Review

Vitamin D can be effective on the prevention of COVID-19 complications: A narrative review on molecular aspects

Editor's Choice

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Abstract: The widespread COVID-19 pandemic has been, currently, converted to a catastrophic human health challenge. Vitamin D (VD) and its metabolites have been used as a palliative treatment for chronic inflammatory and infectious diseases from ancient times. In the current study, some molecular aspects of the potential effects of VD against COVID-19 side-effects have been discussed. An arguable role in autophagy or apoptosis control has been suggested for VD through calcium signaling at the mitochondrial and ER levels. 1,25(OH)2D3 is also an immunomodulator that affects the development of B-cells, T-cells, and NK cells in both innate and acquired immunity. The production of some anti-microbial molecules such as defensins and cathelicidins is also stimulated by VD. The overexpression of glutathione, glutathione peroxidase, and superoxide dismutase, and down-regulation of NADPH oxidase are induced by VD to reduce the oxidative stress. Moreover, the multi-organ failure due to a cytokine storm induced by SARS-CoV2 in COVID-19 may be prevented by the immunomodulatory effects of VD. It can also downregulate the renin-angiotensin system which has a protective role against cardiovascular complications induced by COVID-19. Given the many experimental and molecular evidences due to the potential protective effects of VD on the prevention of the COVID-19-induced morbidities, a VD supplementation is suggested to prevent the lethal side-effects of the infection. It is particularly recommended in VD-deficient patients or those at greater risk of serious or critical effects of COVID-19, including the elderly, and patients with pre-existing chronic diseases, especially those in nursing homes, care facilities, and hospitals.

Keywords: Vitamin D, Calcitriol, COVID-19, Coronavirus, molecular aspects

Abbreviations

VD: Vitamin D; RAS: renin-angiotensin system; PARP: Poly-ADP ribose polymerase-1; COVID-19: Coronavirus 2019 infectious disease; CoV: Coronavirus; Ang: Angiotensin; PARG: poly (ADP-ribose) glycohydrolase; CVD: cardiovascular disease

Introduction

Currently, the Coronavirus-2019 infectious disease (COVID-19) has been distributed worldwide as a catastrophic pandemic condition. Thousands of people die every day due to this infection throughout the world [1]. The pathogen of COVID-19 is the SARS-CoV-2 virus, a positive single-stranded RNA virus that belongs to the Coronavirus (CoV) family. Two worldwide epidemic situations in the past decades were occurred by two well-known members of this family, SARS-CoV and MERS-CoV [2]. The existence of several flexible glycyl residues within the distinct loop of SARS-CoV-2 receptor-binding domains leads to increase affinity to Angiotensin-Converting Enzyme 2 (ACE2) receptor as a transmembrane protein into the membrane of human host cells [3]. This binding mechanism is the main reason for the high virulence and communicability of COVID-19 compared to other viral infections [4]. Although many research projects are being implemented for finding a definite treatment for COVID-19, currently, there is no confirmed curative treatment for the disease. The current therapeutic approaches are concentrated to relieve the symptoms and support the respiratory and cardiovascular systems in affected patients.

Vitamin D (VD) and its metabolites have presented a lot of protective effects against different microbial infections and inflammatory disorders [5–7]. Rather than immunomodulatory functions, these nutritious compounds have also antioxidant effects that can prevent organ damages due to oxidative stress [8]. Moreover, VD can modulate the renin-angiotensin system (RAS) through which some deleterious effects of the SARS-CoV-2 virus could be modified in COVID-19 [9–12].

Although several studies have suggested the preventive role of VD supplementation in acute respiratory infections like COVID-19 [13–15], a handful studies have concentrated on the molecular pathways regarding the virus pathogenesis. In this narrative review, the potential protective effects of VD against COVID-19-induced damages and its related molecular aspects have been discussed.

Pharmacokinetics and pharmacodynamics of vitamin D

VD is one of the fat-soluble vitamins which refer to a group of secosteroids. It plays a key role in calcium and phosphate homeostasis, beside the parathyroid hormone. The diet and cutaneous synthesis are two main resources for VD and 25 (OH) D, a prohormone form which is used as a VD status marker. VD3 (cholecalciferol) can be naturally produced by UVB light, while VD2 (ergocalciferol) may be found in fortified foods and supplements which are usually provided by the individuals over the counter [16, 17].

DBP (VD binding protein) is responsible for transporting the VD and its Metabolites in the circulation. At first, liver hydroxylates VD3 and D2 by the microsomal and mitochondrial 25-hydroxylase. This enzyme is encoded by *CYP27A1* and *CYP2R1* genes which produce 1,25(OH)D. In the kidney, 1a-hydroxylase converts 25(OH)D to 1,25 $(OH)_2D$ (calcitriol), which is the only biologically active form of VD. $1,25(OH)_2D$ leads to calcium absorption. 1,25 $(OH)_2$ D has a similar structure to steroid hormones [16–18]. The calcitriol production process also found in many organs, like the parathyroid gland, placenta, and prostate [19, 20].

24-hydroxylase is the main enzyme that degrades 25 (OH)D and 1,25(OH)2D. This rate-limiting step is regulated by the *CYP24A1* gene which converts these two molecules to inactive forms. These metabolites are soluble in water; hence, they can be excreted in the bile [17, 21].

The parathyroid hormone (PTH) regulates the synthesis of $1,25[OH]_2$ D which is inhibited by circulating FGF23 protein [22]. 25(OH)D is the most suitable indicator of VD status due to its 3-week half-life. Serum 25(OH)D level of less than 10 ng/ml results in several bone diseases. The main stimulant for PTH secretion is a low level of serum ionized calcium. The optimal 25(OH)D value maximally inhibits the PTH secretion [22].

Calcium homeostasis is the main function of calcitriol [23]. $1,25(OH)_2D$ is physiologically affected by its interaction with the VD receptor (VDR) which creates a complex with the retinoic acid X receptor (RXR). VDR-RXR complex is named as VD Response Elements (VDRE) after binding to the specific DNA sequences. VDRE is associated with the genes which contribute to intestinal calcium absorption. Its function is characterized by alteration in gene expression which plays a role in apoptosis, cell growth, and differentiation [21, 24].

VD can also stimulate bone absorption through binding with VDR in osteoblasts. Therefore, RANK ligand (RANKL) expression will be increased which results in the transformation into bone-resorbing osteoclasts [21, 23]. In general, serum 25(OH)D concentrations lower than 20 ng/mL (50 nmol/L) are considered to be VD deficient [25]. Nevertheless, serum 25(OH)D concentrations above 150 ng/mL (375 nmol/L), can be named as a VD toxicity which leads to hypercalcemia and hyperphosphatemia [25].

There is a controversy in determining the therapeutic dosage of VD [25–27]. It has a wide range, depending on body weight, age, sun exposure, etc. However, its recommended therapeutic dosage ranges from 1000 IU/day (25mg/day) for neonates to 7000–10,000 IU/day (175–250 mg/day) or 50,000 IU/week (1250 mg/week) for adults [28, 29]. The preventive dose for infection has been recommended 10,000 IU/d of the vitamin D3 for a few weeks, which should be followed by 5000 IU/d, in at risk people. The therapeutic level is considered at least 40–60 ng/mL (100–150 nmol/L) of 25(OH)D concentrations. For COVID-19 patients, a higher dose of VD might be useful [30]. Moreover, in patients who have not been taking VD, a higher dose for a shorter time is recommended [30, 31].

Pathophysiology of COVID-19

After entering the human body, SARS-CoV-2 similar to the original SARS-CoV attaches to ACE2, a transmembrane enzyme that converts angiotensin (Ang) II to Ang 1-7. When the virus binds to the ACE2 receptor, its entering and replication are facilitated and a chain of deleterious events is triggered. SARS-CoV-2-ACE2 binding leads to the down-regulation of the ACE2 enzyme [32, 33]. Angiotensin II functions are normally modified by ACE2 through the production of Ang (1-7) in the RAS system [34]. In patients with COVID-19, the balance of the RAS system is disturbed, and Ang II/Ang (1-7) ratio is enhanced. This important event

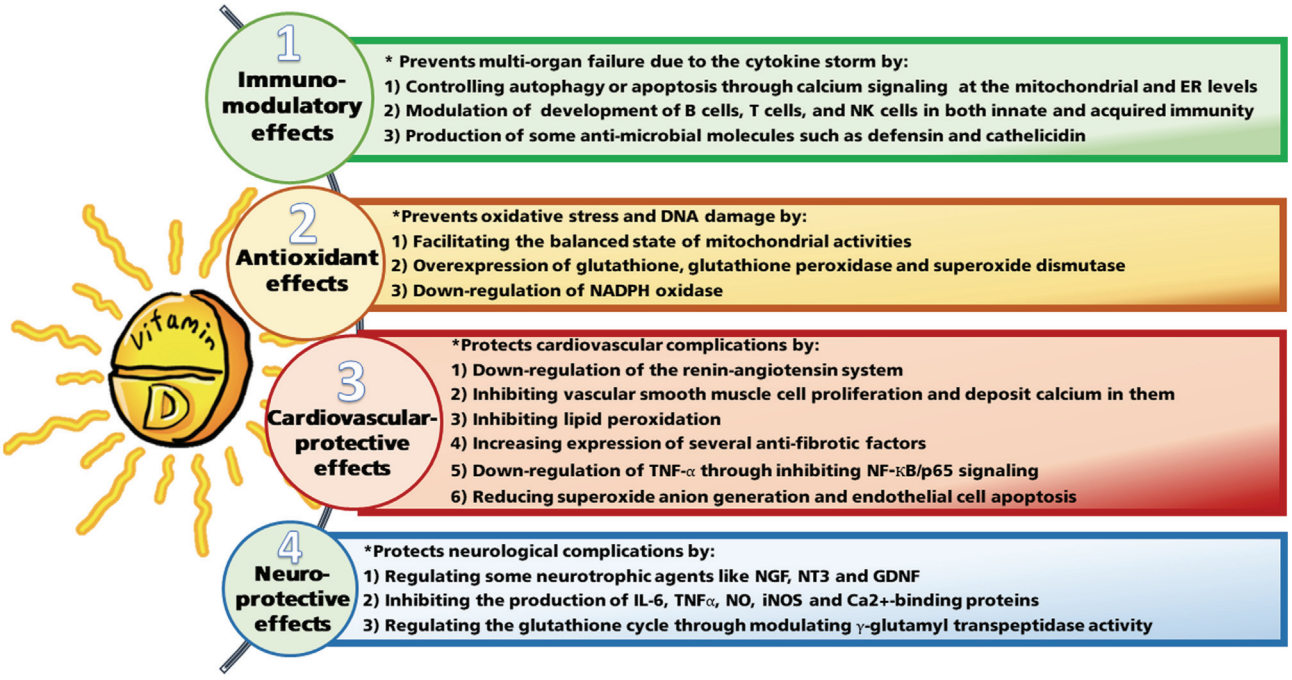

Figure 1. An infographic diagram illustrating the immuno-modulatory (1), anti-oxidant (2), cardioprotective (3) and neuroprotective (4) potencies of vitamin D against COVID-19 and molecular pathways involved (COVID-19: Coronavirus Infectious Disease-2019).

justifies the organ damage induced by the SARS-CoV-2 infection, leading to respiratory, renal, and cardiovascular complications in the patients [34]. Meanwhile, AngII, as a pro-inflammatory factor, over-activates NADPH oxidase and upregulates NF-κB which both have a determinant role in the pathogenesis of inflammatory diseases such as chronic heart and renal failures [35, 36].

NOX1, a homologous enzyme of NADPH oxidase is expressed in endothelial cells, epithelial cells, smooth muscle cells, and interstitial fibroblasts, while NOX2, another homologous enzyme of NADPH oxidase, is expressed in phagocyte cells, and some tissue cells of cardiovascular system, kidney, CNS, and GI tract. The over-activation of Ang II in some pathological conditions, like COVID-19, leads to the upregulation of NOX1 and NOX2 enzymes, resulting in overproducing the reactive oxygen species (ROS) molecules followed by reducing the available cellular NADPH [37]. It creates severe oxidative stress through which DNA damages could occur. The base excision repair (BER) pathway is essentially responsible for repairing these oxidative DNA damages [38]. One of the important enzymes, involved in the BER pathway, is Poly-ADP ribose polymerase-1 (PARP-1) [39], which has an antiviral function by ADP-ribosylation of the virus genome. Some viral families, including Coronaviruses, encode a macrodomain protein with poly (ADP-ribose) glycohydrolase (PARG) activity through which could hydrolyze ADP-ribose attached to viral proteins and genomes and facilitate the viral replication [40] (Figure 1).

Vitamin D and its immunomodulatory functions

Along with the classic functions of VD such as bone health and calcium homeostasis, some immunomodulatory functions such as immune protection, inflammation reduction, and the possible anti-allergic effects have been added to the functions of this hormone-like vitamin [41–43]. Ricciardi et al. (2015) [44] showed that VD can play a role in maintaining energy homeostasis and cell survival by modulating the stress and damage response. Moreover, VD deficiency and T cell imbalance in patients with renal transplantation were reported by Swiderska et al. (2015) [45] as a negative factor in survival. The presence of IL28B rs8099917 GG genotype, IL28B rs12979860 TT genotypes, and IL13 rs20541 T allele were also introduced as negative predictors in survival. Therefore, VD is closely linked to the T cell immune response.

Rizzuto et al. (2012) [46] determined that VD has an arguable role to control the autophagy or apoptosis through calcium signaling at the mitochondrial and endoplasmic reticulum (ER) levels. Calcium signaling plays a modulatory role in autophagy through the Ca^{2+}/calmodulin-dependent protein kinase kinase β (CaMKKβ) activity with AMP-activated protein kinase (AMPK) activation that is a target of rapamycin–dependent autophagy. Medrano et al. (2018) [47] showed that the active form of VD3, 1,25 (OH) 2D3, has the potential to down-regulate the "toll-like

receptor" TLR2 and TLR4 in monocytes and decline the inflammatory responses. Hence, VD promotes the innate immune system using two regulatory mechanisms: CYP24 (24 hydroxylase), and TLR for the prevention of tissue damage as a result of excessive inflammation.

Besides, the induction of cytolytic killing capacity of NK (Natural Killer) cells has been found in an NK cell line, but this effect has not been observed in the healthy control peripheral blood. Although, after adding 1,25(OH)2D3 to the in-vitro differentiating NK cells, the development of NK cells was ruined and their cytotoxicity and IFNγ production was decreased [48, 49]. Accordingly, Dankers et al. (2017) [50] suggested the hypothesis that 1,25(OH)2D3 is an immune homeostasis regulator instead of a general inhibitor of the immune response. Meanwhile, the different immune cells such as dendritic cells, monocytes, macrophages, T cells, and B cells can transform 25(OH)D3 into 1,25(OH)2D3 [51, 52].

In the point of effects of 1,25(OH)2D3 on B cells, it seems that the effect of 1,25(OH)2D3 relies on the differentiation and activation status of B cells [50]. For instance, Chen et al. (2007) [53] reported that 1,25(OH)2D3 decreases the proliferation of B cells, inhibits immunoglobulin class switching, and induces their apoptosis. Shirakawa et al. (2008) [54] presented that after adding 1,25(OH)2D3 to terminally differentiating B cells, it stimulates the development of plasma cells. Moreover, 1,25(OH)2D3 induces the chemokine receptor CCR10 on these plasma cells, and enhances their migration into mucosal sites of inflammation. Moreover, von Essen et al. (2010) [55] determined that T cells are another immunological targets for 1,25(OH)2D3 through differentiation and modulation of cytokine secretion, however, VDR is also needed for the activation of T cells by spreading TCR signaling.

Furthermore, the preventive effect of 1,25(OH)2D3 supplement has been discovered in the initiation and progression of collagen-induced arthritis (CIA) and experimental autoimmune encephalomyelitis (EAE) in the experimental models of Rheumatoid Arthritis and Multiple Sclerosis, respectively. Meanwhile, the causal relationship between VD and autoimmune diseases has not been yet approved, and further investigations about VD supplementation benefits in at-risk individuals are needed [56, 57].

Jian et al. (2018) [58] found that high dose VD (1200 IU) is proper for seasonal influenza prevention by decreasing viral load, rapid alleviation from symptoms, and disease amelioration. Gruber-Bzura et al. (2020) [59] explored that 1,25(OH)2D induces the production of AMPs, such as defensin and cathelicidin, which as endogenous antibiotics can destroy the microbial pathogens and viruses, including the influenza virus. Hence, for a comprehensive outlook on VD effects against viral infections, more randomized clinical trials and large studies are required (Figure 2).

Vitamin D and its antioxidant effects

A balance disruption in the oxidant/antioxidant ratio is defined as oxidative stress. It leads to generation of the ROS molecules that result in several events such as: releasing inflammatory mediator activation, and irreversible oxidative modification of lipids, proteins, and carbohydrates [60, 61].

VD and Calcitriol (its active form) have a vital role in the homeostasis of the body. VD anti-oxidant activity has been proposed since 1993, and it is currently known as a potent non-enzymatic anti-oxidant agent that prevents the ROS generation. VD facilitates the balanced state of mitochondrial activities, and also it prevents oxidative stress, and DNA damage [62, 63]. Tseng et al. (2013) [64] determined that the expression of a nuclear factor, erythroid-2(Nf-E2)-related factor 2(Nrf2) is also increased by VD. Intracellular Nrf2 level is inversely associated with the accumulation of mitochondrial ROS. The interaction between Nrf2 and peroxisome proliferator-activated receptor-coactivator 1 (PGC-1) regulates the expression of mitochondrial deacetylase (SIRT3) which impacts on the oxidative stress cycle. All of these processes are influenced by VD [65, 66]. Moreover, Wimalawansa et al. (2019) [67] showed that the expression of glutathione peroxidase, converting the ROS molecule of H_2O_2 to water, is under the influence of VD. According to Mokhtari et al. (2017) [68], VD may regulate the oxidative stress via prompting the expression of glutathione, glutathione peroxidase, and superoxide dismutase (SOD) that have an antioxidant function by suppressing the expression of NADPH oxidase.

Ke et al. (2016) [69] in their experimental study displayed that oxidative stress due to superoxide dismutase (SOD) and catalase enzymes could reduce the muscular activity, associated with VD deficiency, in rats. Some other studies have determined that the administration of VD in diabetic mice led to suppression of the expression of the NADPH gene, assisting in reduction of the ROS production [70, 71].

Uberti et al. (2016) [72] showed the antioxidant effect of VD in the cultured gastric epithelial cells. They reported that bisphenols (Grisù) mixed with VD may protect gastric epithelium through an antioxidant pathway and reduced ROS production.

According to Cahova et al. (2015) [60], in diabetic patients, hyperglycemia can induce oxidative stress and inflammatory responses that are known as hepatocellular damaging factors. Accumulation of oxidative stress

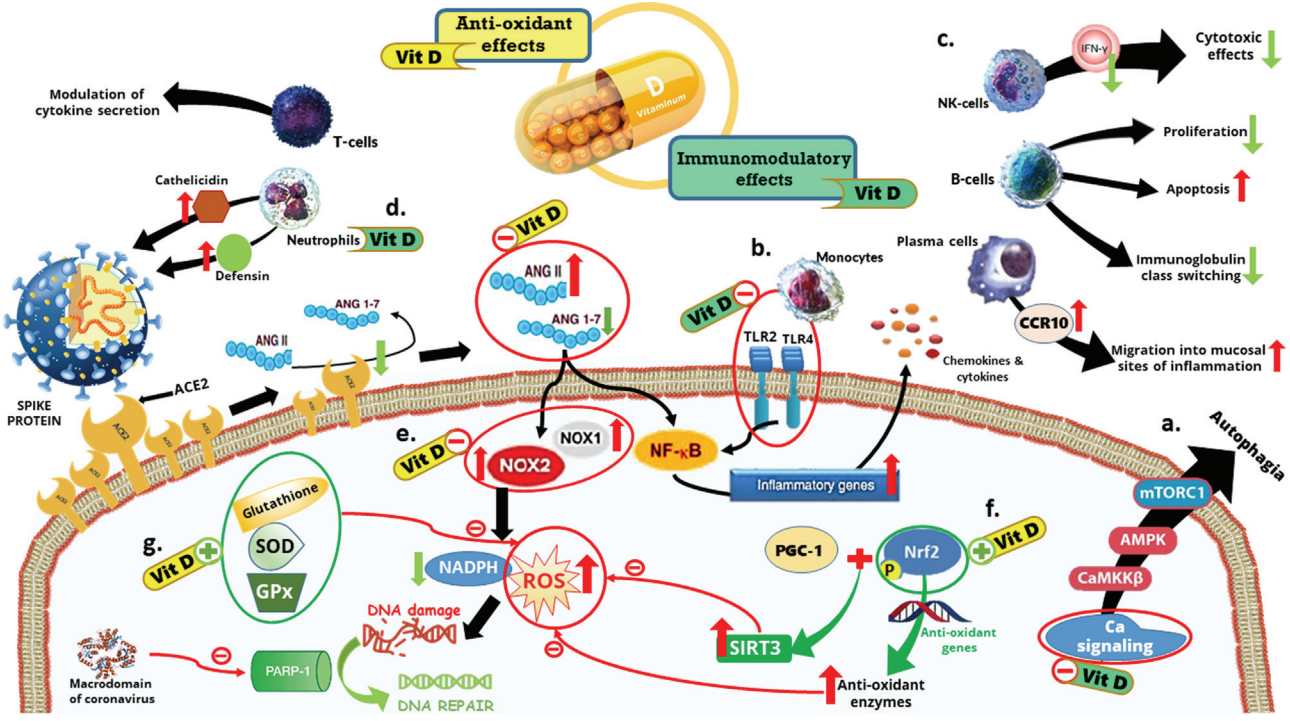

Figure 2. An infographic picture illustrating the molecular pathway of anti-oxidant and immunomodulatory effects of vitamin D against SARS-CoV-2 pathogenesis: (a) Vitamin D controls the autophagy through calcium signaling at the mitochondrial and ER levels. CaMKKβ: Ca^{2+}/calmodulin-dependent protein kinase kinase β, AMPK: AMP-activated protein kinase, mTORC1: mammalian target of rapamycin complex 1; (b) Vitamin D down-regulates the "toll-like receptor" TLR2 and TLR4 in monocytes which declines the inflammatory responses. (c) Vitamin D has immunomodulatory effects on immune system cells. (d) Vitamin D stimulates production of AMPs, such as defensin and cathelicidin, which can destroy viruses. (e) Vitamin D prevents ROS generation, oxidative stress and DNA damage. It also suppresses the expression of NADPH oxidase. (f) The up-regulation of a nuclear factor, erythroid-2(Nf-E2)-related factor 2(Nrf2) by vitamin D leads to the over-expression of anti-oxidant enzymes. Moreover, the interaction between Nrf2 and Peroxisome proliferator-activated receptor-coactivator 1 (PGC-1) regulates the expression of mitochondrial deacetylase (SIRT3). These events that inhibit the oxidative stress cycle, are induced by Vitamin D. (g) The overexpression of glutathione, glutathione peroxidase, and superoxide dismutase are induced by Vitamin D to reduce the oxidative stress. ER: Endoplasmic reticulum, ANG: Angiotensin.

markers in diabetes mellitus (DM) is due to a reduced level of glutathione. It seems that secondary complications of DM are induced by oxidative stress [73]. Alqasim et al. (2017) [74] demonstrated that VD administration in diabetic rats could reduce oxidative stress and improve the inflammation. Alatawi et al. (2018) reported the same results in their study [73]. Another study by Jamilian et al. (2019) showed that co-supplementation of magnesium-zinc-calcium-VD could reduce the inflammation and oxidative stress markers in patients with gestational diabetes [75]. Heidari et al. (2019) in a randomized clinical trial investigated the effect of VD supplementation in Premenstrual Syndrome (PMS). It appears that VD could improve the inflammation and antioxidant markers in VD deficient women with PMS [76]. Igde et al. (2018) exhibited a positive impact of VD on the reduction of plasma concentrations of oxidative stress markers in inflammation-related oxidative stress in asthmatic patients [77]. One another study that was done by Zhu et al. (2019) on human tubular epithelial cells revealed that VD might prevent high glucose concentration induced by oxidative stress [63] (Figure 2).

Vitamin D and cardiovascular protection

The cardiovascular system is commonly involved in the patients with COVID-19 and may be affected through three following ways [78]:

1) The severity of cardiovascular disease (CVD) can be increased in the patients with preexisting CVD;
2) The incidence rate of multiple direct and indirect CVD-attributed complications will be raised including the acute myocardial injury, myocarditis, arrhythmias, and venous thromboembolism;
3) The side effects of therapeutic approaches for COVID-19 may be a threat for the cardiovascular tract.

According to Wang et al. (2020) [79], up to 40% of 138 patients admitted with COVID-19 had pre-existing CVD. Moreover, 7.2% of the patients had elevated cardiac troponin, suggestive for the virus-induced cardiac injury. Saad et al. (2014) [80] had already found that serious cardiac

complications may occur mainly in the form of arrhythmias, including variable tachyarrhythmias and severe bradycardia, which occurred in 15.7% of 70 cases. However, in Huang et al. (2020) [81] research among 41 patients with COVID-19 in China, 5 (12%) patients presented substantially an increased hypersensitive troponin I (hs-cTnI) due to the virus-related cardiac injury, as a common complication.

SARS-CoV-2 may result in downregulating the myocardial and pulmonary ACE2 pathways. ACE2 is expressed in the heart, providing a link between coronaviruse and the cardiovascular system, and its interaction with the virus may directly cause myocardial inflammation [82]. Besides, the up-regulation of 15 pro-inflammatory cytokines leads to a systemic inflammatory response syndrome that may provide a possible mechanism for multi-organ failure (usually involving the heart) in severe cases [83]. The RAS disturbance and increased Ang II have destructive effects on vascular endothelium by increasing the expression of some molecules like IL1B, IL-6, monocyte chemoattractant protein-1 (MCP-1), and the activation of NOX enzymes. These changes can interfere with NO cycle and cause cell damage. Also, elevated Ang II can lead to peroxynitrite damage on the vascular endothelial surface by the over-expression of Profilin-1 [84–86].

Researches about the effects of VD on the cardiovascular system suggest different and controversial outcomes. The findings determine that VD3 is a powerful trigger of nitric oxide, playing an important role in the enhancing of the hypercoagulability state in blood vessels and the control of blood flow. Khan et al. (2018) [87] determined that VD3 significantly reduces the oxidative stress in the vascular system and can reverse cardiovascular damages. Barbarawi et al. (2019) [88] in a meta-analysis on 21 randomized clinical trials involving more than 83,000 people, found that there is no decrease in the major cardiovascular events such as heart attack, stroke, and death in the people taking VD supplements. However, it seems that the relationship between 25-hydroxyVD and CVD is nonlinear and reaches a plateau between 20 and 30ng/ml. Moreover, the Third National Health and Nutrition Examination Survey (NHANES III) has presented no significant association between serum 25-hydroxyVD and CVD-induced mortality [89].

VD can also improve cardiac oxidative stress and inflammatory markers. Murr et al. [90] declared in their study that the chance of death from cardiovascular disease is 1.8 to 2.5 times more in patients with VD deficiency compared to patients with normal VD levels. Besides, Argacha et al. (2011) [91] in their study on VD deficient animal model demonstrated that VD deficiency leads to increased blood pressure and supported vascular oxidative stress in rats. It sounds that VD has a protective role against oxidative stress and inflammation in cardiac tissue.

The definite protection mechanism of VD against CVD has not been obvious, yet. Some studies have declared that the VD receptor is expressed in some cell types of vascular system including endothelial cells, vascular smooth muscle cells, and cardiomyocytes. These cells produce 1α-hydroxylase, converting 25-hydroxyVD to calcitriol. Calcitriol has been shown to improve glycemic control, inhibit vascular smooth muscle cell proliferation and deposit calcium in them, down-regulate the renin-angiotensin system, decrease coagulation, and represent anti-inflammatory properties [92, 93].

Li et al. (2002) [94] showed that VDR-knockout mice had an elevated activation of the renin-angiotensin-aldosterone system (RAAS), high blood pressure, and cardiac hypertrophy, which could be controlled by an ACE inhibitor. Furthermore, the mice given injections of calcitriol demonstrated the suppression of the renin mRNA expression.

Moreover, Plidoro et al. (2013) [95] represented that VD reduces superoxide anion generation and also endothelial cell apoptosis induced by H_2O_2. The activation of MEKs/ERKs-signaling pathway, which inhibits apoptosis, is also occurred by the up-regulation of SirT-1. According to Al-Rashid et al. (2015) study on mice [96], VD down-regulates tumor necrosis factor-α (TNF-α), inducing cardiomyocyte hypertrophy, by inhibiting NF-κB/p65 signaling. Furthermore, Artaza et al. (2009) [97] had already shown that VD has an anti-fibrotic role in cardiovascular system by increasing the expression of several anti-fibrotic factors and reducing the expression of TGF-ß1, plasminogen activator inhibitor 1, and collagens I and III. Wiseman et al. (1993) [98] had earlier determined that VD protects the cell membranes against free radical-induced oxidative damage by inhibition of lipid peroxidation (Figure 3).

Vitamin D and neuroprotection

By presentation of neurological manifestations in the patients with COVID-19, possible neuroinvasive feature of COVID-19 is a remarkable topic of new papers [99]. For example, Mao et al. (2020) [100] reported that 78 (36.4%) of 214 patients had neurological symptoms including CNS symptoms (53 [24.8%]) such as dizziness and headache, PNS symptoms (19 [8.9%]) like hypogeusia and hyposmia and also muscle injury symptoms (23 [10.7%]). In another study, Giacomelli et al. (2020) [101] in Italy reported that 20 (33.9%) of 59 patients had at least one olfactory or taste disorder. Gu et al. (2005) [102] already had determined that rather than cerebral edema and degeneration of neurons in 6 of 8 SARS autopsies, SARS genome sequences were detected by RT-PCR in the brain of all these autopsies. In another autopsy study by Xu et al. (2005) [103] on SARS dead patients, neuronal necrosis, glial hyperplasia, and

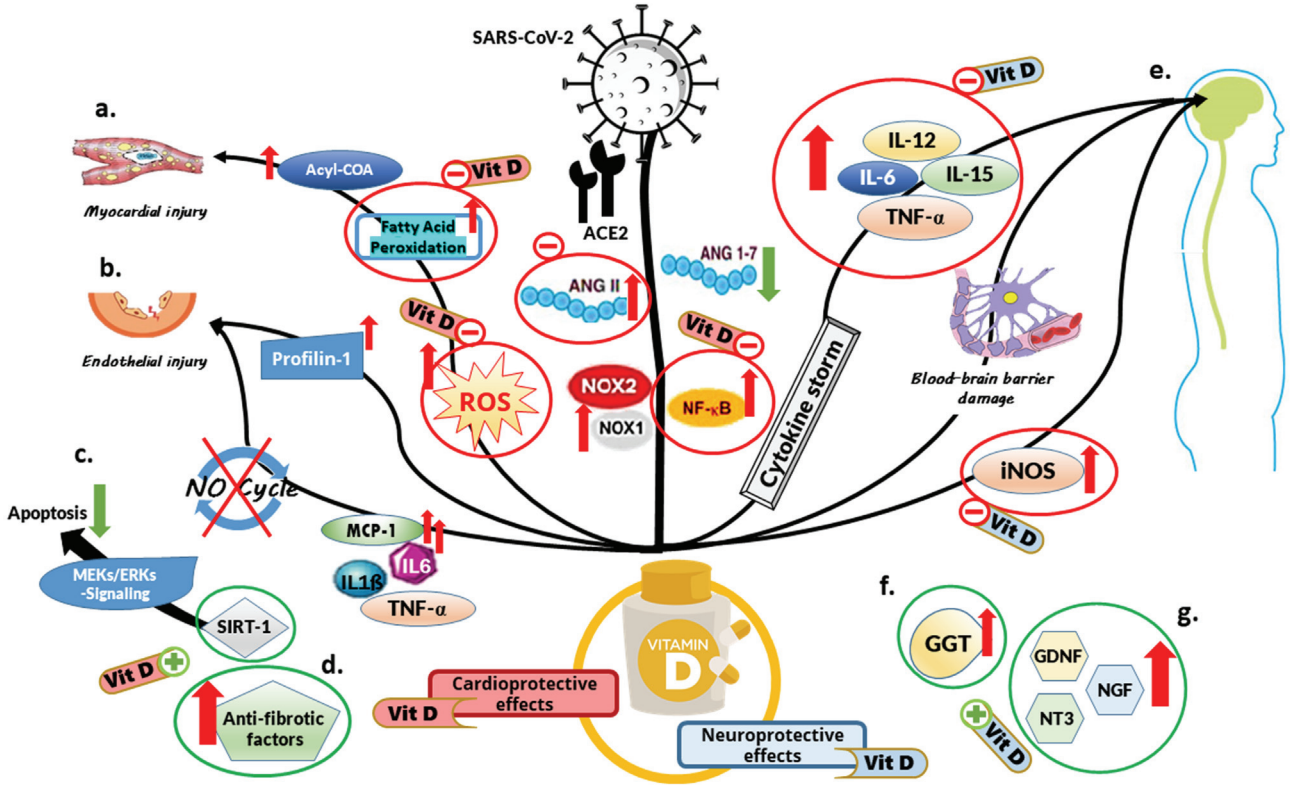

Figure 3. An infographic picture illustrating the molecular pathway of destructive effects of SARS-CoV-2 on cardiovascular and nervous systems in COVID-19 and also the molecular mechanism of vitamin D effects against them: (a) The Interaction of SARS-CoV-2 and ACE2 leads to the RAS disturbance. Hence, myocardial injury is caused by inducing reactive oxygen species and lipid peroxidation, both inhibited by vitamin D. (b) The cytokine storm in which some inflammatory molecules like IL-6, IL-1ß, TNF-α, monocyte chemoattractant protein-1 (MCP-1) are increased, interferes with nitric cycle and leads to the endothelial damage. The over-expression of profiling-1 may cause peroxynitrite damage on the vascular endothelial. Vitamin D counteracts this cytokine storm by inhibiting NF-κB/p65 signaling. (c) The up-regulation of SirT-1 inhibits apoptosis through MEKs/ERKs-signaling activation. (d) Vitamin D has anti-fibrotic role by increasing some anti-fibrotic factors. (e) Vitamin D down-regulates the pro-inflammatory cytokines such as IL-6, IL-12, TNF-α and iNOS which have destructive effects on the brain. (f) The increase of γ-glutamyl transpeptidase (GGT) activity induced by vitamin D, regulates the glutathione cycle. (g) The regulation of nerve growth factor (NGF), neurotrophin 3 (NT3), glial cell line-derived neurotrophic factor (GDNF) counteracts the toxicity of SARS-CoV-2 on nervous system. ANG: Angiotensin; RAS: Renin-Angiotensin System.

edema with the presence of SARS-CoV in brains had been detected. The separation of SARS-COV-2 RNA from the CSF of the patients also strongly suggests that this new virus can also cause neurologic damages [104, 105]. The reported cases of acute myelitis, acute hemorrhagic necrotizing encephalopathy, and meningitis/encephalitis associated with SARS-CoV-2 are also indicative for the neuroinvasive potential of the virus [105–107]. Netland et al (2008) [108] had been already reported that SARS-CoV can spread to CNS through blood circulation or trans-neuronal from the olfactory bulb. Meanwhile, according to some studies, the expression of ACE2, possible receptor of SARS-CoV-2, is detected in neurons and astroglial cells of different parts of CNS especially in cardiovascular-related brain regions [109, 110]. Hence, SARS-COV infection of the regions like the dorsal vagal complex, a critical zone for cardiorespiratory function, could be the cause of mice death primarily as a direct result of CNS involvement, not pulmonary infection [108]. Interaction of the virus and ACE2 can interfere with the balance of the RAS which leads to organ damage by enhancement of Ang II/Ang (1-7) ratio [33]. In addition, interaction of ACE2 in the capillary endothelium and SARS-CoV-2 spike protein may also damage the blood–brain barrier [111].

Putting results of other researches together amplifies the possibility of excessive increase in levels of proinflammatory cytokines/chemokines, as a cytokine storm, in the brain of COVID-19 patients; for example, animal studies on mice revealed that upregulation of and IL-6, tumor necrosis factor-alpha, IL-1, gamma interferon, CCL2, and CCL12 in SARS-COV infected neurons can play an immunopathological role in inflamed brains [108, 112]. Goshal et al. (2007) [113] had already represented an increase of proinflammatory mediators, such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (Cox-2), IL-6, IL-1β, TNF-α, and MCP-1 in microglia of animal

models due to Japanese encephalitis virus infection. Additionally, Bohmwald et al. (2018) [114] showed that culturedCoV-infected glial cells could secrete inflammatory factors such as IL-6, IL-12, IL-15, and TNF-α.

1,25-dihydroxyvitamin D_3 receptor (VDR) is expressed widely in glial cells and neurons of the different regions of the adult brain especially throughout the olfactory system [115, 116]. Also, 1α-hydroxylase (1α-OHase), the enzyme responsible for the formation of the active vitamin, was found by Eyles et al. (2005) in both neurons and glial cells [116]. Thus, VD affects some mechanisms including neurogenesis, neuroprotection, regulation of neurotrophic factors, maintaining neuronal signaling by enhancing neurotransmission, synaptogenesis, and inhibition of degenerative processes including apoptosis [117, 118]. VD can also interfere with the regulation of inflammation, neurodegeneration, and repair processes within the CNS [119]. It also regulates some neurotrophic agents like nerve growth factor (NGF), neurotrophin 3 (NT3), and glial cell line-derived neurotrophic factor (GDNF) [120–122]. GDNF works against ischemia, injury, and 6-hydroxydopamine (6-OHDA) toxicity [123–125].

d'Hellencourt et al. (2002) [126] determined that VD has an anti-inflammatory potency by inhibiting the production of IL-6, TNFα, and NO in activated microglia in vitro. Meanwhile, according to Furman et al. (1996) earlier study [127] on 1,25-(OH)2D3-treated astrocytes, a reduction in tumor necrosis factor α (TNF-α) and macrophage colony-stimulating factor (M-CSF) was reported in them. Moreover, some studies have determined that VD has neuroprotective roles through induction of Ca^{2+}-binding proteins, such as parvalbumin and inhibition of the synthesis of inducible nitric oxide synthase (iNOS), producing nitrite oxide that damages both neurons and oligodendrocytes [128–130]. Dringen et al. (2001) [131] showed that VD has a strong antioxidant function in brain through regulating the γ-glutamyl transpeptidase activity which is involved in the glutathione cycle, in rat brain. In another study by Ascherio et al. (2010), it is revealed that VD also can decrease multiple sclerosis (MS) development by modulation of immune responses [132] (Figure 3).

Vitamin D and clinical outcomes of COVID-19

Some recent studies on COVID-19 patients suggest a reverse correlation between VD serum levels and the severity of their clinical symptoms [133–135]. According to the Alipio study [130] on 212 cases of COVID-19, the serious cases presented the lowest level of 25(OH)D in their serum, while the mild patients showed the highest level. Moreover, the serum level of VD was significantly associated with clinical outcomes. In another report published by Glicio [131], 176 patients with COVID-19 were investigated and it was revealed that most of them had 25(OH)D level below 30 ng/ml, and were classified as severe. Meanwhile, most of the cases with the pre-existing conditions had 25(OH)D level below 30 ng/ml. In a retrospective cohort study including 780 cases with PCR-positive of SARS-CoV-2 in Indonesia, it was revealed that VD deficiency was associated with increased odds of death [136]. Other recent reports have been also presented similar findings [137, 138]. A causal inference model has been also proposed for the highly beneficial role of VD in improving the disease symptoms in COVID-19 and other respiratory infections [13]. It seems that VD supplementation can relieve the clinical outcomes and prevent acute organ damages, particularly among the at-risk patients [139, 140].

Conclusions

SARS-CoV-2, the viral cause of COVID-19, leads to lethal infection with multiple organ damages, particularly in the respiratory and cardiovascular tracts, through upregulation of the RAS pathway and inducing a cytokine storm. Vitamin D and its metabolites have immunomodulatory effects via the development of the immune cells, anti-inflammatory effects, and production of some anti-microbial molecules such as defensins and cathelicidins. VD also has antioxidant effects through modulating the mitochondrial activities, upregulating of glutathione, glutathione peroxidase and superoxide dismutase, and down-regulating the NADPH oxidase. RAS pathway can also be down-regulated by VD which may prevents the cardiovascular complications induced by COVID-19. Moreover, there are many experimental studies because of the potential protective effects of VD against the COVID-19-induced morbidities. The recommended dose for prevention of the infection is 10,000 IU/d of VD for a few weeks, which should be followed by 5000 IU/d, in at-risk people. If the person has not been taking vitamin D, a higher dose for a shorter time is also recommended. It seems VD supplementation therapy, at-least in VD deficient patients, can prevent the lethal side-effects of the infection; An issue needed to be evaluated at the next well-designed clinical trials (Figure 1).

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