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CONTROLLING COVID-19 PANDEMIC THROUGH HORMONE CALCITRIOL

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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, thus could initiate intravascular haemolysis and microvascular thrombosis, and consequent pulmonary microembolisation. These can lead to multiorgan failure and death. Vitamin D adequacy has a potent effect in prevent or minimise the mentioned harmful outcomes. Sufficient exposure to ultraviolet B rays from sunlight or adequate doses of oral vitamin D supplements enhances the immune system. *In vitro* and *in vivo* data suggest that increase expression of anti-inflammatory, antioxidant, and antimicrobial related genes together with the suppression of excessive inflammatory and oxidative process that not only minimize contracting symptomatic COVID-19 infection and associated complications and deaths but also enable rapid recovery. The weaker innate immune system is responsible for complications and deaths from COVID-19. Administration of higher doses of vitamin D can rapidly boost the immune system. It is the most cost-effective way to keep the immune system at high alert and prevent complications and deaths from COVID-19. Therefore, a combination of safe sun exposure and oral vitamin D supplements should be considered proactively to prevent and manage COVID-19. Hydroxychloroquine and ivermectin are two other cost-effective agents that can use in those who have exposed to a person with COVID-19, immediately after PCR positivity, and in early stage of the disease before developing complications.

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 a higher vulnerability to contract COVID-19 and experience complications and death.[2,3]

COVID-19 is a respiratory virus that predominantly spreads through airborne, virus-containing micro-aerosol particles. It can also spread through personal contacts, after touching contaminated surfaces and transferring to mucous membranes via fingers.[1] Following the initial outbreak and the global supply chain crises that affected all industries, initiated in Wuhan, in Hubei Province of China, COVID-19 rapidly spread worldwide.[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, anti-viral agents, and vaccines against COVID-19. Besides, nasopharyngeal swabs, procedures should be developed to use saliva samples for PCR and other procedures, such as rapid antigen testing.

Immune-stimulating effects of Vitamin D

1,25-dihydroxycholecalciferol [1,25$(OH)_2$D; 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 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 incidence of cytokine storm,[15,16] a hyperinflammatory condition caused by an uncontrolled, overactive (auto)immune status.[17] Vitamin D may not necessarily prevent a person from contracting COVID-19, but it will reduce symptomatic disease, complications, and deaths in those who are infected.[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$(OH)_2$D 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. Its 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 immune-modulatory functions of vitamin D.

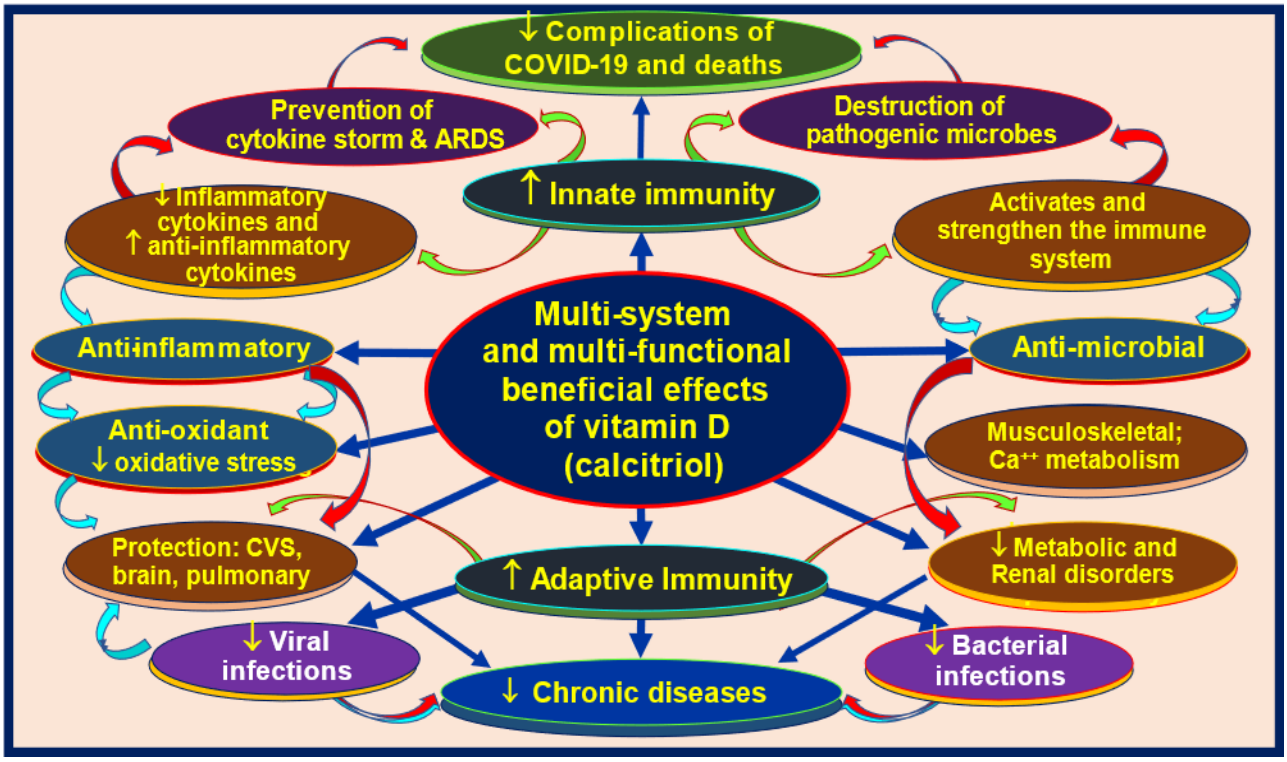

Figure 1: Illustrates a summary of mechanisms that stimulate the innate and adaptive immune system by the hormone, calcitriol [1,25(OH)$_2$D]. It also highlights the key functions of vitamin D: anti-inflammatory, anti-oxidant, and effects on viral growth and control (red ovals), leading to the destruction 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 neutralises microbes, especially viruses in the circulation. Anti-viral activity of calcitriol reduces the replication of coronaviruses. It prevents viruses from getting attached to epithelial cells and entry into cells and increased the 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).

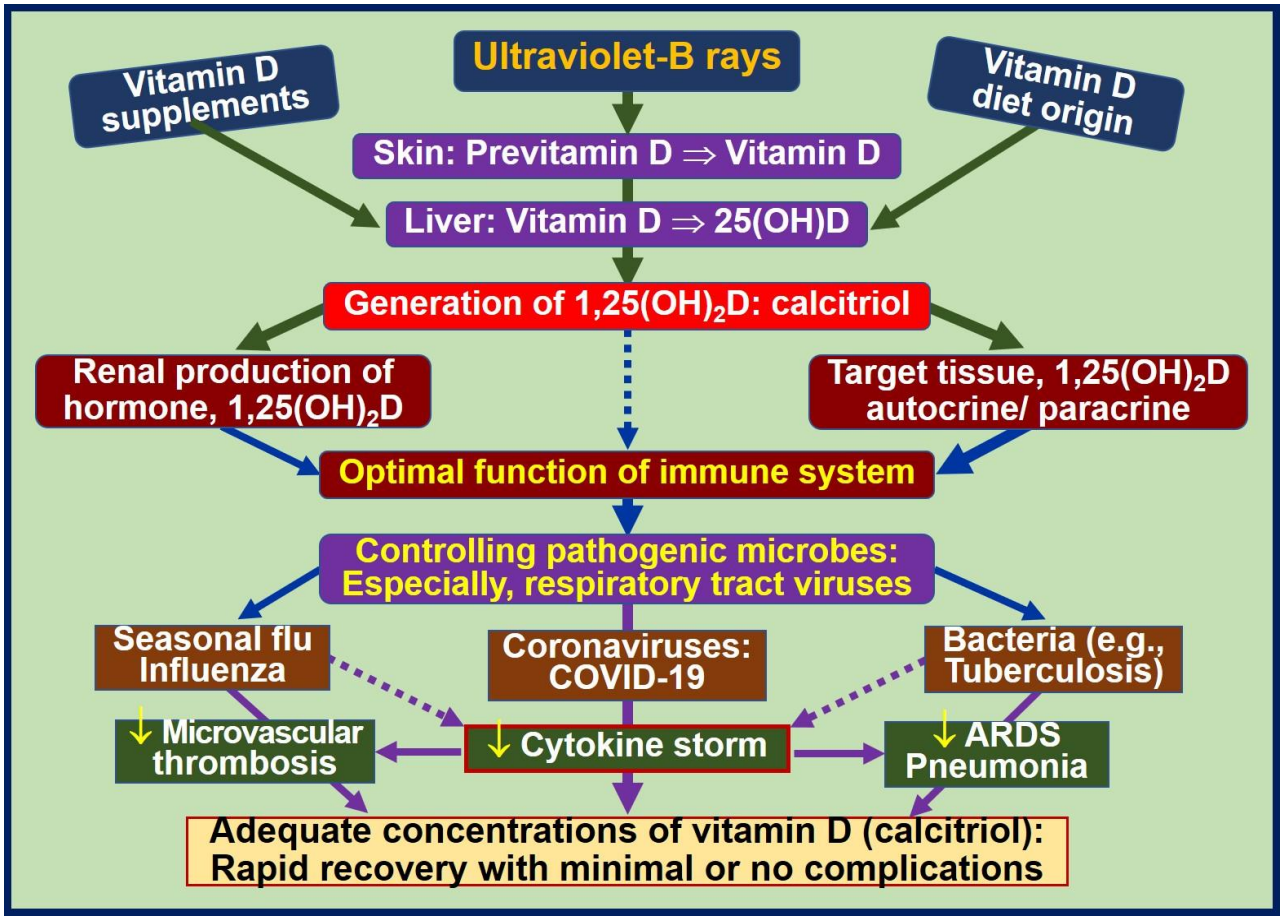

Figure 2: The figure illustrates the activation of vitamin D into, it's hormonal form, calcitriol, and controlling pathogenic organisms. Actions of calcitriol also prevent microvascular thrombosis and embolism, lung injury (epithelial cell damage, pneumonia, etc.), and prevent cytokine storm and ARDS.

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 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 correctible 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 5 ng/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 admissions the treatments for persons with COVID-19.[89] Over 50, extensive vitamin D(COVID-19 RCTs currently registered in global clinical registries of which data will be available 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 coronaviral diseases

The recommendation during the viral epidemics and the COVID-19 pandemic, it for individuals to take higher doses of vitamin D supplementation, preferably between 4,000 and 6,000 IU/day or 50,000 IU per week or every other week throughout infectivity, which is likely to last for more than 8 to 12 months.[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 concertation, it could still strengthen the immune system sufficient to prevent complications and deaths from COVID-19 infection.[13,36]

When one's shadow is shorter than the height, standing under the sun is the right time for sun exposure. During this period, the sun's UVB rays reach the earth at an acute angle, enabling penetration of 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 a few scientific organisations, or causal exposure to sunlight will not generate adequate amounts of vitamin D to have benefit in overcoming COVID-19. The overall goal is to maintain the serum 25(OH)D concentration over 30 ng/mL.[20,93-95]

Vitamin D reported reducing the risk of getting the common cold or pneumonia.[91,96] It also enhances cellular immunity [97] and the expression of anti-inflammatory and anti-oxidation-related genes,[100], thus reducing the severity of influenza/common cold.[97-99] Considering the potent beneficial effects of calcitriol in enhancing the innate immunity and the urgent need for boosting of the immune system, supplementing with high doses of vitamin D_3 is a reasonable, cost-effective option for disease prevention.[1,28,86][67,68]

The above-mentioned can achieve through upfront oral loading of vitamin D, doses between 200,000 and 600,000 IU, taking 50,000 IU daily (or every other day) over 5 to 7 days. For COVID-19 prevention and

treatment, begin to take daily doses, even up to 10,000 IU unlikely to have a protective effect within a short period. Irrespective of the mentioned regimens, a daily maintenance doses of vitamin D, approximately 4,000 IU to maintain the serum 25(OH)D concentration above 30 ng/mL and to protect from coronaviruses and other viral infections.

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)$_2$D$_3$] 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, K_2, 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 supports that maintaining serum 25(OH)D concentrations above 30 ng/mL (75 nmol/L) significantly reduces microbial and respiratory virus infections and complications.[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 economic 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 K_2, vitamin A, C and K_2, 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.

REFERENCES

1. Wimalawansa, S.J., *Global epidemic of coronavirus—COVID-19: What can we do to minimise risks?* European J. Biomed & Pharma Sci., 2020; 7(3): 432-438.
2. Armitage, R. and L.B. Nellums, *COVID-19 and the consequences of isolating the elderly.* Lancet Public Health, 2020.
3. Reyes-Ortiz, C.A., C. Williams, and C. Westphal, *Comparison of Early Versus Late Palliative Care Consultation in End-of-Life Care for the Hospitalised Frail Elderly Patients.* Am J Hosp Palliat Care, 2015; 32(5): 516-20.
4. Wu, Z. and J.M. McGoogan, *Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention.* JAMA, 2020.
5. Aygun, H., *Vitamin D can prevent COVID-19 infection-induced multiple organ damage.* Naunyn Schmiedebergs Arch Pharmacol, 2020; 393(7): 1157-1160.
6. Leow, L., et al., *Vitamin D, innate immunity and outcomes in community acquired pneumonia.* Respirology, 2011; 16(4): 611-6.
7. Villamor, E., et al., *Vitamin D serostatus and dengue fever progression to dengue hemorrhagic fever/dengue shock syndrome.* Epidemiol Infect, 2017; 145(14): 2961-2970.
8. Han, J.E., et al., *High Dose Vitamin D Administration in Ventilated Intensive Care Unit Patients: A Pilot Double Blind Randomized Controlled Trial.* J Clin Transl Endocrinol, 2016; 4: 59-65.
9. Yamshchikov, A.V., et al., *Vitamin D for treatment and prevention of infectious diseases: a systematic review of randomised controlled trials.* Endocr Pract, 2009; 15(5): 438-49.
10. Vyas, N., et al., *Vitamin D in Prevention and Treatment of COVID-19: Current Perspective and Future Prospects.* J Am Coll Nutr, 2020; 1-14.
11. Whittemore, P.B., *COVID-19 fatalities, latitude, sunlight, and vitamin D.* Am J Infect Control, 2020.
12. Yousef, S., et al., *Study protocol: Worldwide comparison of vitamin D status of immigrants from different ethnic origins and native-born populations-a systematic review and meta-analysis.* Syst Rev, 2019; 8(1): 211.
13. Wimalawansa, S.J., *Fighting against COVID-19: Boosting the immunity with micronutrients, stress reduction, physical activity, and vitamin D.* Nutrition and Food Science Journal (Sci Literature), 2020; 3(1)(126): 1-4.
14. D'Avolio, A., et al., *25-Hydroxyvitamin D concentrations are Lower in patients with positive PCR for SARS-CoV-2.* Nutrients, 2020; 12(5).
15. Hojyo, S., et al., *How COVID-19 induces cytokine storm with high mortality.* Inflamm Regen, 2020; 40: 37.
16. Iannaccone, G., et al., *Weathering the Cytokine Storm in COVID-19: Therapeutic Implications.* Cardiorenal Med, 2020; 1-11.

17. Sims, JT, et al., *Characterisation of the cytokine storm reflects hyperinflammatory endothelial dysfunction in COVID-19.* J Allergy Clin Immunol, 2020.
18. Wimalawansa, S.J., *COVID-19: Evolution and prevention.* Trends Telemed E-Health, 2020; 2(3): 1-5.
19. Wimalawansa, S.J., *Vitamin D; What clinicians would like to know.* Sri Lanka Journal of Diabetes, Endocrinology and Metabolism, 2012; 1(2): 73-88.
20. Wimalawansa, S.J., *Non-musculoskeletal benefits of vitamin D.* J Steroid Biochem Mol Biol, 2018; 175: 60-81.
21. Jiang, Y., et al., *Physiological and pathological implications of retinoid action in the endometrium.* J Endocrinol, 2018; 236(3): R169-R188.
22. Keane, K.N., et al., *Molecular actions of vitamin D in reproductive cell biology.* Reproduction, 2017; 153(1): R29-R42.
23. Pludowski, P., et al., *Vitamin D supplementation guidelines.* J Steroid Biochem Mol Biol, 2018; 175: 125-135.
24. Oliver, S.M., *The immune system and new therapies for inflammatory joint disease.* Musculoskeletal Care, 2003; 1(1): 44-57.
25. Wimalawansa, S.J., Razzaque, D. M.S, Al-Daghri, N.M, *Calcium and Vitamin D in Human Health: Hype or Real?* J Steroid Biochem Mol Biol, 2017; 180: 4-14.
26. McCartney, D.M. and D.G. Byrne, *Optimisation of Vitamin D Status for Enhanced Immuno-protection Against Covid-19.* Ir Med J, 2020; 113(4): 58.
27. Zhou, Y.F., BA. Luo, and L.L. Qin, *The association between vitamin D deficiency and community-acquired pneumonia: A meta-analysis of observational studies.* Medicine (Baltimore), 2019; 98(38): e17252.
28. Grant, W.B., et al., *Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths.* Nutrients, 2020; 12(6): 1626.
29. Tsujino, I., et al., *Pulmonary activation of vitamin D3 and preventive effect against interstitial pneumonia.* J Clin Biochem Nutr, 2019; 65(3): 245-251.
30. Adams, J.S., et al., *Potentiation of the macrophage 25-hydroxyvitamin D-1-hydroxylation reaction by human tuberculous pleural effusion fluid.* J Clin Endocrinol Metab, 1989; 69(2): 457-60.
31. Antal, AS, et al., *Impact of vitamin D3 on cutaneous immunity and antimicrobial peptide expression.* Dermatoendocrinol, 2011; 3(1): 18-22.
32. Aloia, J.F. and M. Li-Ng, *Re: epidemic influenza and vitamin D.* Epidemiol Infect, 2007; 135(7): 1095-6. author reply 1097-8.
33. Fleming, D.M. and A.J. Elliot, *Epidemic influenza and vitamin D.* Epidemiol Infect, 2007; 135(7): 1091-2. author reply 1092-5.
34. Lucock, M., et al., *Early lifecycle UV-exposure calibrates adult vitamin D metabolism: Evidence for a developmentally originated vitamin D homeostat that may alter related adult phenotypes.* Am J Hum Biol, 2019; 31(4): e23272.
35. Miraglia Del Giudice, M., C. Indolfi, and C. Strisciuglio, *Vitamin D: Immunomodulatory Aspects.* J Clin Gastroenterol, 2018. 52 Suppl 1(Proceedings from the 9th Probiotics, Prebiotics and New Foods, Nutraceuticals and Botanicals for Nutrition & Human and Microbiota Health Meeting, Rome, Italy, September), 2017; S86-S88.
36. Wimalawansa, S.J., *Achieving population vitamin D sufficiency will markedly reduce healthcare costs.* EJBPS, 2020; 7(3): 136-141.
37. Premkumar, M., et al., *Vitamin D homeostasis, bone mineral metabolism, and seasonal affective disorder during 1 year of Antarctic residence.* Arch Osteoporos, 2013; 8: 129.
38. Ianevski, A., et al., *Low Temperature and Low UV Indexes Correlated with Peaks of Influenza Virus Activity in Northern Europe during 2010(-)2018.* Viruses, 2019; 11(3).
39. Imai, C.M., et al., *Depression and serum 25-hydroxyvitamin D in older adults living at northern latitudes - AGES-Reykjavik Study.* J Nutr Sci, 2015; 4: e37.
40. Devaraj, S., et al., *Low vitamin D levels in Northern American adults with the metabolic syndrome.* Horm Metab Res, 2011; 43(1): 72-4.
41. Reichrath, J., R. Saternus, and T. Vogt, *Challenge and perspective: the relevance of ultraviolet (UV) radiation and the vitamin D endocrine system (VDES) for psoriasis and other inflammatory skin diseases.* Photochem Photobiol Sci, 2017; 16(3): 433-444.
42. Saraiva, G.L., et al., *Influence of ultraviolet radiation on the production of 25 hydroxyvitamin D in the elderly population in the city of Sao Paulo (23 degrees 34'S), Brazil.* Osteoporos Int, 2005; 16(12): 1649-54.
43. Pletz, M.W., et al., *Vitamin D deficiency in community-acquired pneumonia: low levels of 1,25(OH)2 D are associated with disease severity.* Respir Res, 2014; 15: 53.
44. Ginde, A.A., J.M. Mansbach, and C.A. Camargo, Jr., *Vitamin D, respiratory infections, and asthma.* Curr Allergy Asthma Rep, 2009; 9(1): 81-7.
45. Czaja, A.J., *Factoring the intestinal microbiome into the pathogenesis of autoimmune hepatitis.* World J Gastroenterol, 2016; 22(42): 9257-9278.
46. Jin, D., et al., *Lack of Vitamin D Receptor Causes Dysbiosis and Changes the Functions of the Murine Intestinal Microbiome.* Clin Ther, 2015; 37(5): 996-1009 e7.
47. Laplana, M., JL Royo, and J. Fibla, *Vitamin D Receptor polymorphisms and risk of enveloped virus infection: A meta-analysis.* Gene, 2018; 678: 384-394.
48. Platitsyna, N.G. and T.V. Bolotnova, *Vitamin D deficiency as a risk factor for chronic non-*

infectious diseases. Adv Gerontol, 2017; 30(6): 873-879.
49. Eroglu, C., et al., *The relation between serum vitamin D levels, viral infections and severity of attacks in children with recurrent wheezing.* Allergol Immunopathol (Madr), 2019; 47(6): 591-597.
50. Arihiro, S., et al., *Randomised Trial of Vitamin D Supplementation to Prevent Seasonal Influenza and Upper Respiratory Infection in Patients With Inflammatory Bowel Disease.* Inflamm Bowel Dis, 2019; 25(6): 1088-1095.
51. Jolliffe, D.A., et al., *Vitamin D receptor genotype influences risk of upper respiratory infection.* Br J Nutr, 2018; 120(8): 891-900.
52. Wagner, C.L., et al., *Vitamin D administration during pregnancy as prevention for pregnancy, neonatal and postnatal complications.* Rev Endocr Metab Disord, 2017; 18(3): 307-322.
53. Zdrenghea, M.T., et al., *Vitamin D modulation of innate immune responses to respiratory viral infections.* Rev Med Virol, 2017; 27(1).
54. Morris, S.K., et al., *Maternal vitamin D supplementation during pregnancy and lactation to prevent acute respiratory infections in infancy in Dhaka, Bangladesh (MDARI trial): protocol for a prospective cohort study nested within a randomised controlled trial.* BMC Pregnancy Childbirth, 2016; 16(1): 309.
55. Sabatier, I., et al., *Stroke by carotid artery complete occlusion in Kawasaki disease: case report and review of literature.* Pediatr Neurol, 2013; 49(6): 469-73.
56. Bäcker, A., *Slower COVID-19 morbidity and mortality growth at higher solar Iirradiance and elevation.* Social Science Research Network. Rochester, NY., 2020.
57. Neher, R.A., et al., *Potential impact of seasonal forcing on a SARS-CoV-2 pandemic.* Swiss Med Wkly, 2020; 150: 20224.
58. Wang J, T.K., Feng K, X Lin, W Lv, K Chen, L Wang, *High temperature and high humidity reduce the transmission of COVID-19.* SSRN Electron J, 2020; 19(13): 1-13.
59. Chung, C., et al., *Vitamin D-Cathelicidin Axis: at the Crossroads between Protective Immunity and Pathological Inflammation during Infection.* Immune Netw, 2020; 20(2): e12.
60. Fabbri, A., M. Infante, and C. Ricordi, *Editorial - Vitamin D status: a key modulator of innate immunity and natural defense from acute viral respiratory infections.* Eur Rev Med Pharmacol Sci, 2020; 24(7): 4048-4052.
61. Trovas, G. and S. Tournis, *Vitamin D and COVID-19.* Hormones (Athens), 2020.
62. Singh, S., R. Kaur, and R.K. Singh, *Revisiting the role of vitamin D levels in the prevention of COVID-19 infection and mortality in European countries post infections peak.* Aging Clin Exp Res, 2020.
63. Aldridge, R.W., et al., *Black, Asian and Minority Ethnic groups in England are at increased risk of death from COVID-19: indirect standardisation of NHS mortality data.* Wellcome Open Res, 2020; 5: 88.
64. Holmes, L., Jr., et al., *Black-White Risk Differentials in COVID-19 (SARS-COV2) Transmission, Mortality and Case Fatality in the United States: Translational Epidemiologic Perspective and Challenges.* Int J Environ Res Public Health, 2020; 17(12).
65. Rhodes, J.M., et al., *Perspective: Vitamin D deficiency and COVID-19 severity - plausibly linked by latitude, ethnicity, impacts on cytokines, ACE2, and thrombosis (R1).* J Intern Med, 2020.
66. Kakodkar, P., N. Kaka, and M.N. Baig, *A Comprehensive Literature Review on the Clinical Presentation, and Management of the Pandemic Coronavirus Disease 2019 (COVID-19).* Cureus, 2020; 12(4): e7560.
67. Dawson-Hughes, B., et al., *effect of vitamin D supplementation on wintertime and overall bone loss in healthy postmenopausal women.* Ann Intern Med, 1991; 115(7): 505-12.
68. Tau, C., et al., *Twice single doses of 100,000 IU of vitamin D in winter is adequate and safe for prevention of vitamin D deficiency in healthy children from Ushuaia, Tierra Del Fuego, Argentina.* J Steroid Biochem Mol Biol, 2007; 103(3-5): 651-4.
69. Tan, J., et al., *An initial investigation of the association between the SARS outbreak and weather: with the view of the environmental temperature and its variation.* J Epidemiol Community Health, 2005; 59(3): 186-92.
70. Zumla, A., et al., *Coronaviruses - drug discovery and therapeutic options.* Nat Rev Drug Discov, 2016; 15(5): 327-47.
71. Poon, A.H., B. Mahboub, and Q. Hamid, *Vitamin D deficiency and severe asthma.* Pharmacol Ther, 2013; 140(2): 148-55.
72. Finklea, J.D., R.E. Grossmann, and V. Tangpricha, *Vitamin D and chronic lung disease: a review of molecular mechanisms and clinical studies.* Adv Nutr, 2011; 2(3): 244-53.
73. Jolliffe, DA, et al., *Vitamin D to prevent exacerbations of COPD: systematic review and meta-analysis of individual participant data from randomised controlled trials.* Thorax, 2019; 74(4): 337-345.
74. Martineau, A.R., et al., *Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data.* BMJ, 2017; 356: i6583.
75. Carter, S.J., M.N. Baranauskas, and AD Fly, *Considerations for obesity, vitamin D, and physical activity amidst the COVID-19 pandemic.* Obesity (Silver Spring), 2020.
76. Russell, B., et al., *Associations between immune-suppressive and stimulating drugs and novel*

COVID-19-a systematic review of current evidence. Ecancermedicalscience, 2020; 14: 1022.
77. Hanff, T.C., et al., *Is There an Association Between COVID-19 Mortality and the Renin-Angiotensin System-a Call for Epidemiologic Investigations.* Clin Infect Dis, 2020.
78. Kaparianos, A. and E. Argyropoulou, *Local renin-angiotensin II systems, angiotensin-converting enzyme and its homologue ACE2: their potential role in the pathogenesis of chronic obstructive pulmonary diseases, pulmonary hypertension and acute respiratory distress syndrome.* Curr Med Chem, 2011; 18(23): 3506-15.
79. Hughes, D.A. and R. Norton, *Vitamin D and respiratory health.* Clin Exp Immunol, 2009; 158(1): 20-5.
80. Zhang, P., et al., *Association of Inpatient Use of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality Among Patients With Hypertension Hospitalized With COVID-19.* Circ Res, 2020.
81. Radujkovic, A., et al., *Vitamin D Deficiency and Outcome of COVID-19 Patients.* Nutrients, 2020; 12(9).
82. Danser, A.H.J., M. Epstein, and D. Batlle, *Renin-Angiotensin System Blockers and the COVID-19 Pandemic: At Present There Is No Evidence to Abandon Renin-Angiotensin System Blockers.* Hypertension, HYPERTENSIONAHA12015082, 2020.
83. Diaz, J.H., *Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19.* J Travel Med, 2020.
84. Chen, S., et al., *Ponatinib Protects Mice From Lethal Influenza Infection by Suppressing Cytokine Storm.* Front Immunol, 2019; 10: 1393.
85. Gunn, J., et al., *An Analysis of Biomarkers in Patients with Chronic Pain.* Pain Physician, 2020; 23(1): E41-E49.
86. Kow, CS, M.A. Hadi, and S.S. Hasan, *Vitamin D Supplementation in Influenza and COVID-19 Infections Comment on: "Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths" Nutrients, 2020; 12(4): 988.* Nutrients, 2020; 12(6).
87. Daneshkhah, A., et al., *Evidence for possible association of vitamin D status with cytokine storm and unregulated inflammation in COVID-19 patients.* Aging Clin Exp Res, 2020; 32(10): 2141-2158.
88. Soy, M., et al., *Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment.* Clin Rheumatol, 2020; 39(7): 2085-2094.
89. Entrenas Castillo, M., et al., *effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalised for COVID-19: A pilot randomised clinical study.* J Steroid Biochem Mol Biol, 2020; 203: 105751.
90. Finamor, D.C., et al., *A pilot study assessing the effect of prolonged administration of high daily doses of vitamin D on the clinical course of vitiligo and psoriasis.* Dermato-endocrinology, 2013; 5(1): 222-234.
91. Grant, W.B., F. Al Anouti, and M. Moukayed, *Targeted 25-hydroxyvitamin D concentration measurements and vitamin D3 supplementation can have important patient and public health benefits.* Eur J Clin Nutr, 2020; 74(3): 366-376.
92. Xiao, L., H. Sakagami, and N. Miwa, *ACE2: The key Molecule for Understanding the Pathophysiology of Severe and Critical Conditions of COVID-19: Demon or Angel?* Viruses, 2020; 12(5).
93. McDonnell, S.L., et al., *Serum 25-Hydroxyvitamin D Concentrations >/=40 ng/ml Are Associated with >65% Lower Cancer Risk: Pooled Analysis of Randomized Trial and Prospective Cohort Study.* PLoS One, 2016; 11(4): e0152441.
94. Wimalawansa, S.J., *Biology of Vitamin D.* J steroids Horm Sci, 2019; 10((1)198): 1-8.
95. Haq, A., et al., *Clinical practice guidelines for vitamin D in the United Arab Emirates.* J Steroid Biochem Mol Biol, 2018; 175: 4-11.
96. Lei, G.S., et al., *Mechanisms of Action of Vitamin D as Supplemental Therapy for Pneumocystis Pneumonia.* Antimicrob Agents Chemother, 2017; 61(10).
97. Rondanelli, M., et al., *Self-Care for Common Colds: The Pivotal Role of Vitamin D, Vitamin C, Zinc, and Echinacea in Three Main Immune Interactive Clusters (Physical Barriers, Innate and Adaptive Immunity) Involved during an Episode of Common Colds-Practical Advice on Dosages and on the Time to Take These Nutrients/Botanicals in order to Prevent or Treat Common Colds.* Evid Based Complement Alternat Med, 2018; 2018: 5813095.
98. Cantorna, M.T., *Mechanisms underlying the effect of vitamin D on the immune system.* Proc Nutr Soc, 2010; 69(3): 286-9.
99. Wong, A.P., et al., *Review: Beyond conventional therapies: Complementary and alternative medicine in the management of hypertension: An evidence-based review.* Pak J Pharm Sci, 2018; 31(1): 237-244.
100. Sharifi, A., et al., *effect of single-dose injection of vitamin D on immune cytokines in ulcerative colitis patients: a randomised placebo-controlled trial.* APMIS, 2019; 127(10): 681-687.
101. Hoffmann, M., et al., *SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor.* Cell, 2020; 181(2): 271-280 e8.
102. Kong, J., et al., *VDR attenuates acute lung injury by blocking Ang-2-Tie-2 pathway and renin-*

angiotensin system. Mol Endocrinol, 2013; 27(12): 2116-25.
103. Liu, Z., et al., *Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2.* J Med Virol, 2020.
104. Tomaschitz, A., et al., *Independent association between 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D and the renin-angiotensin system: The Ludwigshafen Risk and Cardiovascular Health (LURIC) study.* Clin Chim Acta, 2010; 411(17-18): 1354-60.
105. Fedson, D.S., *Treating the host response to emerging virus diseases: lessons learned from sepsis, pneumonia, influenza and Ebola.* Ann Transl Med, 2016; 4(21): 421.
106. Xu, J., et al., *Clinical Relevance and Role of Neuronal AT1 Receptors in ADAM17-Mediated ACE2 Shedding in Neurogenic Hypertension.* Circ Res, 2017; 121(1): 43-55.
107. Xu, J., et al., *Vitamin D alleviates lipopolysaccharideinduced acute lung injury via regulation of the reninangiotensin system.* Mol Med Rep, 2017; 16(5): 7432-7438.
108. Yuan, W., et al., *1,25-dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter.* J Biol Chem, 2007; 282(41): 29821-30.
109. Holick, M.F., *Vitamin D status: measurement, interpretation, and clinical application.* Ann Epidemiol, 2009; 19(2): 73-8.
110. Merzon, E., et al., *Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study.* FEBS J, 2020.
111. Wimalawansa, S.J., *Vitamin D deficiency: Effects on oxidative stress, epigenetics, gene regulation, and aging.* Biology (Basel), 2019; 8(2): pii: E30.
112. Tamerius, JD, et al., *Environmental predictors of seasonal influenza epidemics across temperate and tropical climates.* PLoS Pathog, 2013; 9(3): e1003194.
113. Lowen, A. and P. Palese, *Transmission of influenza virus in temperate zones is predominantly by aerosol, in the tropics by contact: a hypothesis.* PLoS Curr, 2009; 1: RRN1002.
114. Akhtar, S., et al., *Pharmacotherapy in COVID-19 patients: A review of ACE2-raising drugs and their clinical safety.* J Drug Target, 2020; 1-35.
115. Aleksova, A., et al., *COVID-19 and renin-angiotensin system inhibition: role of angiotensin converting enzyme 2 (ACE2) - Is there any scientific evidence for controversy?* J Intern Med, 2020.
116. Kuba, K., et al., *A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury.* Nat Med, 2005; 11(8): 875-9.
117. Yan, T., R. Xiao, and G. Lin, *Angiotensin-converting enzyme 2 in severe acute respiratory syndrome coronavirus and SARS-CoV-2: A double-edged sword?* FASEB J, 2020; 34(5): 6017-6026.
118. Pinto, B.G.G., et al., *ACE2 Expression Is Increased in the Lungs of Patients With Comorbidities Associated With Severe COVID-19.* J Infect Dis, 2020; 222(4): 556-563.
119. Gracia-Ramos, A.E., *Is the ACE2 Overexpression a Risk Factor for COVID-19 Infection?* Arch Med Res, 2020; 51(4): 345-346.
120. Martin, T.A., et al., *Enhanced tight junction function in human breast cancer cells by anti-oxidant, selenium and polyunsaturated lipid.* J Cell Biochem, 2007; 101(1): 155-66.
121. Taylor, C.E. and C.A. Camargo, Jr., *Impact of micronutrients on respiratory infections.* Nutr Rev, 2011; 69(5): 259-69.
122. Smith, G., Wimalawansa, S..J, *Reconciling the irreconcilable: micronutrients in clinical nutrition and public health.* Vitamins & Minerals, 2015; 4(1): 1-4.
123. Willershausen, B., et al., *The influence of micronutrients on oral and general health.* Eur J Med Res, 2011; 16(11): 514-8.
124. Arabi, YM, R. Fowler, and F.G. Hayden, *Critical care management of adults with community-acquired severe respiratory viral infection.* Intensive Care Med, 2020; 46(2): 315-328.
125. Biesalski, H.K., et al., *26th Hohenheim Consensus Conference, September 11, 2010 Scientific substantiation of health claims: evidence-based nutrition.* Nutrition, 2011; 27(10 Suppl): S1-20.
126. Tsai, F. and W.J. Coyle, *The microbiome and obesity: is obesity linked to our gut flora?* Curr Gastroenterol Rep, 2009; 11(4): 307-13.