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Reducing Risks from COVID-19: Cost-Effective Ways of Strengthening Individual's and the Population Immunity with Vitamin D

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Abstract

In addition to being involved in the regulation of calcium and phosphate metabolism and the musculoskeletal functions, vitamin D has immune modulatory effects through several independent pathways. Its active hormone, calcitriol [1,25$(OH)_2$D] effect both innate and adaptive immune systems essential for optimal immune functions. Vitamin D deficiency exacerbates immune-related disorders, including type 1 diabetes, multiple sclerosis, rheumatoid arthritis, psoriasis, respiratory infections, including COVID-19. In those with COVID-19, complications and the number of deaths is higher in those who are older than 70 years, persons with a darker skin colour and/or ethnic minorities living in colder climatic regions, institutionalized persons, and with pre-existing chronic diseases. These groups of people have exceedingly high prevalence of severe vitamin D deficiency and thereof weaker immune systems. Collectively, these increases the vulnerability to microbial infections, particularly respiratory viruses, and for developing severe complications and deaths. Vitamin D related immune protective effects includes, the generation of anti-microbial peptides cathelicidin and defensins and antibodies against invading pathogens; the initiation of immune defences via natural killer cells, macrophages, and epithelial cells; the enhanced expression of angiotensin-converting enzyme 2 (ACE-2) and diminish expression of inflammatory cytokines; and reduce replication and enhance elimination of viruses from the body. The severity of complications and deaths associated with COVID-19 markedly increases in the presence of severe hypovitaminosis D: serum 25(OH) D concentration of less than 10 ng/mL. Excess complications and deaths from COVID-19 can be cost-effectively prevented with rapidly boosting the immunity using upfront loading, high doses of vitamin D; this will create an equivalent of internal "body armour"-defence system, that protects against COVID-19.

Introduction

The novel coronavirus COVID-19 is a highly infectious disease that causes acute, lower respiratory tract infections[1]. Approximately 12% of infected persons may require medical care for associated complications[1]. The highest risks for complications and death are in persons older than 70 years, individuals with a darker skin colour, and those with pre-existing pulmonary and cardiac diseases, hypertension, diabetes, obesity, or immuno compromised status. Vitamin D deficiency is common among all of the mentioned categories. Such vulnerabilities highlight the importance of having a strong immune system to prevent complications and to overcome COVID-19 infection.

Respiratory viruses, including COVID-19, spread primarily through the air—via inhalation of smaller droplets and aerosol forms—and also transfer into the body through mucous membranes via contaminated fingers or by other means, the oral route, and

through close personal contact. In the past several months, considerable experience has been gained across the world with reference to the pattern of COVID-19 transmission, response to experimental therapies[1], and rates of complications, especially in intensive care setups. It is important to refine the current approaches in dealing with COVID-19 not only based on recently published science and the understanding of the biology of COVID-19 but also from the lessons learned from recent experiences and SARS.

The current situation with the COVID-19 global pandemic is unprecedented. It is heartening to see that a few of the larger pharmaceutical companies have agreed to work together to develop armamentaria against COVID-19, including testing procedures, vaccines, and anti-viral agents[1]. Nevertheless, cooperation and partnerships between private and public entities are less than expected. Industry and academic research laboratories have failed to develop safe, effective, and affordable anti-coronaviral medications and vaccines for previous epidemics, which demonstrates some of the technological difficulties faced in responding to this pandemic. The field is also muddled due to competing interests and the greed of selling antiviral agents and vaccine that may not be safe, than using already available highly cost-effective and safe agents, as described here.

Vitamin D and the immune system

Over the years, vitamin D has been analysed through thousands of scientific studies. Vitamin D is not only a vitamin; once it is converted into its active form, it functions as an important steroid hormone that influences every tissue in the body. Food contains little vitamin D. Most of the vitamin D needs, therefore, are generated in the skin after exposure to solar ultraviolet B (UVB) rays in humans.

Having physiological serum 25(OH)D concentrations has been shown to be effective in preventing and alleviating many diseases, including the respiratory infections caused by coronaviruses[1]. Dietary habits, including the avoidance of dairy, vegetarian and vegan diets, and marked reductions (avoidance)in the intake of fat; insufficient exposure to sunlight; and excessive use of sunscreens or wearing clothing that prevents almost all skin exposure to sunlight, increase the prevalence of hypovitaminosis D[2,3].

Vitamin D deficiency is so common, it is a pandemic that affects over 2.5 billion people[4]. More than half of people, particularly those in industrialized western nations located away from the equator; they are vitamin deficient, especially during the winter months. Many randomized controlled trials (RCTs) have reported on the effectiveness of vitamin D in reducing the prevalence and severity of respiratory tract infections such as influenza[5,6].

Mechanisms of action of vitamin D that enhance immunity

Calcitriol, the active form of vitamin D, has several independent mechanisms that positively modulating the immune system—the body's natural defence system. Mechanisms include the production of the anti-microbial peptides cathelicidin and defensin stimulation of the defensive actions of white blood cells, natural killer cells, macrophages, and epithelial cells in the respiratory tract[7,8]; and generation of neutralizing antibodies against invading pathogens[9]. Collectively, these reduce viral replication and increase the rate of elimination of viruses and bacteria[10]. In addition, vitamin D has anti-inflammatory, antioxidant, and favourable stabilization effects on cell membranes[11].

Vitamin D also reduces inflammation and cytokine storm[12] and protects cells, especially the vulnerable epithelial cells in the lungs, thus reducing the risks of acute respiratory distress syndrome (ARDS) and pneumonia. Calcitriol, also down-regulates the renin–angiotensin hormonal system (RAS) and thus reduces the entry of COVID-19 into human cells through the angiotensin-converting enzyme 2 (ACE-2) receptors in lung and on mucous membrane cells[13,14], which is a key target site in preventing the virus from entering the body[1].

Additional benefits of vitamin D

Several studies have reported that vitamin D sufficiency leads to less cancer and fewer heart attacks[15] and also reduces *all-cause mortality*[16,17]. For those who live in northern latitudes, in the absence of taking vitamin D supplements during winter, serum 25(OH)D concentrations will gradually decrease. Most people would experience vitamin D deficiency and thus have less-robust immune systems[18,19], which increases their vulnerability to respiratory track, viral infections[20,21]. In addition to reducing the risks of metabolic disorders and chronic diseases, such as cancers, cardiovascular disease, chronic respiratory tract infections, hypertension, and diabetes mellitus[22,23], vitamin D reduces the risks associated with bacterial and viral infections[24,25].

In addition, vitamin D has important physiological effects on maintaining the tight junctions in epithelial tissues and preventing viral entry; destroying bacteria and viruses via the antimicrobial peptides cathelicidin and defensins; maintaining a physiological balance of cytokines and antioxidants, mitochondrial respiration, and enhancing the activity of the innate immune system[10,26]. Collectively, these effects prevent the occurrence of cytokine storms and their associated risks.

Observational and intervention (supplementation) clinical trials provide evidence of strong associations

of higher serum 25(OH)D concentrations with reduced incidence of influenza, respiratory syncytial virus infections, herpesvirus, hepatitis B and C viruses, dengue, human immunodeficiency virus, and pneumonia[27]. Current evidence suggests that higher serum 25(OH)D concentrations reduce the incidence, and severity, and deaths associated with COVID-19[28].

Broader functions of vitamin D

Vitamin D has broader physiological functions. In addition to the beneficial immune system effects, vitamin D adequacy reduces musculoskeletal disorders, the severity of metabolic disorders, autoimmune diseases, and cancer; improves reproductive biology; and promotes gene transcription[29,30]. Vitamin D is involved in skeletal mineralization and bone formation, controlling cell proliferation and maturity, the prevention of cancer, brain development, mitochondrial energy generation, and respiratory and anti-oxidant functions[1,31]. Several of these functions are relevant to the control of COVID-19 infection.

1,25 dihydroxyvitamin D [1,25$(OH)_2$D] is an immune modulator; works in conjunction with controlling inflammation[19], through suppressing the expression of inflammatory cytokines and increasing beneficial cytokines[32]. In addition, calcitriol enhances the actions of transcription factors that are involved in the physiological functions of the lungs, including cyclic AMP receptor response element binding protein 1 (CREB1) a transcription factor and cyclic AMP response element binding protein complex (CRE-CREB-BP), involved in activation of renin gene (the rate limiting step of RAS) regulation[33], hypoxia-inducible factor α2 [HIFα2]-Epas, and SMAD4, and vitamin D receptor (VDR)[34]. Therefore, it is not surprising that vitamin D deficiency increases the risk of infections, especially viral infections in the respiratory system[35].

Winter, viral epidemics and hypovitaminosis D

Respiratory tract infections are most common during the winter and in cold weather conditions[36]. Most people do not expose their skin to sunlight in cold weather. Even then, the winter, sunlight has little UVB rays, and those reaching the earth come at an angle that prevents the rays from penetrating the skin surface. During the drier winter periods, when sunlight and temperatures are low, most viruses live longer outside the body. Because of these combined effects, serum 25(OH)D concentrations are lower during the winter, and respiratory tract infection prevalence is the highest among people living in northern latitudes[37].

Higher serum 25(OH)D concentrations correlate with lower rates of cancer, diabetes, high blood pressure, asthma, cardiovascular diseases, preeclampsia, autoimmune diseases, depression, anxiety, and sleep disorders[15,23,38]. Vitamin D is known to activate more than 200 key genes[39,40]. Having darker skin and living in northern countries can lead to prolonged hypovitaminosis D, which has major disadvantages with regard to procreation and survival, and detrimental if one contracts COVID-19. Because of the weather, people migrated to Europe from central Africa were not getting adequate amounts of sunlight to generate vitamin D. This became worse due to the adoption of diets predominantly consist of grain, instead of fish and meat that they used to. From an evolutionary point of view, those who acquired mutation and develop lighter skin had a major survival advantage, enabling them to colonized the northern communities[10]. However, this did not apply to indigenous circumpolar people of the Arctic (Eskimos; Inuit), who continue to eat fatty fish containing vitamin D on a daily basis.

Efficacy of vitamin D on respiratory viral diseases

Data related to COVID-19 are still emerging. However, a substantial data, based on studies of other coronaviruses suggest that the rate of infection and mortality associated with COVID-19 are likely to be inversely related to population serum 25(OH)D concentrations. Rates of infection are highest among people with serum 25(OH)D concentrations that are less than 10 ng/mL (25 nmol/L), which is by definition considered as severe vitamin D deficiency[41-44].

In addition, those with serum 25(OH)D concentrations of less than 10 ng/mL (25 nmol/L) have higher morbidity and the most acute respiratory tract infections[5,45,46], chronic obstructive pulmonary disorder (COPD)[46], and bronchitis[5]. Moreover, vitamin D has a protective effect against the severity of asthma[47]. In addition, calcitriol enhances the mitochondrial functions, including the capacity for its antioxidant activity, respiration that generate energy[11,48,49], and apoptosis. Figure 1 summarizes the key pathways involving in reduction of respiratory viral infections and associated complication with vitamin D adequacy.

Relevance of vitamin D to lung epithelial cells

Previous research suggested that the ACE-2 signaling pathway is involved in the worsening morbidity and mortality associated with sepsis-induced and acute lung injury models[50]. However, recent data refute this and support beneficial functions of ACE-2, including reducing the concentration of angiotensin-II, increases vasodilatory peptide angiotensin$_{(1-7)}$ and minimize cytokine storm[51,52]. In lung cells, in an animal model, activation of VDR by calcitriol attenuated the worsening of acute lung injury; it was suggested that this happen through the blocking of the Ang 2-Tie-2-MLC kinase pathway and the RAS[53,54]. Independently, calcitriol regulates the expression of RAS, which consists of renin, angiotensin 1 angiotensin-converting enzymes (ACE and ACE-2), and angiotensin II.

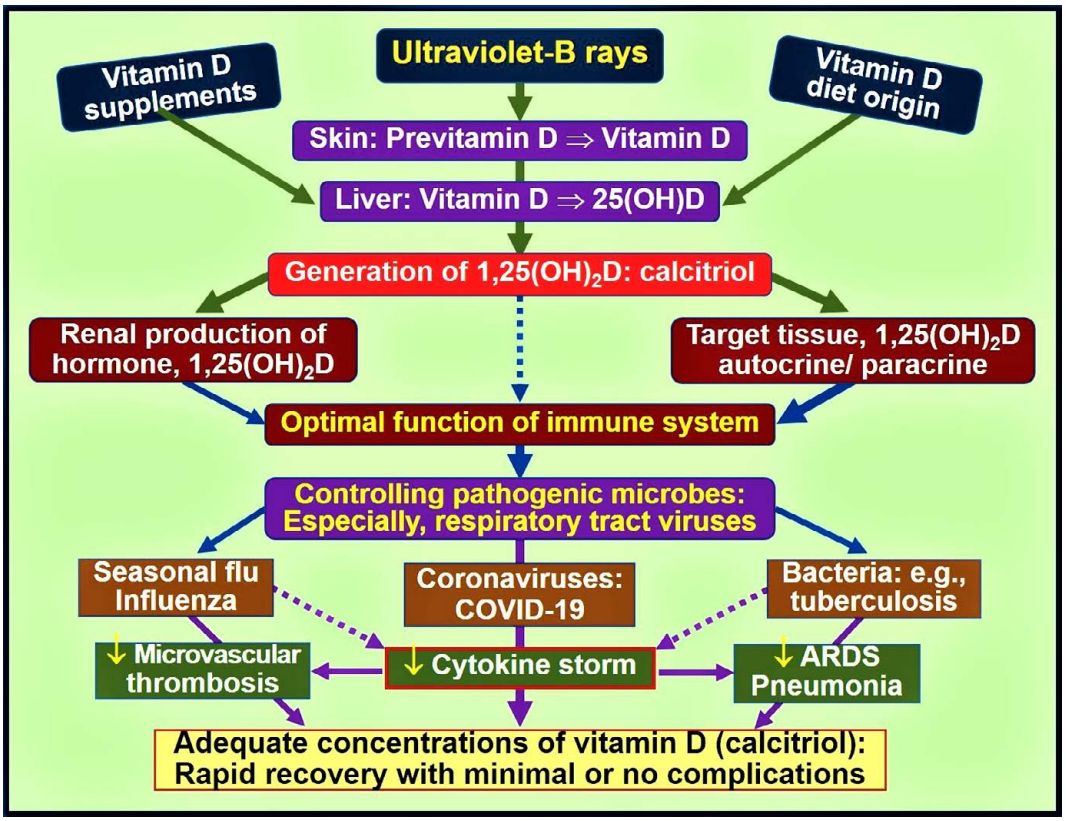

Figure 1: The major source of vitamin D, generation of previtamin D is through the conversion of 7-dehydrocholesterol following the exposure to UVB rays. The final activation step of 25(OH)D into 1,25(OH)$_2$D (calcitriol) occur both in renal tubular epithelial tissues and in target tissues cell. The latter is most important for optimal immune and other autocrine and paracrine functions of calcitriol. Having physiological levels [i.e., serum 25(OH)D concertation above 30 ng/mL (75 nmol/mL)] protects against respiratory viral diseases.

Maintaining a regulatory balance of the RAS through vitamin D sufficiency also exerts a protective effect on lipopolysaccharide-induced toxicity and the viral-mediated lung injury associated with severe acute respiratory syndrome (SARS) coronavirus[55,56]. More than a decade ago several publications by Penninger et al and others demonstrated that ACE-2 acts as a functional receptor for the SARS coronavirus family of viruses[56-59].

The action of endocytosis of SARS-CoV-2, follows it binding to ACE-2 receptors in epithelial cells, it downregulates the expression of ACE-2. This reduction of the availability of ACE-2, otherwise would proteolytically cleave excess angiotensin-II into a shorter form, angiotensin$_{(1-7)}$, increase the vulnerability for the cytokine storm. The latter has a potent vasodilatory function, opposite that of angiotensin-II. It dilates blood vessels, reduces intravascular pressure, and prevents pulmonary hypertension and the development of ARDS.

Protective mechanisms--ACE-2, vitamin D, and lung epithelial cells

The tight junctions of epithelial cells not only allow the passage of substances and fluid transfers across membranes (i.e., acting as a tissue barrier) but also prevent microbes, especially viruses[60]. Vitamin D in conjunction with other micronutrients, such as selenium and zinc, strengthen the physiological functions, as a safety barrier of tight cell junctions in the epithelial cells[61,62].

Controversy exists as to whether ACE and angiotensin receptor blockers (ARBs) hurt or benefit the recipients with reference to COVID-19[63,64]. Although this issue is not fully resolved, current evidence suggests that increase expression of ACE-2 is beneficial in controlling coronaviruses[65,66]. However, it can be a dual-edge sword. One could suggest that the theoretical increase of the available ACE-2, in part due to upregulation following the use of ARBs and ACE, might enhance the rate of COVID-19 entry into the lung cells via the ACE-2 receptor, thus potentially worsening the condition. Current data do not support this view. Excess ACE-2 spills into the bloodstream as a soluble receptor and likely acts as a decoy receptor for COVID-19, thus reducing the active viral load.

In fact, this ACE-2–COVID-19 attachment in the circulation neutralizes the virus and prevents it from reaching ACE-2 receptors in lung epithelial cells. Virus can replicate only within a host cell. Because this binding is occurring in extracellular fluid, the virus cannot

replicate[67,68]. Therefore, contrary to some publications and comments, the *in vivo* upregulation of ACE-2 likely mitigates the effects of COVID-19. Nevertheless, the outcome effects of the ACE remain a matter of controversy.

Vitamin D doses needed to maintain serum 25(OH)D concentration to overcome infections

In many nations, most of the population is vitamin D insufficient or deficient. However, the cause varies among countries. The most common cause is insufficient exposure to summer-like sunlight. This is because of sun avoidance, having darker skin colour, and/or geographic latitude. In addition, some groups are inherently vulnerable, including the elderly and the disabled, the obese, certain ethnic groups, and those taking medications that enhance the catabolism of vitamin D.

Multiple regimens can be used to increase serum 25(OH)D concentrations to reduce the risk of infections. For example, administering 10,000 IU/day (250 micrograms) daily or 50,000 IU capsules once a week for a few weeks or between 200,000 and 400,000 IU as a single dose would raise the blood vitamin D concentration relatively quickly. However, doses between 400 and 1,000 IU per day will not raise the serum 25(OH)D concentration quickly and adequately; such will takes several months or a year to (or may not) increase the serum concentration to a protective level. In emergency situations, larger doses are needed to rapidly raise serum 25(OH)D to build up the immunity to prevent illness.

Such doses should be followed up with suitable maintenance doses to prevent the level from decreasing to baseline values. Whatever the dose and frequency of administration, the goal is to increase serum 25(OH) D concentrations above 40 ng/mL (100 nmol/L) and maintain it at that level. Keeping individual and population serum 25(OH)D levels in excess of 40 ng/mL (100 nmol/L) will maintain the overall immunity by stimulating multiple immune mechanisms. From a nutritional point of view, a combination of vitamin D and other nutrients, such as vitamin K_2, vitamin A (and a smaller dose of C), magnesium, zinc, and selenium are more beneficial than are of those components individually (a synergy)[69,70].

Supplementing with oral vitamin D is likely to be the most cost-effective intervention for curtailing disease. The efficacy of such supplementation is comparable to an effective vaccine but much safer and economical to use. For the cost of providing intensive care unit care for one individual with COVID-19 (with costs varying from $10,000 to $125,000). This amount is adequate to protect more than 10,000 people, using any of the oral vitamin D supplement regimens described. Despite this, only few are using this simple intervention to protect themselves.

Alternative ways of achieving the needed concentration of vitamin D in blood

In sunny countries, most people can achieve appropriate serum concentrations by exposing one-third of their skin surface to direct sunlight (not through windows because glass filters a significant amount of UVB rays) for more than 30 minutes each day (can be 10 minute segments), preferably between 10 AM and 2 PM. During this period, the angle of the sun's rays is narrow enough to penetrate the skin surface. After midday, the temperature and humidity often are too high to be out in the sun in equatorial countries. The amounts of vitamin D generated in the skin is dependent on the darkness of the skin (density of melanin pigment), the exposed dose of UVB rays, and the time of the day and the month. Nevertheless, mentioned doses of vitamin D could generate an adequate amounts of 25(OH)D and calcitriol to boost the immunity in most people[69].

A complementary effective option is to mandate that food preparers and manufacturers fortify certain staple food items with specific, high doses of vitamin D until the outbreak is over. Such specified amounts should be at least four to six times greater than the normally recommended amounts. After the outbreak, the levels of fortification can be returned to generally recommended levels. The goal is to bring the serum vitamin D concentration in the nation above the mentioned protective levels to combat against, and overcome COVID-19, which is in excess of 40 ng/mL (100 nmol/L)[1]. This is another cost-effective intervention.

Benefits and cost-estimation of vitamin D supplementation and micronutrient food fortification to overcome COVID-19

Micronutrient supplementation programs using targeted food fortification are highly effective in alleviating specific nutritional deficiencies[71]. Over the past few decades, such programs have been successfully employed with iodine, iron, calcium, vitamin A, etc., to overcome micro-nutritional deficiencies[70]. Alternatively, a combination of micronutrients can be supplied: vitamin D_3, vitamin K_2, and antioxidants[72,73], based on the deficiencies in the community. One can also add, vitamin A and C, essential fatty acids such as omega 3, iron, iodine, and magnesium, a combination that enhances the efficacy of vitamin D in boosting the immune system[70]. Vitamins A, D, E, and K are fat soluble and therefore, one requires certain amount of fat in the diet with the supplement to enhance absorption[74,75]. One should not forget the importance of consuming natural anti-oxidant that are present in most of the coloured vegetables[62]. Except vitamin D and perhaps vitamin B_{12} most other essential vitamins can be obtained through a balanced diet[71].

Supplementation of vitamin D and/or focussed food

fortification with micronutrients, when targeted properly are highly cost-effective interventions[71]. Therefore, not only governments but also industries and companies and larger departments with many employees should consider utilising such approaches to maintain vitamin D sufficiency in their employees through their employee health offices. Employee should be provided the opportunity for sun exposure at staggered times during working hours, and either provide or reimburse employees to obtain micronutrient supplements[19] to improve health[62]. This is likely to reduce sicknesses and absentees of employees and thus, improve productivity. This can be accomplished by facilitating employees.

In food fortification programs, enrichment of nutrients adds, approximately 2% to the total cost of the food, but a higher benefit in disease risk reduction[71]. These programs provide major population health benefits[76]. This extra cost should be absorbed by the manufacturers of fortified food and through the increased turnover of enriched food products. Under ordinary circumstances, the best way to obtain micronutrients is via an affordable balanced diet. Expensive organic food does not increase nutritional value of food. A targeted micronutrient programs for commonly consume fortify food by most people should be provided to the communities in need.

Cost-effectiveness and the efficacy of broader vitamin D supplementation programs

Oral vitamin D supplements, doses between 2,000 and 5,000 IU per day or taking 50,000 IU capsules, one every other week to enhance the immunity will cost less than $8/person per year on individual basis: other essential micronutrients might cause an addition $15/person, per year. However, in emergency situation as with COVID-19, larger community-based programs can be set up to provide higher doses of vitamin D (e.g., between 200,000 and 400,000 IU in liquid formula per person) to protect them from the virus, costing around $0.50 per person. Considering the overall benefits, including the prevention of COVID and its complications and deaths, such programs considered extremely cost-effective. For comparison, the costs of treatment in an intensive care unit for a patient, is between $10,000 and 125,000 (USD).

On average, rectifying vitamin D deficiency costs less than 0.1% of the cost of investigations and treatment of worsening comorbidities and complications associated with hypovitaminosis D, including COVID-19[11]. In comparison, the average cost of managing a vitamin D deficiency-associated disease (e.g., diabetes, obesity, multiple sclerosis and related complications) is between $6,000 to $18,000/year, while the cost of ameliorating hypovitaminosis D is approximately $8 per person/year[19]. Despite the high benefits relative to the cost of correcting vitamin D deficiency and the reduction in comorbidities and complications, a large number of people are significantly suffering from this easily treatable vitamin D malnutrition.

There is no one standard formula to implement the above-mentioned, as the needs vary in different population. In the case with vitamin D, the gold standard is to achieve and maintain the population serum 25(OH) D concentration above 30 ng/mL (Optimal range, between 30 and 60 ng/mL; the targeted average of 40 mg/mL). In the era of COVID-19, vitamin D supplementation is the most cost-effective public health intervention not only to overcome COVID-19 but also to prevent and improving both acute and chronic diseases. These approaches will markedly reduce the overall health care costs[19].

Considering the immense benefits to the society, it is considered unethical for governments and healthcare providers not addressing this issue (and refusing to reimburse) highly effective, easily preventable nutritional disorder. In addition to the loss of lives, the opportunity cost for not doing so can be several orders of magnitude higher. For example, an island nation like Sri Lanka, with a population of 21.6 million, everyone above are 10 years should have been protected using oral vitamin D at a total costs of $2.4 million: a fully feasible program. This cost was equivalent to the loss of opportunity costs over a 6-hour period during the COVID-19 pandemic. If such a program was implemented by the government, lockdowns and curfews would have been totally unnecessary, including the current, second wave of COVID 19. Despite this, government failed to take such opportunities and led a path to an economic destruction, mass-scale human misery, massive unemployment, and increase deaths.

Conclusion

Having a balanced diet, especially with adequate quantities of micronutrients, such as vitamin D, vitamin K_2 and C, trace minerals, and antioxidants, will lead to maintaining a strong immune system. In most countries, certain communities have one or more micro nutritional deficiencies that increase their vulnerability to disorders, such as metabolic, communicable, and non-communicable diseases. In addition to nutrient supplementation, fortification of foods with vitamin D and other essential micronutrients will have a significant impact on overall health and disease prevention[71,76]. Most of the disease spread, prediction models (e.h., RO) related to COVID-19 in 2020, miserably failed[77], so as the lack of availability of safe, effective, and affordable antiviral agents and vaccine against COVID-19, making the situation worse.

As described, maintaining serum 25(OH)D concentrations above 40 ng/mL (100 nmol/L) is known to significantly reduce microbial infections, particularly respiratory, including COVID-19. Enrichment of food is an

economical and effective approach for the alleviation of micronutrient malnutrition in a target population or for an entire country. In the case of COVID-19, those with vitamin D deficiency is the most susceptible group, in part because of weaker immune systems. A nationwide campaign must be launched immediately to strengthen the immunity of the populous. This can be achieved cost-effectively by proper guidance on sun exposure using the mass media, supplementation, and targeted food fortification.

Abbreviations

Angiotensin-converting enzyme 2 (ACE-2)

Acute respiratory distress syndrome (ARDS)

25-hydroxy vitamin D [25(OH)D]

1,25 dihydroxyvitamin D [$1,25(OH)_2D$]

COVID-19 (SARS-CoV-2)

Renin–angiotensin hormonal system (RAS)

Randomized controlled trials (RCTs)

Ultraviolet B (UVB) rays

Vitamin D receptor (VDR)

Conflicts of Interest

The author declares no conflict of interests. He received no funding for this work or assistance in professional writing for this article.

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