system through several mechanisms.^[29,75] These include the production of cathelicidin and defensins that effectively neutralizes the microbes in circulation, reduce replication and prevent viruses from getting attaching to epithelial

cells, and increase the rate of elimination of viruses.^[29,76] (Figure 1).

The deaths caused by COVID-19 are attributed to acute respiratory distress syndrome (ARDS) following cytokine storms.^[77-79] The latter initiates a vicious cycle, producing pathological concentrations of inflammatory cytokines and vasoconstrictive peptide hormone, angiotensin-II. Combining the above and in conjunction with effect from coronavirus further stimulates the expression of inflammatory cytokines.^[77,80] This further increases the risk of a cytokine storm.

The incidences are highest among those with severe vitamin D deficiency.^[81] The resultant diffused inflammation and oxidative stress injure the pulmonary epithelial and vascular endothelial cells and damage the basement membranes of arteries and capillaries (Figure 1). The latter causes intravascular thrombosis and micro-embolisation and fluid diffusion into tissue spaces in the lungs, causing pulmonary oedema.^[82,83] Emerging data suggest that adequate concentrations of calcitriol could prevent it (Figure 2).

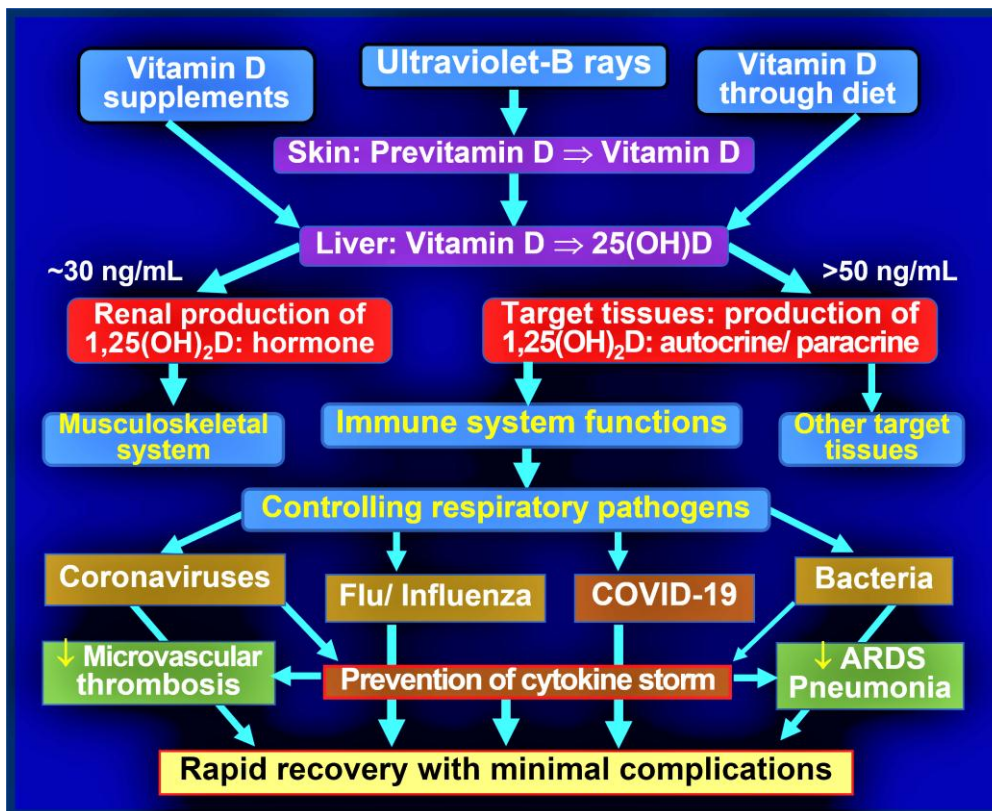


Figure 2: The figure illustrates the activation of vitamin and the generation of the hormone, calcitriol, and controlling pathogenic organisms. Actions of calcitriol also prevent microvascular thrombosis and embolism, lung injury (epithelial cell damage, pneumonia, etc.), and prevent cytokine storm and ARDS.

Multiple sets of data pointing towards a strong link between severe vitamin D deficiency and complications associated with COVID-19, including cytokine storm and ARDS.^[84] Therefore, it is not surprising that vitamin D deficiency significantly increases COVID-19-associated complications and deaths.^[81] Whereas, vitamin D sufficiency markedly reduces generalised

inflammation (i.e., reduce C-reactive protein concentration), suppresses inflammatory cytokine production, and negates the risk of cytokine storm and ARDS associated with COVID-19.^[84] (Figure 1).

Vitamin D breaks this vicious cycle through multiple mechanisms, including suppressing inflammation and

oxidative stress, and cytokine storm.^[79,85] If this combination persists, it can lead to the development of ARDS and death.^[77,80] (Figure 2). Moreover, vitamin D has a profound effect on stabilising epithelial cells and cell junctions, especially in the lungs, thus reducing fluid leakage from blood vessels and thus preventing the occurrence of pulmonary oedema, pneumonia, and ARDS.^[78,82]

Black Americans and Asians with darker skin colour are dying of COVID-19 at a significantly higher rate than are whites.^[65] Although socioeconomic factors, such as disparities in access to healthcare and economic status, likely play some role, weakened immune systems secondary to a high prevalence of severe vitamin D deficiency are perhaps the most important and easily correctable cause.^[1,13] In parallel, areas with high mortality rates, such as Spain and the northern provinces of Italy and France, especially in the elderly had a high prevalence of vitamin D deficiency that increases vulnerability to COVID-19 (Figure 2).

Correlation between COVID-19 and vitamin D status

The age-specific ratio of COVID-19 in Italy, Spain, France, and China, the severe complications and highest rates of deaths were associated with severe vitamin D deficiency—mean serum 25(OH)D concentration less than 5ng/mL.^[62,86] Since hypovitaminosis D significantly increases the risks of COVID-19, it is a reasonable goal to bring the population's serum vitamin D concentration to greater than 40 ng/mL (thus, achieving above 30 ng/mL) through vitamin D supplementation. Having the mentioned physiological 25(OH)D concentration reduces the incidence of COVID-19 and severity of complications by more than 50%. It also subdues the cytokine storm,^[87,88] and death,^[81] a highly cost-effective approach.^[36]

A recent pilot study demonstrated that the use of a higher dose of calcifediol [25(OH)D], which rapidly increases serum 25(OH)D concentration significantly reduced the severity and the need for ICU treatment/ admission of persons with COVID 19.^[89] Currently there are over 50 vitamin D - COVID-19 RCTs are registered in global clinical registries of which data will be reported from early 2021.

Severe hypovitaminosis is associated with higher risks of symptomatic COVID-19 infections, the severity of complications, and higher mortality.^[81,89] This is particularly striking among the elderly; those with multiple chronic diseases; the imprisoned community; routine night-shift workers, diabetes, obesity, and hypertension; and persons with darker skin. Two shared characteristics common to all mentioned categories are the high prevalence of severe vitamin D deficiency.^[90,91] and low angiotensin-2 (ACE-2) receptor concentration.^[92]

The amounts of vitamin D needed to overcome coronavirus diseases

The recommendation during the viral epidemics and the During viral epidemics and the COVID-19 pandemic, it is recommended that individuals take higher doses of vitamin D supplementation, preferably between 5,000 and 10,000 IU/day or 50,000 IU once to twice a week, throughout the period of infectivity.^[13] Alternatively, for those who do not want or cannot afford to purchase supplements, 30 to 60 minutes of daily exposure of one-third of the skin surface to direct summer-like sunlight between 10.30 AM and 1.30 PM should provide a reasonable amount based on the darkness of the skin. While this may not be sufficient to raise serum 25(OH)D to its physiological concentration, it could still strengthen the immune system sufficient to prevent complications and deaths from COVID-19 infection.^[13,36]

Standing outside, when one's shadow is shorter than the height is the optimal time for sun exposure. During this period, the UVB rays of the sun reach the earth at an acute angle that can penetrate the skin surface to generate vitamin D. This can be achieved by exposure to sunlight in few short periods, such as 10-minute segments each day while protecting the eyes and face. Whereas, taking smaller doses, such as between 400 and 1,000 IU/day as recommended by some governments and scientific organizations, or causal exposure to sunlight will not generate adequate amounts of vitamin D to have benefit to overcome COVID-19. The overall goal is to maintain the serum 25(OH)D concentration over 30 ng/mL.^[20,93-95]

Vitamin D has been reported to reduce the risk of getting the common cold or pneumonia.^[91,96] It also enhances cellular immunity,^{[97][97-99]} and the expression of antioxidation-related genes,^[100] Considering its potent effects on enhancing the innate immune system, supplementing with high doses of vitamin D^[67,68] as a bolus dose (between 200,000 and 500,000 IU) or same up-front dose administered in divided daily doses. Alternatively, a rapid effect can obtain with administering calcifediol 0.5 to 1.0 mg (0.014 mg/kg body weight), cost-effectively.^[1,28,86]

For a longer term protection and as a maintenance dose, vitamin D doses (for adults) between 4,000 and 10,000 IU or 50,000 IU taken weekly or every two week. Obese persons and those with GI absorption issues, require 2 to 3 times higher doses to maintain serum 25(OH)D concentration >50 ng/mL to overcome COVID-19. Persons with hypovitaminosis D, starting even with 10,000 IU daily, takes several weeks or months to build up levels to have protective effects. In all cases, a daily maintenance doses is essential for maintaining serum 25 (OH)D concentration >50 ng/mL to protect from coronaviruses and other viral infections as mentioned.

Mechanisms by which vitamin D protects cells from COVID-19

Receptor ACE-2 and CD209L are expressed in most human tissue, including endothelial cells, lungs, gastrointestinal tract, brain, adipose tissues, kidneys, and liver.^[77,80] In addition to pulmonary epithelial cells, microvascular cells and other cardiovascular cells also express ACE-2 receptors and CD209L, and thus a target for coronaviruses. The latter includes endothelial cell damage, myocarditis, microvascular thrombosis, and embolisation,^[101] and end-organ failure, such as has been seen with COVID-19,^[82,83] (Figure 1). Considering these, microvascular endothelial cells should be considered as an important target for COVID-19 and associated complications.^[102]

Once SARS-CoV-2 enters pulmonary cells,^[103] and downregulates ACE-2 receptors,^[101] This reduces the availability of functional ACE-2 enzyme to cleave vasoconstrictor peptide, prevent the conversion of angiotensin-2 into a vasodilatory peptide, angiotensin₍₁₋₇₎ thus, worsening the situation. Excess build-up of angiotensin-2 also stimulates the synthesis and release of inflammatory cytokine, increasing the risk of a cytokine storm.^[104] The vasodilatory effects of angiotensin₍₁₋₇₎ directly opposite to that of angiotensin-2; it also reduces intravascular pressure and prevents the development of pulmonary hypertension and oedema, and ARDS.

Previous research suggested that the renin-angiotensin-aldosterone hormonal system (RAS) signalling pathway is involved in worsening morbidity and mortality associated with acute lung injury models, such as sepsis-induced lung damage.^[103,105] Calcitriol is tightly involved in regulating the RAS at multiple levels (Figure 1). Calcitriol suppresses renin production, the rate-limiting step of the RAS axis, increases ACE-2, and reduces angiotensin-II concentration. Calcitriol maintains this regulatory balance that is involved in multiple physiological functions. Most importantly, calcitriol's adequate intracellular production within the immune cells will protect against COVID-19-mediated cytokine storm, acute viral-mediated lung injury, and ARDS development.^[106,107]

Actions of vitamin D on the RAS axis

Renin production relies on the cyclic AMP (cAMP)-dependent PKA signalling pathway. Calcitriol [1,25(OH)₂D₃] down-regulates the key rate-limiting step of the RAS, the expression of the enzyme renin, most likely by blocking the formation of the CRE-CREB-CBP complex.^[108] Calcitriol favourably suppresses the RAS at several sites. Suppression of the RAS is one of the key mechanisms that calcitriol contributes to protecting persons with COVID-19. Thus, in those with severe hypovitaminosis D, administration of vitamin D is protective against COVID-19 and other respiratory tract infections.^[53,79,109]

Evidence suggests that irrespective of geographic location, an individual with an adequate concentration of serum 25(OH)D, through prophylactic therapy or daily exposure to summer-like sunlight, will reduce the incidence and severity of the complications associated with COVID-19.^[13,91,110] Despite these, to date, no government seems to understand this fundamental principle of being proactive in preventing COVID-19 using such simple and cost-effective measures.

While vitamin D is essential for the proper functioning of the immune system,^[13,35] it suppresses excessive inflammatory and oxidative stresses and regulates the RAS keeping this system in balance.^[111] Countries with the population serum 25(OH)D concentrations are low and limited availability of ultraviolet-B rays from the sun, have higher COVID-19-related complications and deaths,^[57] so as from other respiratory viruses.^[112,113] The elderly, persons of African and Asian origin with darker skin living in temperate counties, institutionalised persons such as nursing homes, disability centres, and prisons. Hence, as submarine crew and regular night shift workers have a high prevalence of vitamin D deficiency. Therefore, these groups of people are at high risk for complications and deaths following COVID-19. Similarly, those with chronic metabolic disorders such as diabetes, obesity, metabolic syndrome, chronic pulmonary, cardiovascular, and renal diseases, are also at a higher risk of complications from COVID-19.

Controversy about the ACE-2 in COVID-19

Based on speculation, some have suggested that increased availability of ACE-2 could provide further opportunity for COVID-19 to enter lung cells, worsening the condition.^[83,114] Recent data, however, do not support this negative view.^[82,115] Excess ACE-2 leaks into the bloodstream and acts as a decoy receptor for COVID-19. The ACE-2/COVID-19 attachment that occurs in the circulation is tight, enabling neutralisation of the virus. Because this is occurring in extracellular fluid, the virus cannot replicate. Therefore, contrary to the mentioned speculation, the upregulation of ACE-2 mitigates the effects of COVID-19.^[82,115,116]

Earlier data suggest that a blockade of the ACE-2 might prevent the virus from entering the body.^[117-119] However, having higher levels of ACE-2 increases the rate of cleavage of angiotensin-II, thereby reducing its concentration and negating its harmful activity and generating Ang₍₇₋₁₁₎, which is a vasodilator. In the lungs and gut, vitamin D, in conjunction with iodine and selenium, seems to play a role in maintaining the tight cell junctions in the epithelial cells,^[120] thereby protecting cell function and preventing excessive fluid diffusion across cell membranes.

CONCLUSION

Having a balanced diet, with adequate quantities of micronutrients, such as vitamins D, K₂, and C, trace minerals, and anti-oxidants, will lead to maintaining a

more robust immune system. In most countries, some communities have one or more prevailing micronutrient deficiencies that increase vulnerability to various disorders, such as metabolic diseases and communicable and non-communicable diseases. In addition to nutrient supplements, fortification of foods with vitamin D and other essential micronutrients, will significantly impact overall health, disease prevention, and reduce healthcare costs.^[121-123]

In the case of COVID-19, those with vitamin D deficiency are the most susceptible to complications and deaths, primarily because of weaker immune systems. Overall data suggest that maintaining serum 25(OH)D concentration above 50 ng/mL (125 nmol/L) significantly reduces microbial infections and complications from respiratory viruses.^[53,124] However, such effects are most visible in those with severe hypovitaminosis D.^[74] In addition to safe sun exposure and vitamin D supplementation, enrichment of food (i.e., fortification) is another economical and effective approach for the alleviation of micronutrient malnutrition in a target population, as has been done with iodine. The addition of other micronutrients, such as zinc and selenium, vitamin K2, vitamin A, C and K2, resveratrol, magnesium, in combination with essential fatty acids, such as omega-3 would facilitate the maintenance of a strong immune system.^[125,126]

Administrators should consider prompt, nationwide educational and vitamin D supplemental campaigns to strengthen the population's immunity. Raising the population 25(OH)D concentration can cost-effectively achieved by guidance on sun exposure, subsidised vitamin D supplementation programs, and targeted food fortification. Combining these will positively impact the prevention of symptomatic disease, severe complications, and deaths from COVID-19. The modifiable risk factor for COVID-19 that can be easily corrected is vitamin D deficiency. Doing so is the most cost-effective way to protect the vulnerable populations, with a high prevalence of vitamin D deficiency, such as African Americans, the elderly, and institutionalised persons.

Conflicts of Interest: The author declares no conflicts of interest.

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