

Vitamin D may be effective against COVID19 complications: A review on molecular aspects

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Abbreviations:

VD: Vitamin D

RAS: renin-angiotensin system

PARP: Poly-ADP ribose polymerase-1

COVID19: Coronavirus 2019 infectious disease

CoV: Coronavirus,

Ang: Angiotensin

PARG: poly (ADP-ribose) glycohydrolase

CVD: cardiovascular disease

KeyWords: Vitamin D, Calcitriol, COVID19, Coronavirus, molecular aspects

A review on molecular aspects of Vitamin D effects against COVID19

Abstract

The widespread pandemic situation due to COVID19 has been, currently, converted to a catastrophic human health challenge. A lot of restless attempts are carrying out worldwide to find effective therapeutic methods for the reduction of its related mortality and morbidities. Vitamin D (VD) and its metabolites have been a long time as the palliative treatment for chronic inflammatory and infectious diseases. In the current study, some molecular aspects of the potential effects of VD against COVID19 side-effects have been discussed.

An arguable role to control autophagy or apoptosis has been suggested for VD through calcium signaling at the mitochondrial and ER levels. $1,25(\text{OH})_2\text{D}_3$ 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 are also stimulated by VD. It modulates the mitochondrial activities that lead to decrease in oxidative stress and DNA damage. 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 COVID19 may be prevented by the immunomodulatory effects of VD. It can also down-regulate the renin-angiotensin system, which can protect cardiovascular complications induced by COVID19. Given the many experimental and molecular evidence due to the potential protective effects of VD against the COVID19-induced morbidities, a VD supplementation therapy is suggested, at-least in VD deficient patients, to prevent the lethal side-effects of the infection. (Figure 1)

Introduction

Currently, the Coronavirus-2019 infectious disease (COVID19) 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 COVID19 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 glycy 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 COVID19 compared to other viral infections (4). Although many research projects are being implemented for finding a definite treatment for COVID19, 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. Rather than immunomodulatory functions, these nutritious compounds have also antioxidant effects that can prevent organ damages due to oxidative stress. Moreover, VD can modulate the renin-angiotensin system (RAS) through which it may modify some deleterious effects of the SARS-CoV-2 virus in COVID19.

In the current review, the potential protective effects of VD against COVID19-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) just can be found in fortified foods and supplements (5,6).

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, 1 α -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)₂D has a similar structure to steroid hormones (5–7). The calcitriol production process also found in many organs, like the parathyroid gland, placenta, and prostate(8,9).

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 (6,10).

Parathyroid hormone (PTH) regulates the synthesis of 1,25[OH]₂ D which is inhibited by circulating FGF23 protein (11). 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 VD status is 25(OH)D value which maximally inhibits the PTH secretion (11).

Calcium homeostasis is the main function of calcitriol (12). 1,25(OH)₂D is physiologically affected by its interaction with the VD receptor (VDR) which creates a complex with 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 (10,13).

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 (10,12). In general, serum 25(OH)D concentrations lower than 20 ng/mL (50 nmol/L) are considered to be VD deficient (14). 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 hyper-phosphatemia(14).

There is a controversy in determining the therapeutic dosage of VD (14–16). It has a wide range depends 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 (17,18).

Pathophysiology of COVID19

After entering to the human body, SARS-CoV-2 similar to the original SARS-CoV attaches to ACE2, a transmembrane enzyme that converts Angiotensin (Ang) I and AngII to Ang 1,7,9. 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 (19,20). Angiotensin (Ang)II functions are normally modified by

ACE2 through the production of Ang (1,7) in the RAS system (21). In COVID19, the balance of the RAS system is disturbed and Ang II/Ang(1-7) ratio is enhanced, an important event that could justify the organ damage induced by the infection leading to respiratory, renal, and cardiovascular complications in the patients (20). Meanwhile, AngII as a pro-inflammatory factor, over-activates NADPH oxidase and upregulates NF- κ B which have a determinant role in the pathogenesis of inflammatory diseases such as chronic heart and renal failures (22,23).

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 organ tissue cells in cardiovascular, renal, CNS, and GI tracts. The overactivation of AngII in some in pathological conditions, like COVID19, leads to the upregulation of NOX1 and NOX2 enzymes, the events that result in overproducing the Reactive Oxygen Species (ROS) molecules followed by reducing the available cellular NADPH (24). It creates severe oxidative stress through which DNA damages could occur. The base excision repair (BER) pathway is essentially responsible to repair these oxidative DNA damages(25). One of the important enzymes involved in the BER pathway is Poly-ADP ribose polymerase-1 (PARP-1)(26), which using ADP-ribosylation of the virus genome has an antiviral function. 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 (27).

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 (28,29). VD can play a role in maintaining energy homeostasis and cell survival by modulating the stress and damage response (30). VD deficiency and T cell imbalance in renal transplantation have been reported as a negative factor in survival. Moreover, the presence of IL28B rs8099917 GG genotype, IL28B rs12979860 TT genotypes, and IL13 rs20541 T allele are negative predictors in survival. Therefore, VD is closely linked to the T cell immune response (31).

VD has an arguable role to control the autophagy or apoptosis through calcium signaling at the mitochondrial and ER levels. Calcium signaling plays a modulatory role in autophagy through the Ca^{2+} /calmodulin-dependent protein kinase kinase β (CaMKK β) activity with AMP-activated protein kinase (AMPK) activation that is a target of rapamycin-dependent autophagy(32). The active form of VD3, 1,25 (OH) 2D3, has potential in down-regulation of the “toll-like receptor” TLR2 and TLR4 in monocytes with declining 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 (33).

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 from hematopoietic stem cells within the invitro differentiation of NK cells, the development of NK cells is ruined and their cytotoxicity and IFN γ production is decreased (34,35). These kinds of results support the hypothesis that 1,25(OH)2D3 is an immune homeostasis regulator instead of a general inhibitor of the immune

response (36). 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 (37,38).

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 (36). For instance, it has been reported that 1,25(OH)₂D₃ decreases the proliferation of B cells, inhibits immunoglobulin class switching and induces their apoptosis (39). When 1,25(OH)₂D₃ is added 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, enhancing their migration into mucosal sites of inflammation (40). 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(41).

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, as a causal relationship has not been approved between VD and autoimmune diseases, further investigations are needed on VD supplementation benefits in the patients and at-risk individuals(42,43).

In 2018, Jian et al found that high dose VD (1200 IU) is proper for seasonal influenza prevention by viral load decreasing, rapid alleviation from symptoms and disease amelioration (44). The 1,25(OH)₂D-stimulated production of AMPs, such as defensin and cathelicidin, which as endogenous antibiotics can destroy the microbial pathogens and viruses, including the influenza virus (45). Hence, for a comprehensive outlook to VD effect on viral infections, more randomized controlled trials and large studies are required. (Figure 2)

Vitamin D and its antioxidant effects

A balance disruption in the oxidant to-antioxidant ratio is defined as oxidative stress. It leads to generate the ROS molecules that result in several events such as: releasing inflammatory mediator activation, and irreversible oxidative modification of lipids, proteins, and carbohydrates (46,47).

VD and Calcitriol (its active form) have a vital role in the homeostasis of the body. VD antioxidant activity has been proposed since 1993 and it is currently known as a potent non-enzymatic anti-oxidant agent that prevents the ROS generation. It facilitates the balanced state of mitochondrial activities, and also it prevents oxidative stress, and DNA damage (48,49). 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 (50). 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 (51,52). The expression of glutathione peroxidase is also under the influence of VD. This enzyme converts the ROS molecule H₂O₂ to water (53). VD may regulate the oxidative stress through two potent ways: prompts the expression of glutathione, glutathione peroxidase and superoxide dismutase (SOD) that have an antioxidant function, and suppresses the expression of NADPH oxidase (54).

One experimental study displayed that oxidative stress due to superoxide dismutase (SOD) and catalase enzymes could reduce the muscular activity in rats associated with VD deficiency (55). Some other studies determined that the administration of VD in diabetic mice led to suppressing the gene expression of NADPH, assisted to reduce the ROS production (56,57).

In 2016 Uberti et al. 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 (58).

In diabetic patients, hyperglycemia could induce oxidative stress and inflammatory responses that are known as hepatocellular damaging factors. Accumulation of oxidative stress markers in diabetes mellitus (DM) is due to a reduced level of glutathione (46). It seems that secondary complications of DM are induced by oxidative stress (59). Abdulmonim et al. demonstrated that VD administration in diabetic rats could reduce the oxidative stress and improve the inflammation (60). Suliman Alatawi et al. reported the same results in their study (59). Another study showed that co-supplementation of magnesium-zinc-calcium-VD could reduce the inflammation and oxidative stress markers in patients with gestational diabetes (61). A randomized clinical trial study 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 (62). Igde et al. exhibited a positive impact of VD on the reduction of plasma concentrations of oxidative stress markers in inflammation-related oxidative stress in asthmatic patients (63). One another study that was done on human tubular epithelial cells revealed that VD prevented high glucose concentration induced oxidative stress (49). (Figure 2)

Vitamin D and cardiovascular protection

The cardiovascular tract is a commonly involved system in the patients with COVID-19 which can be affected through three following ways (64): The severity of cardiovascular disease (CVD) could be increased in the patients with preexisting CVD; The incidence rate of multiple direct

and indirect CVD-attributed complications would be raised including the acute myocardial injury, myocarditis, arrhythmias, and venous thromboembolism; The side effects of therapeutic approaches for COVID19 may be a threat for the cardiovascular tract.

According to one recent study, up to 40% of 138 patients admitted with COVID19 had pre-existing CVD. Moreover, 7.2% of the patients had elevated cardiac troponin, suggestive for the virus-induced cardiac injury(65). According to another research, 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 (66). However, in a research among 41 patients with COVID19 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 (67).

SARS-CoV2 may result in downregulating the myocardial and pulmonary ACE2 pathways. ACE2 is expressed in the heart, providing a link between coronaviruses and the cardiovascular system, and its interaction with the virus may directly cause myocardial inflammation. Besides, the up-regulation of 15 pro-inflammatory cytokines could lead to a systemic inflammatory response syndrome that may provide a possible mechanism for multi-organ failure (usually involving the heart) in severe cases (68). The RAS disturbance and increased AngII 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 causes cell damage. Also, AngII can lead to peroxynitrite damage on the vascular endothelial surface by the over-expression of Profilin-1(69).

Researches on 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. VD₃ significantly reduces the oxidative stress in the vascular system and can reverse the damages that high blood pressure, diabetes, atherosclerosis, and other diseases inflict on the cardiovascular system(70). 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(71). However, it seems that the relationship between 25-hydroxyVD and CVD was nonlinear and reached a plateau between 20 and 30 ng/ml. Moreover, the Third National Health and Nutrition Examination Survey (NHANES III) presented no significant association between serum 25-hydroxyVD and CVD-induced mortality.(72)

VD can also improve cardiac oxidative stress and inflammatory markers. Murr et al. showed 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 (73). One study on VD deficient animal model demonstrated that VD deficiency leads to increased blood pressure and supported vascular oxidative stress in rats (74). It sounds that VD has a protecting role from oxidative stress and inflammation in cardiac tissue.

The definite mechanism of VD to protect against CVD has not been obvious. Some studies declare 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 1 α -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 (75,76).

Yan Chun Li et al 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(77).

Moreover, VD reduces Superoxide Anion Generation and also endothelial cell apoptosis induced by H₂O₂. The activation of MEKs/ERKs-signaling pathway, which inhibits apoptosis, is occurred by the up-regulation of SirT-1(78). According to studies on mice, VD down-regulates tumor necrosis factor- α (TNF- α), inducing cardiomyocyte hypertrophy, by inhibiting NF- κ B/p65 signaling (79). Furthermore, VD has an anti-fibrotic role in cardiovascular system by increasing the expression of several antifibrotic factors and reducing the expression of TGF- β 1, plasminogen activator inhibitor 1 and collagens I and III (80). Another study shows that VD protects the cell membranes against free radical-induced oxidative damage by inhibition of lipid peroxidation(81). (Figure 3)

Vitamin D and neuroprotection

By presenting of neurologic manifestations in patient with Covid-19, Possible neuroinvasion feature of Covid-19 is a remarkable topic of new papers(82). Forexample, Mao et al has reported that 78(36.4%) of 214 patients had neurologic 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%]) (83). In another study in Italy, 20 (33.9%) of 59 patients reported at least one olfactory or taste disorder(84). In addition to 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(85). Further autopsy studies presents neuronal necrosis, glial hyperplasia, and edema with the presence of SARS-CoV in brains(86). Moreover, presence of SARS-COV RNA in CSF adds support to the theory this new virus can also cause neurologic damages(87,88). The reported Cases of acute myelitis , acute hemorrhagic necrotizing encephalopathy and meningitis/encephalitis associated with SARS-CoV-2 declares the neuroinvasive potential of this virus(88–90). SARS-CoV can spread to CNS trans-neuronally from the olfactory bulb or through blood circulation(91). Besides, expression of ACE2, possible receptor of SARS-CoV-2 is detected in neurons and astroglial cells of different parts of CNS especially in cardiovascular brain regions(92,93). Hence, SARS-COVinfection of regions like dorsal vagal complex, critical for cardiorespiratory function, can be the cause of mice death primarily as a direct result of CNS, not pulmonary,infection(91). Intraction of virus and ACE2 can interfere with the balance of the RAS system which leads to organ damage by enhancement of Ang II/Ang(1-7) ratio(20). In addition, intraction of ACE2 in the capillary endothelium and SARS-CoV-2 spike protein may also damage the blood–brain barrier and enter the CNS(94). Putting results of Other researches together amplifies the possibility of excessive increase in levels of proinflammatory cytokines/chemokines, cytokine storm, in the brain of covid-19 patients; forexample, 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(91,95). Another study represents increase of proinflammatory mediators, such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (Cox-2), IL-6, IL-1 β , TNF- α , and MCP-1 in microglia of animal

models due to Japanese encephalitis virus infection(96). Additionally, CoV infected glial cells cultured secrete inflammatory factors such as IL-6, IL-12, IL-15, and TNF- α (97).

1,25-dihydroxyvitamin D₃ receptor VDR is expressed widely in glial cells and neurons of the different regions of adult brain especially throughout the olfactory system(98,99). Also, 1 α -hydroxylase (1 α -OHase), the enzyme responsible for the formation of the active vitamin and was found in both neurons and glial cells(99). 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(100,101) VD can also interfere with regulation of inflammation, neurodegeneration, and repair processes within the CNS(102) VD regulates some neurotrophic agents like nerve growth factor (NGF), neurotrophin 3 (NT3), glial cell line-derived neurotrophic factor (GDNF)(103–105). GDNF works against ischemia, injury and 6-hydroxydopamine (6-OHDA) toxicity (106–108).

VD also has an anti-inflammatory potency by inhibiting the production of IL-6, TNF α and NO by activated microglia in vitro(109). More study on 1,25-(OH)₂D₃-treated astrocytes represents reduction in tumor necrosis factor α (TNF- α) and macrophage colony-stimulating factor (M-CSF) in them(110). Moreover, VD has neuroprotective roles through induction of Ca²⁺-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 (111–113). Furthermore, VD has a strong anti-oxidant function in brainup; it regulates γ -glutamyl transpeptidase activity, which is involved in the glutathione cycle, in rat brain(114). Vitamin D also can decrease multiple sclerosis (MS) development by modulation of immune responses(115). (Figure 3)

Conclusions

SARS-CoV2, the viral cause of COVID19, through upregulation of the RAS pathway and inducing a cytokine storm leads to lethal infection with multiple organ damages, particularly in the respiratory and cardiovascular tracts. 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, up-regulating of glutathione, glutathione peroxidase and superoxide dismutase, and down-regulating the NADPH oxidase. RAS pathway can also down-regulated by VD which may prevent the cardiovascular complications induced by COVID19. Moreover, there are many experimental studies due to the potential protective effects of VD against the COVID19-induced morbidities. It seems VD supplementation therapy, at-least in VD deficient patients, can prevent the lethal side-effects of the infection; An issue which could be evaluated at the next well-designed clinical trials. (Figure 1)

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Infographic Figures

A review on molecular aspects of Vitamin D effects against COVID19

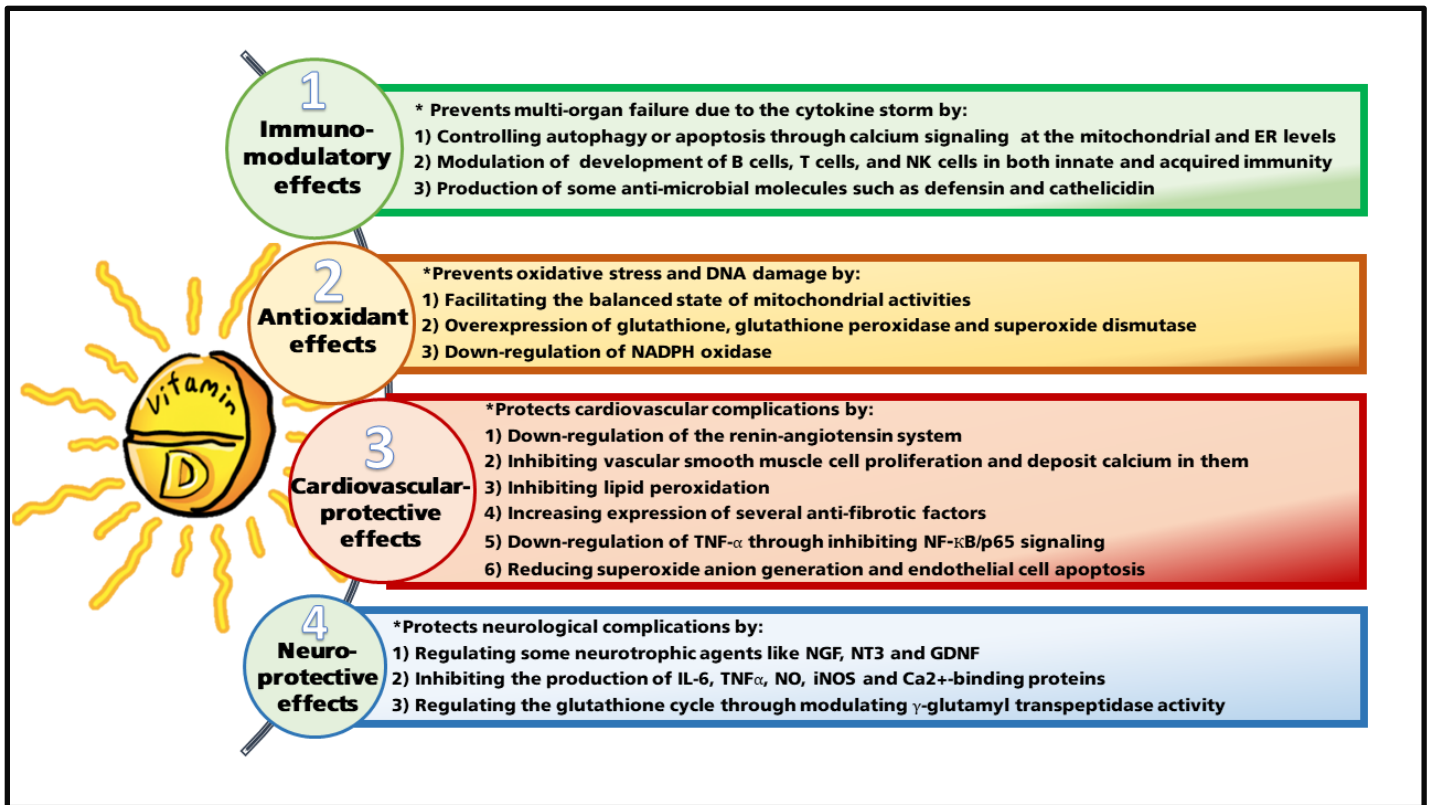


Figure 1. An infographic diagram illustrating the immuno-modulatory(1), anti-oxidant(2), cardioprotective(3) and neuroprotective(4) potencies of vitamin D against COVID-19 and molecular pathways involved.

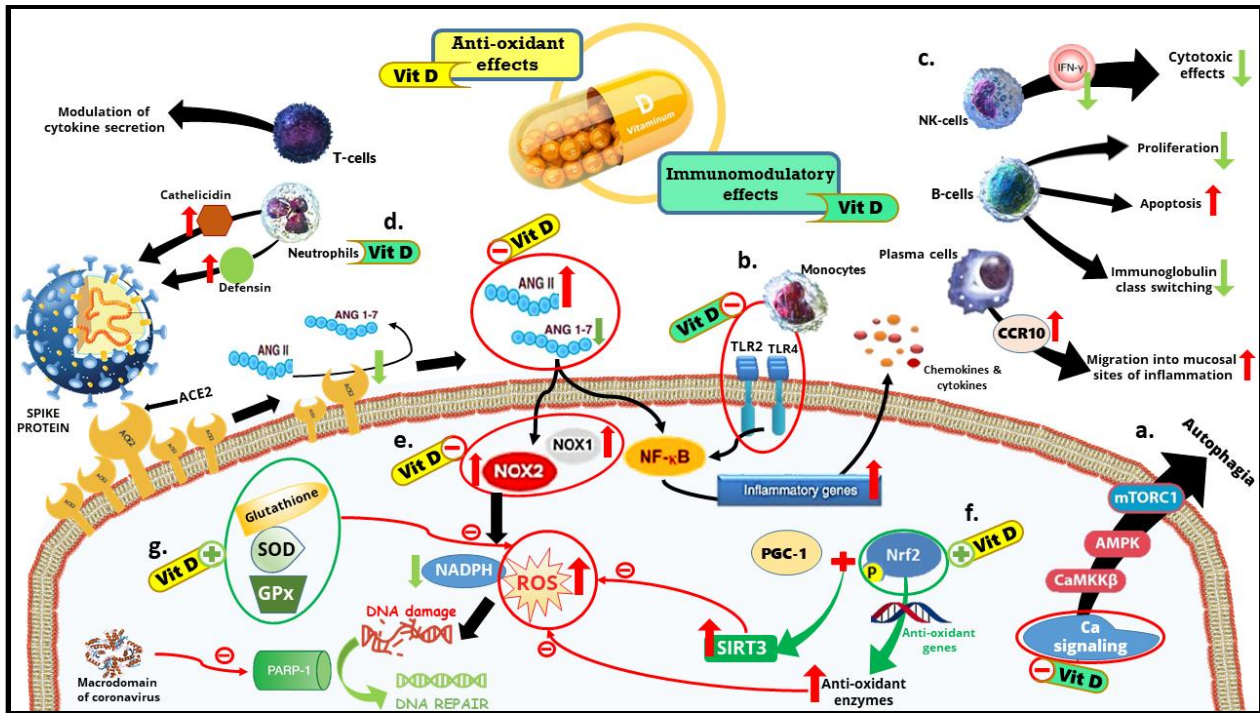


Figure 2. An infographic picture illustrating the molecular pathway of anti-oxidant and immunomodulatory effects of vitamin D against SARS-CoV-2 pathogenesis:

- (a). Vitamin D controls the autophagy through calcium signaling at the mitochondrial and ER levels. (CaMKK β : Ca²⁺/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.
- ANG: Angiotensin

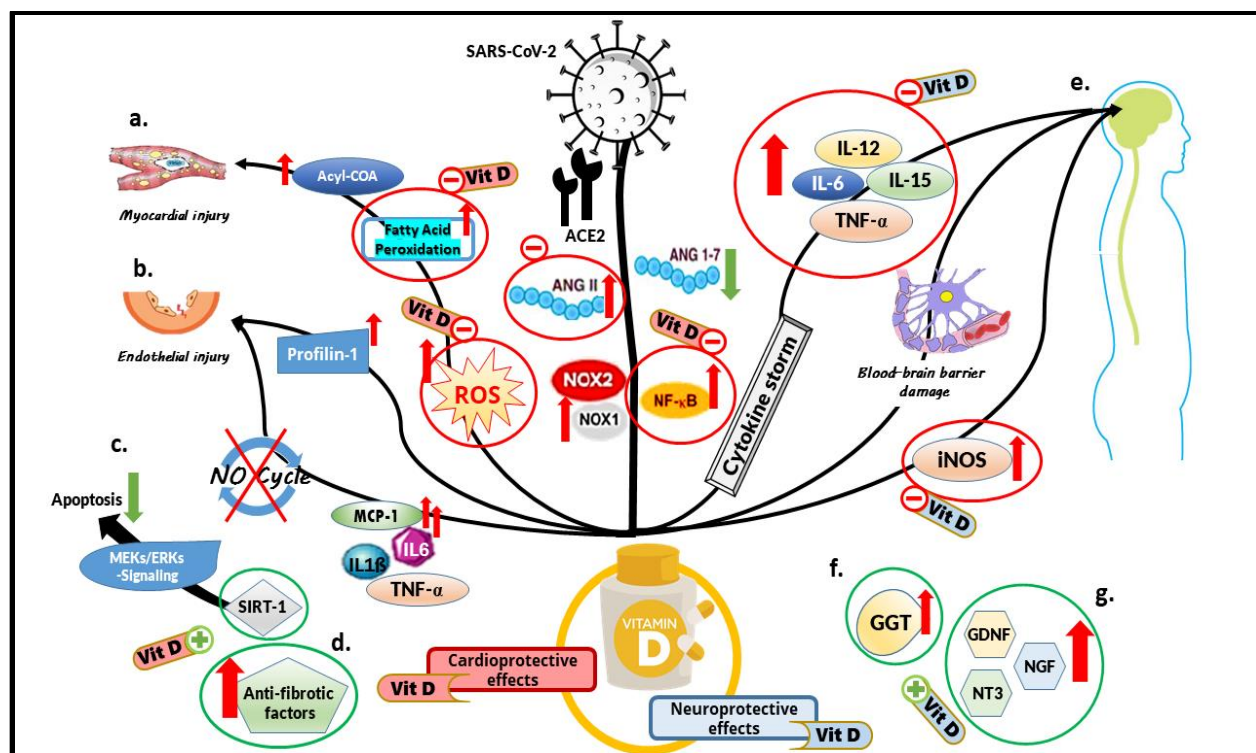


Figure 3. An infographic picture illustrating the molecular pathway of destructive effects of SARS-CoV-2 on cardiovascular and nervous systems in COVID-19 and also the molecular mechanism of vitamin D effects against them:

- (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-1 β , 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 peroxy-nitrite damage on the vascular endothelial. Vitamin D counteracts this cytokine storm by inhibiting NF- κ B/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