



Prospects of vitamin D in the treatment of COVID-19 patient and improving maternal and child health during pandemic

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic is supposed to cause vitamin D deficiency in many people by a direct effect of home quarantine in the affected countries. Generally, vitamin D provides human body with significant health benefits including bone development, specific gene regulation and protection against different diseases. However, deficiency of optimal amount of vitamin D inside human body may result in susceptibility to multiple infectious diseases. Therefore, with vitamin D levels gravely decreased by reduced movement and activity, a number of possible negative outcomes are expected in COVID-19 patients, pregnant women and children during this ongoing pandemic. Vitamin D has a direct inhibitory effect on post infection through a number of mechanisms that promises to make vitamin D a future adjunctive therapy for COVID-19 treatment. Besides, clinical evidence also supports its role in preventing pregnancy complications and improving pregnancy outcomes. Consistent with the manifold role of vitamin D, an increasing number of studies suggest its role in improving the mental health of children who have been adversely affected throughout this pandemic. This review article discusses the potential roles of vitamin D on COVID-19 patients, pregnant women and children focusing its scope to become a supplementary candidate for these vulnerable groups to combat the ongoing pandemic.

INTRODUCTION

The world is now in the merciless clutch of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) outbreak, which is causing exceedingly higher number of deaths of people than any other coronavirus outbreak that the world has witnessed before. SARS-CoV-2 is a novel enveloped RNA beta coronavirus with 79% genetic similarity with SARS-CoV and 50% with MERS-CoV and causes similar clinical manifestations such as pneumonia, fever, dyspnea and acute respiratory distress syndrome (ARDS) as Severe Acute Respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [1].

The virus has spread so rapidly in almost every country and territories of the world from its origin in Wuhan, Hubei Province, People's Republic of China, that it has caused more than 2.3 million deaths along with 107 million confirmed infected cases during the time of writing [2].

Being highly transmissible, this contagious virus presents an alarming threat to the people of affected countries. As a result, the infected countries have employed emergency measures like social distancing and lockdown to reduce the spread of the virus which has forced almost two-third of the global people into quarantine. These complementary restrictive measures

have dramatically changed the daily routines of people in affected countries which has again raised the concern of alteration of their normal metabolic pattern. For example, vitamin D is primarily produced inside human body upon sunlight exposure. However, due to staying at home for months and consequently having a reduced sunlight exposure, the drop in serum vitamin D level in people who are experiencing the prolonged lockdown or other movement restrictions during this pandemic is expected to be analogous to that seen in winter.

Vitamin D plays significant roles in maintaining body health in different ways such as by preventing cardiovascular diseases, cognitive deterioration, Type 1 and Type 2 diabetes, by improving the development of autoimmune diseases as well as by participating in immune regulations [3,4]. Likewise, low levels of vitamin D has been linked to hypertension, cognitive impairment, glucose intolerance, increased autoimmune and infection rate [3,4]. Vitamin D has been observed to limit rhinovirus replication, attenuate Respiratory Syncytial virus (RSV) and lessen the risk of developing influenza, advocating its role against respiratory RNA viruses [5, 24]. Regarding COVID-19 susceptibility and maternal health, the immunomodulatory effects of vitamin D are well acknowledged [6,7]. Moreover, low levels of vitamin D have been linked with many pregnancy complications in different studies [7]. Therefore, any imbalance in vitamin D profile caused by prolonged lockdown in COVID-19 patients and pregnant women may lead to undesirable consequences. Additionally, months of social isolation and restricted out-of-home activities have left many children struggling with their mental health. Children are constantly exposed to COVID-19 updates and have to battle with their hurled-up emotions over a number of reasons like loss of a close one. Consequently, there is a sharp incline in mental health issues among children and adolescents following the COVID-19 outbreak [8]. Different studies have also suggested the potential roles of vitamin D in improving mental health [9]. With only a few globally approved, licensed vaccines and specific antiviral drugs, this pandemic calls for effective adjunctive therapy. As the virus spreads in new geographical areas and a potential vaccine being available to the mass population is both time consuming and costly, cost-effective supplementary therapeutic candidates such as vitamin C and honey have already been recognized for their pharmacological effects against SARS-CoV-2 [10,11].

Recent epidemiological data on COVID-19 and a century worth of research behind vitamin D suggest that it could be a potential, complementary therapeutic agent in mitigating COVID-19 [24,26,27,30].

Here, we sought to explore the possible roles of vitamin D in the treatment of COVID-19 patient and improving maternal health. Herein, we also discuss the beneficial aspects of vitamin D on children's mental health which is at risk or adversely affected by this continuing global crisis.

GENERAL ROLES OF VITAMIN D IN HUMAN

Vitamin D is classically recognized for its role in calcium absorption and in bone mineralization. Deficiency of vitamin D is known to cause myopathy, osteoporosis, osteomalacia, sarcopenia, rickets, juvenile as well as rheumatoid arthritis [12,13,3].

The largest organ, skin, is the site of synthesis of vitamin D. Ultraviolet B (UVB) rays of wavelength 290 to 315 nm drive the cutaneous synthesis of pre-vitamin D₃ from 7-dehydrocholesterol (7-DHC) (Figure 1). Vitamin D₃ formed from thermal isomerization of pre-vitamin D₃ is hydroxylated once by 25-hydroxylase in the liver to form the relatively inactive metabolite, 25-hydroxyvitamin D (calcifediol). The second hydroxylation is mediated by 1 α -hydroxylase in the kidney to form the active hormone, 1,25-dihydroxyvitamin D (calcitriol) [5]. While cutaneous synthesis accounts for most of the vitamin D, diet provides only a minor portion of the required amounts of vitamin D in the human body. Moreover, except for a few dietary sources such as fatty fish, egg yolk and mushrooms, most of the common foods do not contain vitamin D. Afterwards, the vitamin D metabolites bind to its primary transport protein called Vitamin D binding protein (DBP) present in the blood plasma for systemic transport to the target organs. Ultimately, all biological actions of the hormonal form of vitamin D (calcitriol) in the target cells are mediated by a transcription factor called Vitamin D receptors (VDRs) present on the nuclei of most cells. Binding of the ligand calcitriol to VDR on the nucleus modulates cell-specific gene expression. Most cells in the body, including skin, heart, stomach, brain, pancreas and activated B and T cells have nuclear VDR [14]. Upon binding of Calcitriol with VDRs, the retinoic receptor of the heterodimer VDR subsequently binds to the Vitamin D response element

(VDRE) in the promoter of vitamin D regulated genes [5]. This modulates 3–5% of the human genome, enabling vitamin D to exhibit pleiotropic effects [15].

Despite utilizing the largest organ with large surface area for UVB exposure, vitamin D synthesis is strictly dependent on both the amount of UVB reaching the dermis and the amount of 7-DHC present in the skin. This is because dietary vitamin D intake does not suffice the recommended optimal vitamin D levels as does synthesis of endogenous vitamin D. Epidermal

concentration of 7-DHC declines with age, placing elderly population under an increased risk of developing vitamin D deficiency [16]. Co-incidentally, the severity of COVID-19 also increases with aging. The amount of UVB penetrating the dermis is hindered by the type of clothing, sunscreen, season, altitude and type of day-to-day activity, time spent away from windows, or outside as well. As a result, being house bound for long durations greatly suppresses cutaneous synthesis of vitamin D.

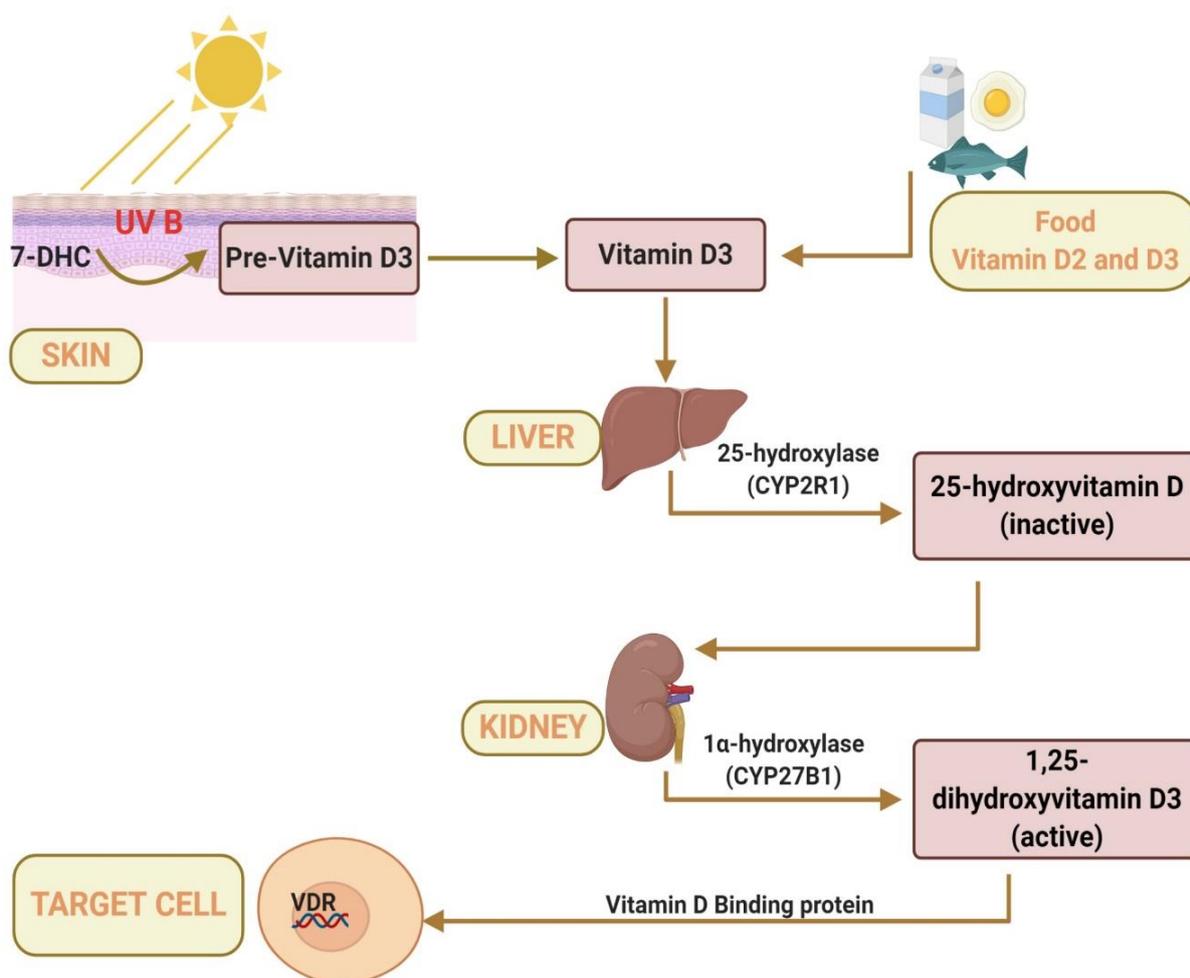


Figure 1. The metabolic pathway of Vitamin D. In the skin, 7- dehydrocholesterol absorbs UVB and is converted to pre-vitamin D3. Pre-vitamin D3 then rapidly transforms into vitamin D3. Dietary vitamin D can be in the form of vitamin D2 (animal source) and vitamin D3 (plant source). The vitamin D is hydroxylated once in the liver and a second time in the kidney. The active metabolite, calcitriol, then travels in blood with the help of vitamin D binding protein to target cells. UVB: Ultraviolet B, VDR: vitamin D Receptor, CYP2R1: Cytochrome P450 Family 2 Subfamily R Member 1, CYP27B1: Cytochrome P450 Family 27 Subfamily B Member 1. The figure was created in BioRender.com and imported under the terms of premium subscription.

The presence of VDR in most cells of the body indicates that the extra skeletal effects stretch far beyond calcium absorption and bone health. Among many pathways that calcitriol regulates, a significant number is devoted to antineoplastic actions and thus plays a crucial role in preventing cancer progression [15]. Besides these, different studies have revealed the association of vitamin D deficiency with variety of diseases including cardiovascular diseases, type 1 and type 2 diabetes mellitus and multiple sclerosis [3].

Additionally, vitamin D plays crucial roles for different groups of people like children, adolescents and pregnant women who are the center of attention during the ongoing pandemic. Expression of VDR by almost all cells and the enzyme that converts calcifediol to calcitriol by some immune cells indicate vitamin D's role in modulating both the innate and adaptive immune system [4]. This key enzyme and VDR are also expressed by the cells present in placenta reflecting its potential roles during pregnancy [17]. Vitamin D, being able to bind to VDR in neuronal and glial cells, highlights its neurosteroid function in the central nervous system and hence in mental wellbeing [18]. Above all, the multiple roles of vitamin D in human body seem to be seemingly important with other dietary metabolites in order to maintain good body health. And therefore, the lack of synthesis of vitamin D due to reduced activity during this lockdown may leave one individual unhealthy and increase the risk of disease. With the general roles of vitamin D being described so far, the later part of this article sheds light on the necessity of vitamin D supplementation for regulating the immune system and for the mental wellbeing of children and women during pregnancy.

The half-life of circulating calcitriol is only 12 hours whereas it is about 2 weeks for 25(OH) D (Calcifediol) [19]. Therefore, serum 25(OH) D level instead of calcitriol is a reliable indicator of blood vitamin D levels. And thus, serum level of 25(OH) D above 30 ng/ml in serum is considered as ideal whereas less than 15 ng/ml is an indicator of vitamin D deficiency [4]. As long as blood level of 25(OH) D does not exceed 150 ng/ml, vitamin D intoxication is very unlikely to occur. Since blood level of 25(OH) D increases only by 1ng/ml for every 100 International Units (IU) vitamin D ingested, the daily recommended vitamin D intake for infants should be at least 400 IU, for children at least 600 IU according to both Endocrine Society and Institutes of Medicine and between 1500–2000 IUs for adults according to

Endocrine Society [20,21]. Considering the limited amount of sunlight exposure in this pandemic, these should be the minimum doses of every age range.

POTENTIAL ROLES OF VITAMIN D ON COVID-19 PATIENTS

In light of different epidemiological findings on COVID-19, a number of studies have discovered the correlations between the disease susceptibility and vitamin D levels. Assessing the prevalence of COVID-19 cases worldwide, it is revealed that people in countries with high latitude and colder temperatures and with low means of vitamin D are most affected [22]. In fact, the major coronavirus epidemics, SARS and COVID-19, all thrived in colder temperatures and disproportionately affected the people in these regions compared to those in comparatively warm and hot atmosphere [23].

A number of observational and clinical trials have shown that vitamin D supplementation could reduce the risk of respiratory diseases like influenza and direct correlations of low vitamin D levels and COVID-19 severity exist [24]. COVID-19 and influenza are both caused by respiratory tract viruses and both were very likely to reach their peaks in winter. Promising clinical trials with vitamin D supplements against influenza could also be extended to COVID-19. Moreover, people with tuberculosis share similar symptoms with COVID-19 patients. Cod liver oil, a rich source of vitamin D was used unknowingly as a remedy for Tuberculosis for its remarkable health-restoring ability [25]. Higher levels of calcitriol have shown to be effective in alleviating severe pneumonia [26]. Low 25(OH) D levels have also been related to high COVID-19 case-fatality rates, while increasing serum 25(OH) D levels have shown to abate the disease severity [27] indicating that vitamin D might play pivotal roles in reducing COVID-19 severity and death rates as well. Additionally, high doses of vitamin D3 on mechanically ventilated intensive care unit (ICU) patients have helped them get discharged from the hospital considerably earlier than planned in one study and have shown to increase mRNA expression of the Human Cationic Antimicrobial Protein (hCAP18) in critically ill, ventilated patients in another study, suggesting the effective role of vitamin D in post SARS-CoV-2 infection treatment [28,29]. Thus, suppressing severe pneumonia and disease severity could save patients on the brink of death. Moreover, reduced hospital stays and expedited

recovery time is not only a relief for the patient but also allows new patients to be admitted. This is particularly essential in this COVID-19 crisis as hospitals are brimming with patients and the healthcare system is facing challenges.

Besides the classical roles of vitamin D in maintaining homeostasis of calcium and bone metabolism, the

immunomodulatory effects of vitamin D have become clearer in last few decades. Hence, the deficiency of vitamin D can increase the susceptibility of a number of infections. For example, it is known to modulate 3 pathways during episodes of common cold i.e., physical barrier, cellular natural immunity and adaptive immunity (Figure 2) [30].

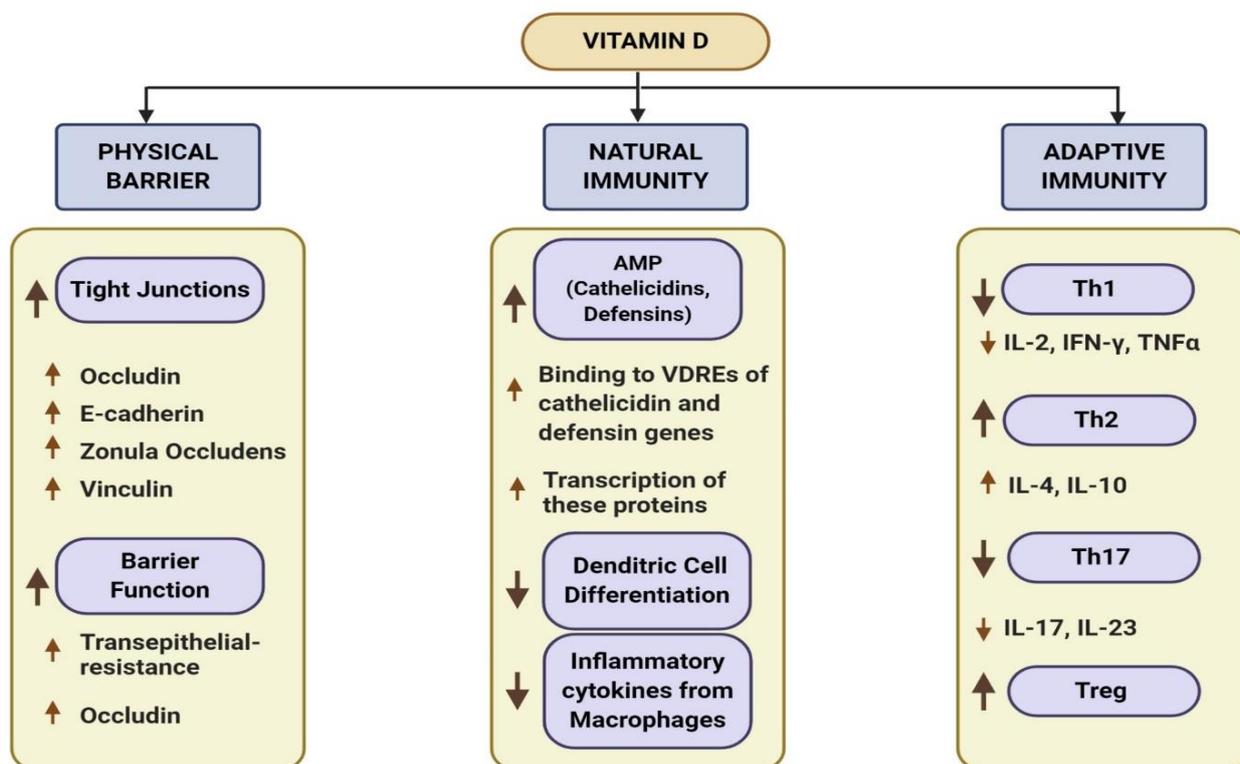


Figure 2. Immunomodulatory roles of vitamin D. Vitamin D improves barrier function by promoting tighter junctions and maintaining barrier function in the epithelium. It also enhances expression of Antimicrobial peptides and inhibits dendritic cells and macrophages from causing excessive inflammation. Again, Vitamin D downregulates Th1 and Th17 responses as well as upregulates Th2 and Treg responses to abate the cytokine storm. AMP: antimicrobial peptide, Th: helper T cell, Treg: regulatory T cell, TNF α : tumor necrosis factor, IFN- γ : interferon γ , IL: interleukin. The figure was created in BioRender.com and imported under the terms of premium subscription.

Calcitriol upregulates occludin, E-cadherin, vinculin and promotes translocation of “zonula occludens” that are essential for maintaining tight junction between epithelial cells [31]. It has also shown to contribute to epithelial barrier function by increasing trans epithelial resistance. As epithelial tissue is the entry site of SARS-CoV-2, barrier integrity is crucial which is oftentimes disrupted upon viral infection [32].

VDR, the receptor of calcitriol, is expressed in many immune cells of myeloid and lymphoid lineage, suggesting its role as an immunomodulator both in

autocrine and paracrine manner [33,25]. Following infection, macrophages use Toll-like receptors (TLR) to recognize foreign antigens. Binding of TLR causes enhanced expression of both VDR and the 1- α -hydroxylase, the enzyme that synthesizes calcitriol from serum 25-hydroxyvitamin D [34]. Metabolically active calcitriol binds to VDR which then recognizes and binds to VDREs in the promoters of genes that code for antimicrobial peptide (AMP) [35]. As a result, enhanced transcription of the human cathelicidin antimicrobial peptide (*camp*) and defensin β 2 (*defB2*) occur. Defensins and cathelicidins are body's host

defense peptides which act against viruses. Multi antiviral mechanisms of defensins target viral envelopes, capsids and inhibit viral replication, while cathelicidin have shown to inactivate virus and reduce influenza A viral replication in infected mice [36,37]. Moreover, vitamin D also improves innate immunity by acting as a potent inhibitor of dendritic cell differentiation and pro-inflammatory cytokine secretion from macrophages to prevent uncontrolled inflammation [38]. This is essential because infection by SARS-CoV-2 triggers a T helper1 (Th1) cell response leading to a dysfunctional immune response referred to as “cytokine storm” which is injurious to lung health [39]. In fact, COVID-19 severity is fueled by this pro-inflammatory “cytokine storm” in the lung lining leading to severe pneumonia and COVID-19 associated Acute Respiratory Distress Syndrome (ARDS).

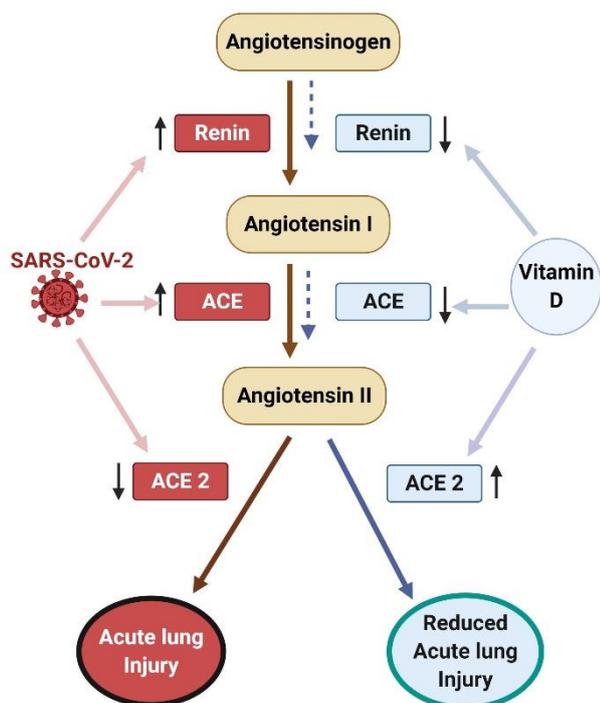


Figure 3. Vitamin D and Renin-Angiotensin System. The proposed therapeutic effect of Vitamin D as a negative regulator of the renin-angiotensin system that could reduce lung injury following SARS-CoV-2 infection. SARS-CoV-2 binds to ACE2 and causes a downregulation of ACE2. This increases Angiotensin II concentration and eventually leads to acute lung injury. Vitamin D, on the contrary, increases ACE2 concentration and thus lowers Angiotensin II concentration. ACE: angiotensin converting enzyme. The figure was created in BioRender.com and imported under the terms of premium subscription.

As a modulator of adaptive immunity, vitamin D inhibits production of inflammatory cytokines and

enhances cytokine production by the T helper type 2 (Th2) cells and thus causing the shift from Th1 to Th2 response [25,38]. It also suppresses the inflammatory Th17 response and induces Treg response and help preventing further havoc in the cytokine storm [25,40].

Vitamin D may also protect against COVID-19 severity by increasing the expression of angiotensin-converting enzyme 2 (ACE2) by the lung cells [41]. SARS-CoV-2 uses ACE2 receptor for entry into cells, a receptor that is found in most body tissues but with more prominent expression in respiratory, oral epithelial and alveolar cells [41]. Binding of the virus with ACE2 causes down regulation of the ACE2 receptors. As a result, less ACE2 remains that can degrade Angiotensin II known to increase blood pressure, cause ARDS and even myocarditis [41]. To prevent these adverse effects and multiorgan failure from COVID-19, the therapeutic approach of vitamin D is that it increases ACE-2 that then breaks down angiotensin II (Ang II) and suppresses ACE and renin expression that are essential for Ang II formation (Figure 3) [41,42].

Furthermore, an in vitro study demonstrated calcitriol’s effectiveness in reducing SARS-CoV-2 viral load in African green monkey Vero E6 cells [43]. The same study also reported that post-infection treatment of human nasal epithelial cells, the primary target of SARS-CoV-2, with calcitriol proved to be more beneficial than most other prophylactic compounds. This study showed a direct inhibitory effect of vitamin D against SARS-CoV-2. Thereby, with only limited and nonspecific current therapeutic agents, vitamin D may be an effective prophylactic combination of vitamin D3 and primaquine significantly reduces lung inflammation and alleviates inflammatory cytokines in pneumonia than primaquine alone, proposing its potential in treating pneumonia associated with COVID-19 [44]. Patients with ARDS often have damaged alveoli as the cells undergo apoptosis upon infection, greatly reducing their oxygen saturation. One study showed that vitamin D deficient mice had greater bronchoalveolar lavage fluid (BALF) cellular inflammation and hypoxia [45] suggesting that vitamin D could have positive impacts on severe ARDS patients. Overall, a notable number of in vitro and in-vivo studies are emerging that relate and show how vitamin D reduces post-infection viral load in infected cells and COVID-19 associated lung damage and examine more effectively than other prophylactic candidates. Although no animal studies have been conducted till now to directly state that vitamin D

could prevent the infection of COVID-19 in the first place, epidemiological trends of countries with high mean vitamin D levels and their corresponding low number of cases and the immunomodulatory effects of vitamin D can be considerable factors for its protective role.

ESSENTIAL ROLES OF VITAMIN D ON PREGNANT WOMEN AND INFANTS

Natural disasters and viral outbreaks affect the world in a similar fashion and thus most of them involve a common vulnerable group. For example, the pregnant women were hardest hit during the Spanish flu, the deadliest outbreak of the world so far but the reason behind it still remains a subject of debate [46]. The outbreak of Severe Acute Respiratory Coronavirus (SARS-CoV) was also linked to many pregnancy complications [47] and hence since most about the COVID-19 is still unknown therefore, the impact of the SARS-CoV-2 on pregnant woman cannot be entirely ignored. As a result, the pregnant women still remain another center of great attention and care during COVID-19 pandemic. Different studies have suggested that the influences of vitamin D in the maintenance of good maternal health during pregnancy and healthy infants travel beyond intestinal calcium absorption and bone metabolism. However, maternal 25-hydroxyvitamin D is significantly lower in black and Hispanic women than in white women as melanin competes with 7-DHC in absorbing UVB [48,49]. Although skin pigmentation and season are important determinants of vitamin D synthesis, it has been seen 84% of pregnant women in India had vitamin D insufficiency and 95.7% of neonates had hypovitaminosis D which is much unexpected in a tropical country with abundant sun exposure [50]. It can thus be reasoned that vitamin D insufficiency might be quite common during pregnancy all around the world [51].

Spending months inside a home in quarantine further diminishes serum 25(OH) D levels, the demand for which escalates as increasing levels of calcitriol is made throughout pregnancy [52]. This increased synthesis of calcitriol during pregnancy is not only to increase calcium absorption for fetal growth but also to provide the required amount of vitamin D for the fetus (Figure 4). Again, the fetal vitamin D levels are so strongly associated with maternal levels that vitamin D supplementation of pregnant women prevents neonatal vitamin D deficiency as evidenced

by cord blood vitamin D level measurement [53]. Both placental and decidual tissues are able to synthesize VDR and 1 α -hydroxylase [54]. The expression of these vitamin D signaling components increases during the first trimester and thus again suggests the increased synthesis of calcitriol and its potential roles in fetal development [54].

Calcium is indispensable for fetal bone mineralization and accounts for 30g of calcium in the fetal skeleton at term, most of which is derived from maternal nutrition [55]. If maternal intestinal calcium absorption is restricted, the fetus might derive its necessary calcium from maternal bone resorption resulting in maternal bone loss [56]. To prevent bone loss of the mother and to ensure proper skeletal mineralization of the fetus, the classical role of calcium absorption of vitamin D increases to double maternal intestinal calcium uptake (Figure 4) [57]. While some animal models demonstrate the lack of function of the components of vitamin D signaling in active transport of calcium and phosphorus across the placenta [58,59], another study suggests the possible role of VDR in placenta involved in transplacental calcium transfer as hypothesized from positive correlation between placental VDR and fetal femur length [60].

Moreover, maternal vitamin D deficiency can result in enamel defects, congenital rickets as well as craniotabes in neonates [61-63]. In addition to that, vitamin D has also been shown to be associated with fertility in mice [64] and in the regulation of HOXA10, a gene involved in embryogenesis and implantation [65,66]. Tolerance of the semi-allogeneic fetus possessing half of the genes from the father-throughout pregnancy might require the suppression of the adaptive immune system and enhanced stimulation of the innate immune system to compensate for the compromised immunity [54,67]. The immunomodulatory and immunosuppressive effects of vitamin D explained earlier could suggest a role in implantation tolerance. Calcitriol also induces the differentiation of endometrial cells into decidual cells, synthesis and secretion of human placental lactogen and regulates human chorionic gonadotropin, progesterone and estradiol secretion in trophoblasts, all of which are essential during pregnancy and any dysregulation may give rise to a number of complications [68-70].

Besides, vitamin D deficiency is correlated with a number of different adverse pregnancy outcomes. Pre-eclampsia and eclampsia are directly related to 10% to

15% of maternal deaths, with early onset preeclampsia increasing risk of maternal mortality by 20 folds [71,72]. Vitamin D deficiency is a significant risk factor of severe and mild forms of preeclampsia in pregnant women [73-76]. In fact, a 10 ng/mL increase in 25-hydroxyvitamin D in pregnant women has shown to cause a 63% decrease in risk of early onset of severe preeclampsia [76]. Vitamin D is also associated with an increased risk of low birth weight, Small for Gestational Age (SGA) babies and preterm birth [77-

81]. Again, supplementation of vitamin D has been shown to reduce the risk of gestational diabetes [82]. Moreover, optimal level of vitamin D during gestation is crucial for prenatal brain development and proper alveolarization. Mice progeny born to mothers with low 25(OH)D levels have unusual brain sizes and shapes due to uncontrolled neuronal proliferation (Figure 4) [83]. This backs up vitamin D's role in maintaining an orderly brain development, morphology and cellular proliferation in embryos.

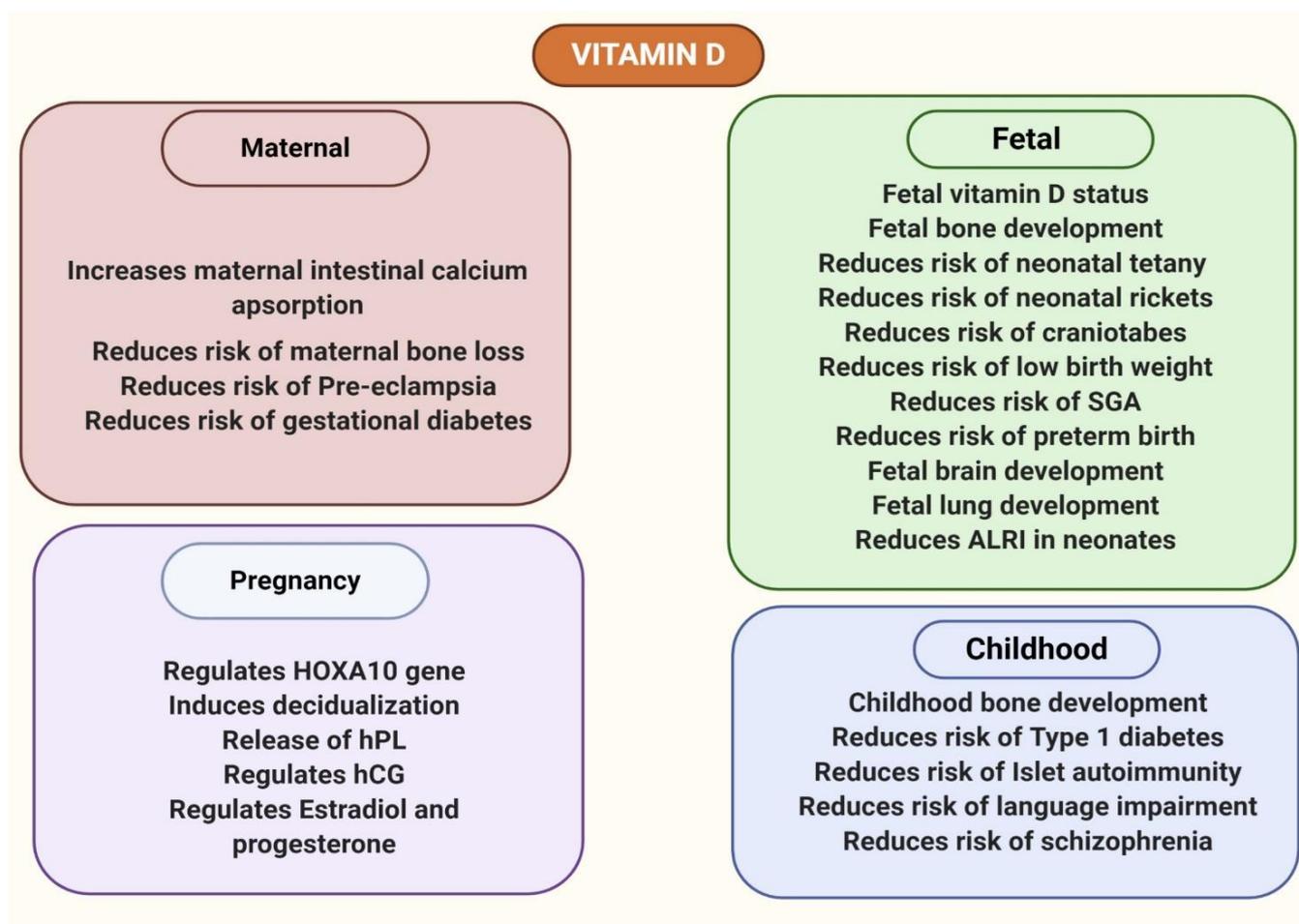


Figure 4. Possible roles of vitamin D regarding pregnancy as determined from clinical outcomes and mouse models: in maternal health, maternal-fetal interface, in the fetus and later life of the child. hPL: human placental lactogen, hCG: human chorionic gonadotropin, SGA: small for gestational age, ALRI: acute lower respiratory infection. The figure was created in BioRender.com and imported under the terms of premium subscription.

Maternal vitamin D also regulates proteins involved in surfactant synthesis and alveolar inflation in the fetus, a deficiency of which leads to low lung volume and stiffness in mice [84]. Lower surfactant levels and increased collagen deposition during alveolar development as shown in this study suggests its importance in pregnancy to prevent babies born with

impaired lung function and incidents like this during respiratory disease pandemic could be fatal. This is

particularly important as hospital transmission poses a risk factor to newborn babies, putting them in an increased risk of respiratory morbidity and debilitation if they are born with impaired lungs. Study has also linked low vitamin D status to

increased risk in acute lower respiratory infection in neonates [85]. Complication due to hypovitaminosis D during pregnancy does not end but even extends to health problems later in life of child. Vitamin D insufficiency of the mother during pregnancy does not only affect bone development of the child during childhood but also increases risk of developing type 1 diabetes and islet autoimmunity [86-90]. Language impairments in the child and schizophrenia have also been positively associated with maternal and neonatal vitamin D status [91-93].

Although little is known about the effects of COVID-19 in pregnant women, lessons learned from pregnancy complications of SARS-infected mothers indicate the emergency implication of necessary measures to improve maternal health in this pandemic. Miscarriage, preterm delivery and intrauterine growth restriction was seen among 12 patients who contracted SARS-CoV [47]. Mouse hepatitis virus, a species of coronavirus, has shown to be transmitted in utero from the infected mother mice to the mice fetus [94]. In humans, placental infection with SARS-CoV-2, miscarriage, maternal vascular malperfusion has been observed in pregnant women with COVID-19 [95-97].

Vitamin D deficiency is widely prevalent in pregnant women despite taking prenatal vitamins [98]. This, combined with only minimal exposure to sunlight during quarantine is supposed to greatly deplete serum 25(OH) D levels in pregnant women. In this case, 120,000 IU doses given at 20, 24, 28, and 32 weeks of gestation will be sufficient and safe for pregnant women with inadequate sun exposure [98]. Existing literature provide various implications of vitamin D in preventing pregnancy complications and improving postnatal outcomes. Taken together, the supplementation of vitamin D could be an alternative remedy to ensure good maternal and child health during this pandemic. However, little is known if maternal vitamin D has genetic or epigenetic effects on the developing fetus which offers new areas to be addressed to more effectively demonstrate the pivotal roles of vitamin D on pregnant woman, fetus and infant.

VITAMIN D SUPPLEMENTATION IN IMPROVING CHILDREN'S MENTAL HEALTH DURING COVID-19 PANDEMIC

To prevent the transmission of the highly contagious COVID-19, government of nearly all countries

implemented disease containment measures. Along with wearing masks, washing hands, maintaining social distance and avoiding public gatherings, the government has also ordered emergency school closure and home quarantine. All previous viral outbreaks of the world were reported to have psychological impacts on affected people i.e., post-outbreak depressive symptoms following 2003's SARS outbreak, high level of concern, worry and anxiety due to swine flu (H1N1) outbreak, post-traumatic stress disorder (PTSD) and anxiety-depression following the Ebola outbreak [99-102]. Although these quarantine policies are commendable to bring down COVID-19 infection rates, lack of social contact, and separation from school friends further threaten the mental health of children. Not only do these outbreaks cause panic and worry, but restrictive measures such as quarantine and isolation have caused PTSD in 30% children, boredom, isolation frustration, loneliness and depression in people who had been quarantined [103-106].

Many education institutions have shifted to online education providing remote and pre-recorded classes. Lack of in-person contact with peers, teachers and friends, separation from an infected family member, grief of a lost family member, fear of their parents losing their job or suffering financial crisis, exposure to endless reports of deaths is likely to worsen the mental health of a child. COVID-19 trauma might have similar psychological effects as childhood emotional abuse in children. Childhood trauma and emotional abuse lead to heightened stress in later life [107]. Many parents and teachers have reported seeing children become withdrawn and depressed especially due to at home classes [108]. Their inability to focus and learn are signs of depression that could prevail even later in life.

Besides quarantine, vitamin D status is also associated with psychological disorders. Evidence suggests that low vitamin D status is associated with depression and depressive disorder, attention deficit hyperactivity disorder (ADHD) in children, PTSD, low mood and impairment of cognitive performance [109-113]. Moreover, Vitamin D supplementation has been shown to lower the depressive symptoms in people with depressive symptoms [114,115]. COVID-19 trauma and vitamin D deficiency due to quarantine could have integrated negative effects on the mental health of children. Additionally, high pro-inflammatory cytokines, as in the cytokine storm induced by SARS-CoV-2, are involved in the

pathogenesis of severe post-traumatic psychiatric symptoms [116]. Prolonged imbalance of pro- and anti-inflammatory cytokines could have potential negative impacts in physical health. Suppressing CD4+ T cell cytokines and pro-inflammatory response mentioned previously, vitamin D aids in rectifying the imbalance.

The presence of VDR and 1 α -hydroxylase (CYP27B1) in both neurons and glial cells highlights neurosteroid function of vitamin D in the central nervous system and hence in mental wellbeing [117]. Calcitriol also might have an anti-neuroinflammatory activity as seen by its potential of reducing the production of inflammatory molecules in neuron-glia cultures [118]. It has also shown its anti-oxidative properties against reactive oxygen species to protect dopaminergic neurons [119]. Moreover, *in vitro* studies have revealed its role in the synthesis of nerve growth factor (NGF) and regulation of neurotrophin (NT) [120-122]. VDR is not only expressed in the brain micro vascular endothelial cells of the blood brain barrier [123] but is extensively distributed in many regions of the brain, namely in the cingulate cortex, limbic system, hypothalamus, cerebellum, hippocampus, and cerebral cortex [124,125], with many of the regions showed co-expression of both VDR and 1 α -hydroxylase [117]. VDR mutant mouse models exhibit anxiety-like behavior and vitamin D deficient mice have depression-like behavior, both of which have risen during the past couple of months in children [126,127]. This demonstrates how vitamin D could be a sole factor behind anxiety and depression.

Although many factors are thought to interplay in the pathogenesis of depression and have yet to be fully understood, advances have been made that have found potential links in the etiology of depression. Dysregulation of neuronal calcium signaling is linked to major psychiatric and neuronal diseases [128,129]. Vitamin D maintains neuronal calcium homeostasis by controlling the expression of genes involved in neuronal calcium signaling [130]. The long-discussed neurotransmitter, serotonin for its role against depression [131] is up regulated by vitamin D via inducing tryptophan hydroxylase 2 (TPH2), the gene responsible for synthesizing serotonin [132,133]. It has not only proved to enhance serotonin as well as repress serotonin reuptake in *in-vitro* serotonergic neuronal cells, exhibiting its antidepressant properties [134]. Thus, the ability of vitamin D in neuroplasticity and potentiation opens new insight in its role as alternative Selective Serotonin Reuptake Inhibitor

(SSRI) antidepressants. Another neurotransmitter, dopamine, is also well known for its role against the physiology of depression [135-137]. Calcitriol has shown increased dopaminergic neuron differentiation and the production of dopamine [138]. It also stimulates the expression of the antioxidant, glutathione and inhibits the expression of gamma-glutamyl transpeptidase, key enzyme of glutathione metabolism to prevent glutathione depletion and thus has a protective role against neurodegeneration [129,140].

Mitochondrial dysfunction, such as impaired oxidative phosphorylation and membrane polarity are linked to the onset of depression, whereas vitamin D has shown to increase oxidative function [141,142]. By reduction of Ca²⁺ level in the brain, increasing glutathione, inhibiting the toxicity of reactive oxygen species, inducing nerve growth factors, vitamin D exhibits its neuroprotective effect (Figure 5) [140].

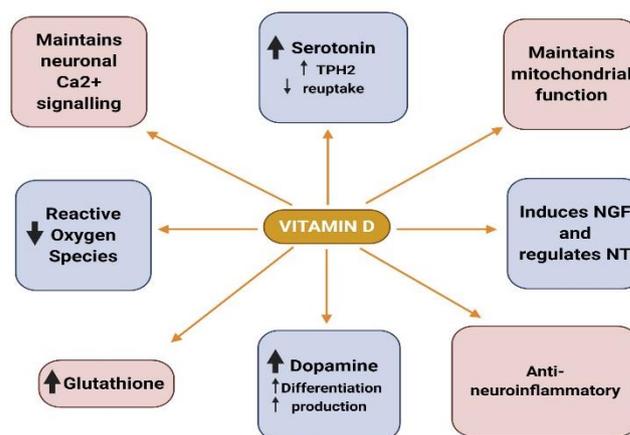


Figure 5. Possible roles of Vitamin D: protective role against depression and neuroprotection. By controlling neuronal calcium signaling, sustaining serotonin levels and enhancing dopamine production, vitamin D protects against major psychiatric diseases and depression, respectively. By reducing inflammatory molecules, increasing NGF and increasing oxidative function, vitamin D aids to maintain healthy neurones and prevent mitochondrial dysfunction respectively. NGF: nerve growth factor, TPH2: tryptophan hydroxylase 2, NT: neurotrophin. The figure was created in BioRender.com and imported under the terms of premium subscription.

Childhood and adolescence are considered as the window of opportunity for cognitive development and prolonged home quarantine and other restrictive measures may retard the developmental process. Consequently, these may give rise to many short terms and long-term psychological effects. Therefore,

preventing negative psychological outcomes of COVID-19 trauma is crucial to prevent predisposed children from developing depression and other disorders. Children dealing with forgetfulness, distraction and restlessness, the prominent signs of stress and anxiety could see changes in their mood and mental health by raising their 25(OH) D levels as shown in different studies. However, lack of direct clinical trials and human studies on exploring the roles of vitamin D on children mental health may require further interventions to establish vitamin D as protective candidate for children suffering from psychological disorders.

FUTURE PERSPECTIVES

Above all, the vitamin D status seems to be an individual risk factor for everyone as evidenced in different epidemiological and observational studies discussed earlier. But there is still lack of enough clinical experiments that can significantly draw the functional roles of vitamin D in preventing COVID-19 severity and reducing mortality. However, depending on the general roles of vitamin D and its function in maintaining good lung health and preventing infection of respiratory tract diseases, people can maintain balanced serum vitamin D level during this pandemic. Hence, it should be advisable for everyone to intake vitamin D supplements or consume fatty fish, or food fortified with vitamin D. Loading doses of 200,000-300,000 IU for vitamin D repletion and subsequent smaller doses according to age, gender and lifestyle is recommended to maintain vitamin D above 30ng/ml [32].

The effect of vitamin D on the cardiovascular and respiratory health in pregnant women suffering from respiratory diseases still remains poorly understood. The lack of studies of mental disorder in children should also be briefly mentioned. On the contrary, the importance of vitamin D in the nervous system is underappreciated, till now. The role of vitamin D in mental disorders is only extensively studied in older adults. Yet again, association between vitamin D deficiency and mental health is largely unexplored in children. More animal models and clinical trials should be conducted so the results can be extrapolated to children and pregnant women as well. Nonetheless, based on the extant literature, this article suggests that vitamin D could be a potential candidate for COVID-19 prophylaxis and complementary treatment. However, more animal studies and clinical trials are

needed to study the preventive effects of vitamin D against COVID-19. Moreover, it also appears to be a promising agent for combatting pregnancy comorbidities and ameliorating built-up anxiety and depression in children during hard times like the ongoing pandemic which again requires further investigations to confirm its effectivity.

CONCLUSION

Although the confirmatory and clinical data to postulate direct impact of vitamin D on COVID-19 patients, pregnant woman and children's mental health are scarce, given the strong biological evidence, it seems logical to take vitamin D supplementation especially by the people in the regions where its deficiency predominates. Again, the safeness of its use makes it indispensable to advocate in order to maintain a sound body health. Therefore, uncertain dietary intake of vitamin D to prevent COVID-19 severity should benefit the consumers a much by the time the true correlation establishes. Moreover, the observational and epidemiological studies involving COVID-19 and vitamin D suggest immediate further investigations on vitamin D and its roles in respiratory tract diseases not only for combating COVID-19 but also for any other forthcoming severe respiratory virus outbreak.

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AUTHOR CONTRIBUTIONS

Yusha Araf conceived the study. Md. Asad Ullah designed the study and refined the outline. Nafisa Ahmed conducted the complementary literature searches and reviews. Nafisa Ahmed and Yusha Araf wrote the initial draft. Md. Asad Ullah and Nafisa Ahmed edited and revised the final draft.

CONFLICTS OF INTEREST

There is no conflict of interest among the authors.

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