Received: 26 July 2021 | Revised: 18 September 2021 | Accepted: 21 September 2021

DOI: 10.1002/pro.4190

REVIEW

Vitamin D and COVID-19: A review on the role of vitamin D in preventing and reducing the severity of COVID-19 infection

Mobeen Abdrabbo | Cole M. Birch | Michael Brandt | Kelsey A. Cicigoi | Stephen J. Coffey | Connor C. Dolan | Hannah Dvorak | Ava C. Gehrke | Audrey E. L. Gerzema | Abby Hansen | Ethan J. Henseler | Alyssa C. Huelsbeck | Ben LaBerge | Caterra M. Leavens | Christine N. Le | Allison C. Lindquist | Rickaela K. Ludwig | Jacob H. Reynolds | Nathaniel J. Severson | Brandon A. Sherman | Hunter W. Sillman | Michael A. Smith | Macey A. Smith | Marissa J. Snortheim | Levi M. Svaren | Emily C. Vanderpas | Miles J. Wackett | Alec J. Wozney | Sudeep Bhattacharyya | Sanchita Hati

Department of Chemistry and Biochemistry, University of Wisconsin-Eau Claire, Eau Claire, Wisconsin, USA

Correspondence
Sanchita Hati, Department of Chemistry and Biochemistry, University of Wisconsin-Eau Claire, Eau Claire, WI, USA.
Email: hatis@uwec.edu

Abstract

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a pathogenic coronavirus causing COVID-19 infection. The interaction between the SARS-CoV-2 spike protein and the human receptor angiotensin-converting enzyme 2, both of which contain several cysteine residues, is impacted by the disulfide-thiol balance in the host cell. The host cell redox status is affected by oxidative stress due to the imbalance between the reactive oxygen/nitrogen species and antioxidants. Recent studies have shown that Vitamin D supplementation could reduce oxidative stress. It has also been proposed that vitamin D at physiological concentration has preventive effects on many viral infections, including COVID-19. However, the molecular-level picture of the interplay of vitamin D deficiency, oxidative stress, and the severity of COVID-19 has remained unclear. Herein, we present a thorough review focusing on the possible molecular mechanism by which vitamin D could alter host cell redox

Abbreviations: ACE2, angiotensin-converting enzyme 2; ARE, antioxidant response element; cAMP, cyclic adenosine monophosphate; CBS, cystathionine β-synthase; CRE, cAMP response element; CREB, cAMP response element-binding protein; Cys, cysteine; G6PD, glucose-6-phosphate dehydrogenase; GCL, glutamate-cysteine ligase; GR, glutathione reductase; GSH, glutathione; GSSG, oxiglutathione; H_2O_2, hydrogen peroxide; HIV, human immunodeficiency virus; IFN-γ, interferon-gamma; IL, interleukins; LMW, low-molecular-weight; Nrf2, nuclear factor-erythroid factor 2-related factor 2; $O_2^{\bullet-}$, superoxide ion; $OH^{\bullet}$, hydroxyl radical; PD, peptidase domain; PDI, protein disulfide isomerase; RAAS, renin-angiotensin-aldosterone system; RBD, receptor-binding domain; ROS, reactive oxygen species; RSV, respiratory syncytial virus; RXR, retinoid X receptor; S protein, spike protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SOD, superoxide dismutase; Th, T helper; TNF-α, tumor necrosis factor-alpha; Trx, thioredoxin; TXNIP, thioredoxin-interacting protein; VDR, vitamin D receptor; Vitamin D_3, 1 α,25-dihydroxycholecalciferol [$1\alpha,25(OH)_2D_3$].

status and block viral entry, thereby preventing COVID-19 infection or reducing the severity of the disease.

KEYWORDS

cholecalciferol, COVID-19, oxidative stress, SARS-CoV-2, vitamin D

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) is a highly infectious respiratory disease caused by a novel coronavirus known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] To date, about 180 million people have been infected by COVID-19 and more than 3.8 million people have died worldwide as a result.[2] The current outbreak of infections with SARS-CoV-2 has led scientists to investigate the genomic and structural details, the molecular mechanism of viral entry into host cells, and the infectivity rate of this novel coronavirus. Phylogenetic analyses of the coronavirus genomes have shown that SARS-CoV-2 belongs to the *Betacoronavirus* genus. SARS-CoV-2 is an enveloped virus, and the genome of this virus with a positive-sense single-stranded ribonucleic acid (RNA) genome consisting of about 30 kb nucleotides.[3] SARS-CoV-2 contains four structural proteins, namely spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. The entry of SARS-CoV-2 into human cells initiates through the transmembrane S proteins that exist as trimers and protrude from the virus surface. The S protein of SARS-CoV-2, which plays a key role in the receptor recognition and cell membrane fusion process, is composed of two subunits, S1 and S2. The S1 subunit contains a receptor-binding domain (RBD) that recognizes and binds to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell surface while the S2 subunit mediates viral cell membrane fusion by forming a six-helical bundle via the two-heptad repeat domain.[4,5] ACE2 is a type I membrane protein expressed in multiple organs such as the lungs, heart, kidneys, testes, intestines, and endothelial cells of arteries. The primary physiological role of ACE2 is in the conversion of angiotensin II (Ang II) to Ang-(1–7), a peptide hormone that induces vasodilatory, anti-inflammatory, antifibrotic, antiangiogenic, and antihypertensive effects.[6] The crystal structure of SARS-CoV-2 RBD bound to ACE2 revealed that there are thirteen hydrogen bonds and two salt bridges at the protein–protein interface.[7] A close analysis of the structure showed four intramolecular disulfide bonds between cysteine residues in the RBD of SARS-CoV-2. Among these four disulfide bonds, three (Cys336–Cys361, Cys379–Cys432, and Cys391–Cys525) are in the core of the RBD and provide structural architecture by stabilizing the β-sheets. The fourth disulfide bond (Cys480–Cys488) is present in the loop region at the C-terminal of the RBD.[7] This disulfide bridge is responsible for maintaining a conformation that favors strong interaction between SARS-CoV-2 RBD and ACE2 receptor.[7,8] Computational and experimental studies have revealed a higher binding affinity of the SARS-CoV-2 RBD for the ACE2 receptor than that of SARS-CoV, another type of coronavirus.[8,9] The SARS-CoV contains only two disulfide bonds in the RBD as well as one less residue between the Cys480 and Cys488, which alters the length of the loop formed by the Cys480–Cys488 disulfide bond. It is believed that these differences could contribute to the stronger binding between the SARS-CoV-2 RBD and the ACE2 receptor and may be the reason for the differences in the viral infectivity and proliferation among coronaviruses. The reduction of the Cys480–Cys488 disulfide bond to thiols causes a significant conformational change in the loop region, which in turn results in reduced binding as confirmed by binding free energy calculations.[8,9] A very recent study demonstrated that the disruption of disulfide bonds within the RBD of the SARS-CoV-2 spike protein prevents fusion and viral entry.[10]

Similarly, the disulfide linkages in the ACE2 receptor are also reported to contribute to the severity of SARS-CoV-2 infection. The human ACE2 receptor sequence contains eight cysteine residues, of which six are conserved across ACE2 receptors of other species and form three disulfide bonds (Cys133–Cys141, Cys344–Cys361, and C530–C542). The Cys133–Cys141 disulfide bond is a part of a loop at the ACE2 dimer interface that contributes to the entry of SARS-CoV-2. These cysteine residues (Cys 133 and Cys 141) are mostly conserved among species apart from pigs, belugas, and cattle, where a leucine has replaced Cys133.[8] Species lacking the Cys133–Cys141 disulfide bond are not affected by SARS-CoV-2.[8] These observations indicate that the disulfide bonds play important roles in the binding of SARS-CoV-2 to the human ACE2 receptor. In particular, the disulfide bonds Cys133–Cys141 of the ACE2 receptor and Cys480–Cys488 of the spike glycoprotein play vital roles in receptor binding and viral infectivity mechanisms.[8]

The thiol-disulfide forms of cysteine residues are modulated by the redox status of the cellular

environment. Redox status is regulated by intracellular levels of reactive oxygen species (ROS)/reactive nitrogen species (RNS) and antioxidants. ROS are comprised of oxygen-containing free radical and nonfree radical chemical species, which are the by-products of cellular respiration and other biological processes such as prostaglandin synthesis and xenobiotics metabolism by cytochrome P450 systems.[11,12] The most common ROS is the superoxide ion ($O_2^{\bullet -}$), which is produced by NADPH oxidase, xanthine oxidase, and peroxidases, and is involved in reactions that lead to the generation of other ROS such as hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\bullet}$), hypochlorous acid, and so on.[12] The common RNS are nitric oxide (NO), nitrosyl anion (NO^-), peroxynitrite ($ONOO^-$), and so on. These ROS and RNS, together known as RONS, act as signaling molecules and regulate important biological and physiological processes such as cell division, stress and inflammation response, immune function, and autophagy.[13,14] The production and neutralization of RONS must be tightly regulated to have an intercellular redox balance. The uncontrolled production of RONS leads to oxidative stress, creates an oxidative environment that is damaging to lipids, proteins, and DNA, and can also contribute to chronic diseases.[13] The oxidative environment also facilitates the binding of SARS-CoV-2 with the ACE2 receptor.[8,9] Under an oxidative environment, cysteine residues form disulfide bonds that favor the tight binding of S proteins of SARS-CoV-2 with the human ACE2 receptor.[9] This supports the observations that SARS-CoV-2 seems to heavily affect or have worsening severity among the older population and populations with underlying health conditions that are associated with the elevation of oxidative stress. Maintaining the reduced form of cysteine minimizes the binding affinity between SARS-CoV-2 and the ACE2 receptor.[8,9] Antioxidants eliminate RONS and have the potential to reduce viral infectivity and the severity of SARS-CoV-2 infection.[15]

The role of vitamin D in the prevention of the ongoing SARS-CoV2 infection has been investigated.[16–18] However, there is no consensus in the scientific community about the efficacy of vitamin D supplementation in preventing and reducing the severity of the COVID-19 infection. For example, recent clinical studies have not found any direct correlation between vitamin D supplementation and COVID-19 outcomes.[19,20] On the other hand, it has been observed that the COVID-19 cases are much lower and less severe in countries closer to the equator than those farther away from the equator; likely due to increased sun exposure, which is the natural source of vitamin D.[17] Furthermore, clinical studies by Meltzer et al.[21] have shown that the relative risk of COVID-19 infection nearly doubles for patients with vitamin D deficiency. Because of these inconsistent reports, it seems critical to understand the role of vitamin D at the molecular level, especially in the context of COVID-19 infection. As the binding of the viral protein with the host cell receptor depends on the thiol-disulfide balance,[8,9] it has become increasingly important to explore the role of vitamin D in maintaining the redox status of the host cell. Herein, we explored the molecular mechanism by which vitamin D could prevent and reduce the severity of COVID-19 infection. We investigated vitamin D's skeletal and nonskeletal functions. For the latter case, the impact of vitamin D on the immune system and the regulation of antioxidants, both low molecular weight (LMW) thiols and redox proteins, are thoroughly examined.

2 | VITAMIN D AND ITS SKELETAL AND NONSKELETAL FUNCTION

Vitamin D is a fat-soluble secosteroid and is an essential micronutrient in many metabolic processes.[22] One major function of vitamin D is supporting skeletal health; it plays a crucial role in calcium homeostasis and bone metabolism. Vitamin D has antioxidant properties and helps regulate inflammation and oxidative stress in a variety of tissues. It reduces the risk of many diseases such as inflammatory and autoimmune disorders, chronic kidney disease, cardiovascular disease, type 1 diabetes mellitus, hypertension, and some cancers.[23–25] All of these diseases are also known to be associated with increased oxidative stress.

2.1 | Discovery of vitamin D

In the early 20th century, the bone disorder rickets was found to be more prevalent in areas of low sun exposure. This correlation established a link between sunlight and skeletal health.[24] Eventually, this led to the discovery of a new vitamin that is synthesized through UV light. This supplement was named vitamin D; it manages serum calcium and phosphorus levels and promotes optimal absorption of those minerals.[25] The preservation of bone mineral homeostasis ensures the proper development, remodeling, and maintenance of bone.[24] Additionally, vitamin D supports the health of other organ systems and cellular functions, namely cell proliferation, immune system response, and protection against malignant tumor formation.[26,27] The source of vitamin D is mainly through sun exposure, however, it can also be obtained through dietary sources and supplements.[27]

Vitamin D has two main forms—D_2, ergocalciferol, is formed through irradiation by UV light in plants, and D_3, cholecalciferol, is formed through irradiation by UV light in animals. Cholecalciferol is formed specifically by converting 7-dehydrocholesterol to its metabolically active form 1,25-dihydroxycholecalciferol [1α,25-dihydroxyvitamin D_3 or $1\alpha,25(OH)_2D_3$].[28] The active form [$1\alpha,25(OH)_2D_3$], which will be referred hereafter as vitamin D, is important for biological functions in animals. The crystal structure of vitamin D was solved and published in 1996 by Suwińska & Kutner through X-ray diffraction.[29] The chemical structure of vitamin D [$1\alpha,25(OH)_2D_3$] is shown in Figure 1. It was found that the bond shapes and angles are consistent with steroid-like compounds, providing structural evidence that vitamin D is fat-soluble.

2.2 | Vitamin D and vitamin D receptor

The active form of Vitamin D, $1\alpha,25(OH)_2D_3$, is a signaling molecule, which regulates the expression of ~3% of the transcribed genome in target cells. Most biological functions of vitamin D such as proliferation and differentiation of several cell lines including keratinocytes, endothelial cells, osteoblasts, and lymphocytes are mediated by vitamin D receptor (VDR), which is a transcription factor and is widely distributed among different cell lineages.[30] VDR belongs to the family of steroid receptors and forms a heterodimer with the retinoid X receptor (RXR).[31] VDR/RXR heterodimers bind to the vitamin D response elements in target genes, resulting in either activation or repression of transcription of target genes. In fact, VDR is composed of two distinct domains—the ligand-binding domain binds the vitamin D hormone, and the DNA-binding domain binds the genomic DNA. The liganded VDR/RXR complex modulates the activity of RNA polymerase II and the transcription of hundreds of target genes per cell type. Therefore, the liganded VDR plays an important role in the maintenance of skeletal as well as nonskeletal functions such as cardiovascular, renal, metabolic, and immune functions.[32,33]

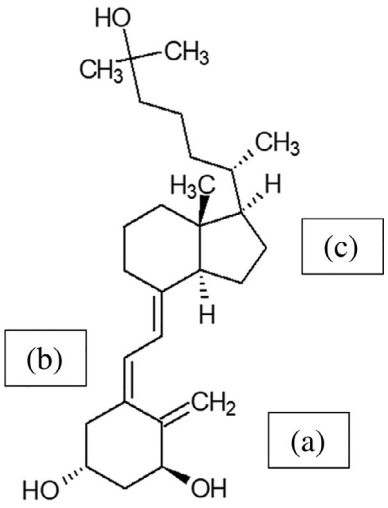

FIGURE 1 Structure of 1,25-dihydroxycholecalciferol, the active form of vitamin D_3. The A ring (a) is connected to the CD-ring system (c) by a triene system (b). The A ring mediates the interactions with the vitamin D receptor

2.3 | Vitamin D structure and its skeletal function

One crucial role of vitamin D is maintaining the blood serum calcium and phosphate homeostasis; it aids in bone mineralization and maintenance. Working in conjunction with the liver, skeletal system, intestines, and parathyroid hormone, vitamin D increases calcium ion (Ca^{2+}) concentration when serum Ca^{2+} level is below normal (2.2–2.6 mM).[23] It signals the intestine to increase absorption of Ca^{2+} from digested materials at the brush border membrane of the intestines. Vitamin D-bound or liganded VDR regulates the expression of calcium channel TRPV6 (a member of transient receptor potential family), calcium-binding and translocating protein calbindin-D9K, and the plasma membrane calcium ATPase (PMCA1b). These proteins facilitate Ca^{2+} cellular entry, binding, and basolateral extrusion respectively, to ultimately increase Ca^{2+} serum levels.[34,35] The mechanism of phosphate concentration homeostasis (phosphate level is maintained at 0.8–1.45 mM) by vitamin D is not yet clearly understood. One suggested mechanism is that vitamin D regulates the transcription of type IIb sodium phosphate co-transporter in the brush border membrane of the intestines.[36] This protein actively transports phosphate using a sodium ion gradient and accounts for most of the phosphate transport into the intestinal epithelial cells.[37]

2.4 | Vitamin D and its nonskeletal function

Vitamin D has several health benefits. An important role of vitamin D that has recently come to light is its effect on cellular apoptosis. Both in vivo and in vitro studies have established that higher serum levels of vitamin D (the active metabolite $1\alpha,25(OH)_2D_3$) and its analog EB1089 are inversely correlated with colorectal cancer growth.[38] A more recent epidemiological study reinforced this data by looking at analysis from randomized clinical trials. Serum levels of vitamin D greater than or equal to

40 ng/ml showed a significant reduction in many cancer types. A concentration of ≥40 ng/ml showed a 67% lower risk of cancer in women than a concentration of <20 ng/ml.[39]

The discovery of the active form of vitamin D led to the discovery of VDR and subsequently to the presence of this receptor on cells not originally correlated with vitamin D activity.[40] For example, VDRs on the parathyroid gland and their effect on transcriptional regulation as well as possible epigenetic roles were reported.[40] These findings led to the discovery of vitamin D acting as a regulatory hormone for genes throughout the body, some of which act as important regulators of cell proliferation/cell cycle arrest.[30,41]

3 | VITAMIN D AND THE IMMUNE SYSTEM

Well known for its role in the regulation of Ca^{2+} and maintaining the expression of Ca^{2+} pumps, exchangers, and buffers,[42] vitamin D also plays a role in the body's immune response to bacterial and viral pathogens. Humans have two types of immunity—innate and adaptive, and vitamin D modulates both innate and adaptive immune responses and has an impact on the suppression of the inflammatory process.

3.1 | Vitamin D and immune responses to virus

Several studies have investigated the role of vitamin D in the immune response to the influenza virus, respiratory syncytial virus (RSV), dengue virus, hepatitis C virus, hepatitis B virus, human immunodeficiency virus (HIV), and SARS-CoV-2.[43] In particular, the vitamin D status in patients and the mechanism of its action on the immune system were thoroughly investigated.

Studies were performed where cohorts of patients with HIV had their vitamin D levels monitored in addition to infection progression. It was found that those with lower baseline vitamin D levels experienced faster disease progression.[44,45] Another study found that children with high vitamin D levels were less likely to contract influenza.[46] In the case of Hepatitis C, it was also found that vitamin D supplementation improved the body's response to the virus. Low levels of vitamin D were correlated with a reduced sustained viral response in patients with Hepatitis C.[47–49] In regard to RSV and dengue virus, multiple studies were performed to investigate the role vitamin D plays in disease progression. A mutation in VDR is correlated to more severe disease progression in RSV patients.[50,51] Also, treatment of Dengue-infected monocytic U937 cells with vitamin D resulted in a significant reduction in the number of infected cells; vitamin D also lowered the levels of proinflammatory cytokines.[52] In a separate study, VDR agonists were found to have antiviral activities.[53] It has also been reported that vitamin D has a preventive effect on SARS-CoV-2 viral infection, which causes immune activation and systemic hyperinflammation.[54]

3.2 | Vitamin D and T and B cells activation

Vitamin D plays a role as an immunomodulator in the inflammatory response pathway.[55] T and B cells are the major cellular components of the adaptive immune response. Vitamin D's role in monocytes[43] and T and B cells' immune response is also known. VDRs are expressed at detectable levels only in active T and B cells. Upon activation of an antigenic response and consequentially T and B cells proliferation, VDR levels increase.[55,56] This observation suggests the possibility that vitamin D and VDR have anti-proliferative effects on T and B cells.

3.3 | Vitamin D, cytokine storm, and inflammatory response

In many patients, COVID-19 induces a cytokine storm, which is one of the main factors that cause acute respiratory distress and multiple organ dysfunction syndromes.[57,58] Cytokine storms occur when the inflammatory response is systemically stimulated. This is due to an aggressive inflammatory response with the release of many proinflammatory cytokines. It has been observed that that severely ill COVID-19 patients tend to have a high concentration of proinflammatory cytokines. The proinflammatory cytokines that play a role in cytokine storms include interleukins 1, 2, and 6 (IL-1, IL-2, IL-6), interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α).[59] A proposed mechanism of how cytokine storms are stimulated includes rapid activation of T cells. High amounts of antigen result in elevated levels of immune activation in a local area of infection. This immune response can spill over into the circulatory system, where the proinflammatory response is spread systemically.[60] Since many cytokines are regulated through positive feedback, higher proinflammatory cytokines concentrations lead to upregulation of the immune response. Physiological results of cytokine storms include vasodilation that can lead to decreased blood pressure, hypoxia, organ failure, and ultimately death.

Vitamin D plays an important role in regulating proinflammatory cytokines that can lead to cytokine storms. Specifically, vitamin D can downregulate the production of proinflammatory cytokines (IL-1, IL-2, IL-6, IFN-γ, and TNF-α), increase the production of anti-inflammatory cytokines such as IL-10, IL-4, IL-5, and transform growth factor-beta.[61] T helper (Th) cells are important in activating adaptive immunity and releasing cytokines to direct a specific immune response. The Th1 cell type plays a role in producing pro-inflammatory cytokines whereas the Th2 cell type releases inhibitory cytokines. The binding of dendritic cells to vitamin D via VDR induces inhibition of IL-12 production, a cytokine required for Th1 activation.[62] The interaction of the dendritic cell with vitamin D not only inhibits Th1, but upregulates Th2 and T regulatory lymphocytes, which are important for maintaining equilibrium between inhibitory and inflammatory cytokines.[62] Clinically, low levels of vitamin D have been associated with a decrease in T regulatory lymphocytes, an increase in inflammatory cytokines, and an overall increase in the likelihood of developing severe infection.[63]

3.4 | Vitamin D, Klotho, and Nrf2 regulatory network

COVID-19 infection is associated with cytokine storm and oxidative stress.[58,64,65] Recent studies have indicated that vitamin D plays an important role in reducing oxidative stress through the activation of several antioxidant pathways and the inhibition of ROS-activating pathways. Several studies have revealed a direct correlation between oxidative stress and deficiency of vitamin D.[66,67] Hormones and antioxidant signaling pathways are regulated by vitamin D. One such hormone is Klotho, a phosphate regulating hormone.[68] Klotho has an anti-aging property and reduces oxidative stress.[42] Vitamin D also enhances the activity of nuclear factor-erythroid factor 2-related factor 2 (Nrf2).[69] Nrf2 is an important component in the regulation of oxidative stress; it acts as a transcription factor and controls basal and induced expression of varieties of antioxidant response elements (AREs) and detoxifies ROS via the Nrf2-ARE-signaling pathway.[13,70] Both Nrf2 and Klotho genes are activated when the VDR binds to the RXR and the vitamin D response element.[42]

Moreover, the Nrf2-Keap1 (Kelch-like ECH-associated protein 1) antioxidant pathway is activated by vitamin D. Keap1 is a key sensor of oxidative stress as it acts as a key regulator of the Nrf2 transcription factor. Keap1 acts as a substrate adaptor that catalyzes polyubiquitination of the Nrf2 protein.[13] During states of oxidative stress, Nrf2 is phosphorylated, disassociating it from the Keap1 and allowing it to translocate into the nucleus for expression. Nrf2 binds the ARE, which promotes the upregulation of ARE genes that work to inhibit oxidative stress and maintain the redox balance. The impact of vitamin D in Nrf2 expression provides a potential mechanistic explanation to the findings that countries closer to the equator, whose populations receive more vitamin D, have significantly less severe cases of SARS-CoV2.[17]

4 | VITAMIN D AND THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Studies suggest that vitamin D can lower the risk of COVID-19 infections because it affects the renin-angiotensin-aldosterone system (RAAS).[71] RAAS includes the ACE2 receptor, which is vital for the entry of SARS-CoV-2 into host cells.

4.1 | Renin-angiotensin-aldosterone system

RAAS is an important hormone system that regulates blood pressure, fluid volume, and sodium-potassium balance. The system is mainly comprised of the three hormones—renin, Ang II, and aldosterone. The mechanism of converting prorenin (the inactive form) to renin (the active form) occurs in the juxtaglomerular cells in the afferent arterioles of the kidney. These cells are activated when there is a decrease in blood pressure, beta-activation, or sodium levels in distal convoluted tubules. The active renin is released into the blood and cleaves angiotensinogen into angiotensin I (Ang I) (Figure 2). Ang I is mainly inactive, but it is a precursor for Ang II.[72] Ang I is cleaved by the angiotensin-converting enzyme (ACE) to produce Ang II. The cleavage of Ang II to Ang

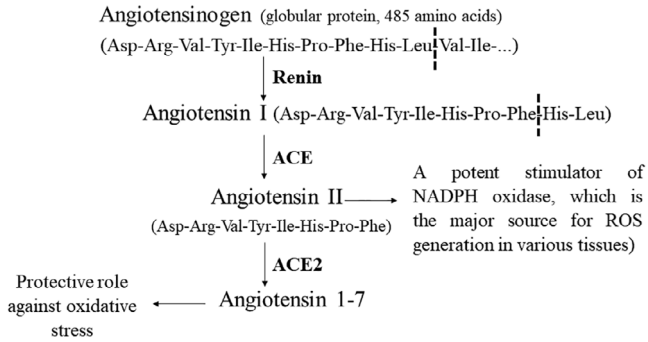

FIGURE 2 The pathway from angiotensinogen to angiotensin 1–7 is shown, along with the enzymes that catalyze these reactions

(1–7) is catalyzed by ACE2. The causation of Ang II includes strong vasoconstriction, proinflammatory, and profibrotic effects. It is also an oxidative stress enhancer.[73] On the other hand, the causation of Ang (1–7), which is an oxidative stress reducer, includes antifibrotic, antiproliferative, vasodilatory, diuretic, and natriuretic effects.[73,74] The ACE2 enzyme is a zinc-metallopeptidase and has an antagonistic relationship with the enzyme ACE. This antagonistic relationship between these two enzymes balances the RAAS pathway.[75]

4.2 | Vitamin D and its effect on RAAS

Vitamin D functions as a negative endocrine regulator of the RAAS. In vivo experiments using VDR-null mice and Cyp27b1-null mice, which lack 1α-hydroxylase required for vitamin D synthesis, demonstrated that vitamin D inhibits the renin gene transcription.[76] It was found that vitamin D targets the cyclic AMP (cAMP) signaling pathway, which plays an important role in the biosynthesis of renin.[76] In this pathway, the cAMP response element-binding (CREB) protein as a transcription factor interacts with the cAMP response element (CRE) that is located within the renin gene promoter. Normally, phosphorylation of the CREB by protein kinase-A helps to recruit coactivator CREB-binding protein (CBP) and its homolog p300. This recruitment of CBP/p300 is required for renin gene transcription activation. However, ligand-activated VDR interacts with the CREB in the presence of vitamin D and blocks CREB from binding to the CRE. Therefore, the formation of the CREB-CBP/p300 complex on the CRE is disrupted and the transcription of renin gene is halted.[76] Renin is significant because it is involved in the rate-limiting step of the RAAS pathway that converts angiotensinogen to Ang I, which gets converted to Ang II by ACE (Figure 2). It is to be noted that Ang II is a stimulator of NAD(P)H oxidase, which triggers ROS formation.[73] Under normal condition, Ang II is converted to Ang 1–7 by ACE2; however, when ACE2 is bound to S protein of SARS-CoV-2, there will be accumulation of Ang II. The presence of Vitamin D is expected to reduce the accumulation of Ang II as it prevents the transcription of renin gene.

4.3 | SARS-CoV-2 infection and the ACE2 receptor

The ACE2 receptor is expressed in the lung, heart, kidney, and intestinal cells. The ACE2 enzyme is made of an N-terminal peptidase domain (PD) and a C-terminal collectrin-like domain, ending in a transmembrane helix. The SARS-CoV-2 virus interacts with the PD of ACE2, which is known to have a claw-like structure for host cell entry. When the S-protein of SARS-CoV-2 merges with the ACE2 receptors, transmembrane serine protease 2 proteolytically cleaves ACE2 and allows the virus particles to enter the host cell, replicate, and have cell-to-cell transmission. In vitro studies demonstrated a direct correlation between the expression of ACE2 and increase in the infection of the lungs and other tissues by SARS-CoV-2.[74] RAAS inhibitors that can block the ACE2 receptor to which S protein latches onto can prevent viral entry into the heart and lungs and protects them from being injured by the SARS-CoV-2 infection.[72,74] There is also a possibility that RAAS inhibitors can cause a retrograde feedback mechanism that upregulates ACE2 receptors, which allows an increase in the binding of the S protein to the ACE2 receptors and therefore causes an increase in viral entry to the heart and lungs.[74]Additionally, as spike glycoproteins bind with the ACE2 receptor, this interaction reduces the ability of ACE2 to convert Ang II to Ang 1–7. This leads to lung injury and pneumonia because of the accumulation of Ang II, a hormone that can increase the presence of ROS in the body, which in turn also increases oxidative stress in the body.[74,77] The interplay between ACE2 and vitamin D has been reported.[78]

5 | VITAMIN D's IMPACT ON THE FUNCTION AND REGULATION OF SUPEROXIDE DISMUTASE, CATALASE, GLUTATHIONE PEROXIDASE, GLUTATHIONE REDUCTASE, AND GLUCOSE-6-PHOSPHATE DEHYDROGENASE

Cells usually maintain a reducing environment and oxidative stress occurs when the cellular levels of ROS outbalance the antioxidants. If ROS levels become too high, the redox environment is driven out of homeostasis, resulting in the oxidation of proteins, DNA, and other cellular components. Mechanisms to maintain redox status, detoxify the ROS, and balance the thiol-disulfide ratio are often triggered by the oxidation of thiol-based redox switches. These pathways are often mediated by redox-sensitive transcription factors, such as proteins with cysteine residues, which in conjunction with LMW thiols are scavengers of ROS such as H_2O_2.[69,79] One of the most abundant LMW thiols is glutathione (GSH), a tripeptide (γ-glutamyl cysteinyl glycine) that functions as a major endogenous antioxidant.[80] GSH is the main cofactor for several enzymes that are responsible for

detoxifying ROS.[14] Homeostasis of the cellular redox environment is also maintained through the action of various ROS-scavenging enzymes, including catalase, superoxide dismutase (SOD), glucose 6-phosphate dehydrogenase, glutathione reductase (GR), and glutathione peroxidase. The regulation and function of these enzymes are dependent on cellular conditions and the physiological concentration of vitamin D.

5.1 | SOD and catalase

SOD and catalase and share a vital role in neutralizing superoxide ion, $O_2^{\bullet -}$ (a major ROS), to ultimately producing H_2O as a product. SOD systems are metalloenzymes and used redox-active metals such as manganese, iron, copper, and so on. SOD systems are present in every living organism on Earth and is essential for life as they dismute the toxic $O_2^{\bullet -}$ to the less toxic hydrogen peroxide, H_2O_2 ($2\ O_2^{\bullet -} + 2H^+ \rightarrow H_2O_2 + O_2$).[81] Catalases are ubiquitous enzymes that catalyze the conversion of H_2O_2 to water and molecular oxygen ($2H_2O_2 \rightarrow 2H_2O + O_2$). The combined action of catalases and SODs helps cells to reduce and remove harmful ROS from the cytoplasm, mitigating oxidative damage to cellular constituents. If the normal function of either of these enzymes is altered, COVID-19 symptom severity is expected to increase as a result of the inhibition of Nrf2-mediated pathways and the NF-κB signaling activation pathway.[14] Studies have suggested the antioxidant property of vitamin D.[82] In particular, a study on Sprague–Dawley male weanling rats revealed that vitamin D deficient muscle encounters oxidative stress that acts as a trigger for increased muscle proteolysis in rats. Furthermore, vitamin D deficiency led to a decrease in SOD and catalase activity in the rat muscle.[82]

5.2 | Glutathione peroxidase, GR, and glutathione

There are several pathways that vitamin D helps regulate and one of the major ones is the glutathione peroxidase (GPx)/GR system. GPx catalyzes the conversion of hydrogen peroxide (H_2O_2) to water using GSH, which gets oxidized to oxiglutathione (GSSG). GR is also known as glutathione-disulfide reductase and is responsible for maintaining the supply of reduced glutathione; GR reduces GSSG back to GSH while oxidizing NADPH to $NADP^+$ (Figure 3).[83]

A current study has found that vitamin D is responsible for the upregulation of the GR as vitamin D supplementation increased the expression of the GR.[84] Jain et al. studied vitamin D's regulatory effects on GR in U937 monocytes.[84] They found that vitamin D supplements increase the levels of GSH, and consequently, the levels of GR in the cell increased as well. This study shows a direct correlation between GSH, GR, and vitamin D concentrations in the cell. GSH has also been found to stimulate vitamin D regulatory gene and increase the cellular concentrations of vitamin D, further supporting the correlation between cellular vitamin D and GSH levels.[85]

Ansari et al. found supporting evidence for a correlation between vitamin D and GPx levels in their study of prediabetic Arab adults.[16] Interestingly, the enhanced expression of GPx was seen more in males than in females. In the presence of glucose, GR activity decreased, which is likely due to a lack of need for reducing agents in the presence of excess glucose. In the study on male weanling Sprague–Dawley rats,[82] GPx and GR activities were measured and found to be more active in the group deficient in vitamin D compared to the control group. As vitamin D levels were normalized, the activity of both GSH related enzymes lowered suggesting an inverse relationship in activity between the vitamin D and these two enzymes. Another study by Dzik et al. suggested that vitamin D deficiency led to higher levels of GPx expression in human skeletal muscle to combat oxidative stress.[86] As vitamin D levels were returned to normal, a significant decrease in GPx was observed. As in the previous study, despite the increased expression of GPx, oxidative stress in the cell was seen in the form of protein carbonyls and 8-isoprostanes in lipids. This suggests that vitamin D is a necessary antioxidant within the cell that cannot be substituted for increased production of either glutathione enzyme.

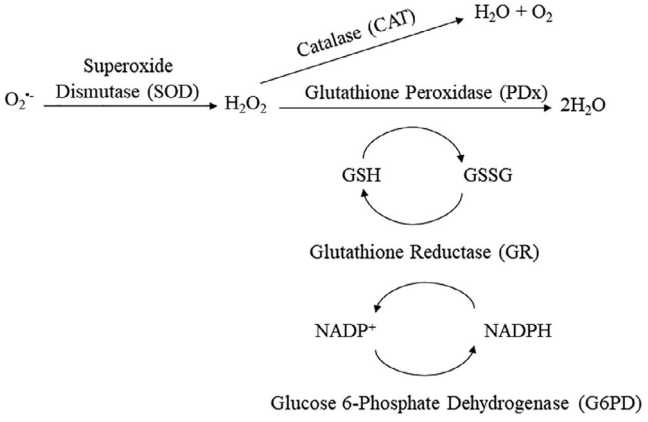

FIGURE 3 Redox enzymes involved in detoxifying superoxide ion

5.3 | Glucose-6-phosphate dehydrogenase

Glucose-6-phosphate dehydrogenase (G6PD) is a key antioxidant enzyme. G6PD is both the first enzyme and the rate-limiting enzyme in the oxidative stage of the pentose phosphate pathway that catalyzes the conversion of glucose-6-phosphate to ribulose 5-phosphate, resulting in the formation of NADPH (Glucose 6-phosphate $+ 2NADP^+ + H_2O \rightarrow$ ribulose 5-phosphate $+ 2NADPH + 2H^+ + CO_2$).[87] G6PD plays an important role in maintaining the intracellular redox balance. In the cell, the antioxidant system such as the glutathione system (GSH, GR, GPx), catalase, and SOD are dependent on NADPH produced by G6PD (Figure 3).

G6PD is a highly regulated gene. Notably, vitamin D acts as a positive regulator for the G6PD gene expression.[87,88] The positive regulation of G6PD results in an increase in the production of the G6PD, whose activity is essential for the prevention of ROS-mediated cell death and serum starvation. Having insufficient levels of G6PD could lead to reduced levels of NADPH impacting the antioxidant system. Deficiency in G6PD increases risk for elevated systolic blood pressure, cardiovascular disease, fibrosis, autoimmune disease, infection, and metabolic disorders.[89]

6 | VITAMIN D AND ITS EFFECTS ON THE BIOSYNTHESIS OF CYSTEINE AND GLUTATHIONE

Vitamin D levels have been shown to affect the biosynthesis of LMW thiols such as cysteine and GSH by upregulating the enzymes involved in their biosynthesis. Cysteine is synthesized from serine and homocysteine in a two-step process involving cystathionine β-synthase and cystathionine γ-lyase. Transcription of the *cbs* gene has been shown to be strongly induced by vitamin D treatment.[90,91] Vitamin D treatment was also shown to trigger cystathionine γ-lyase activation in high glucose treated adipocytes.[83] GSH synthesis is a two-step reaction—first, an adduct is formed between glutamate and cysteine and then the glycine is added to the adduct. Glutamate and cysteine are added together by the enzyme gamma-glutamylcysteine synthetase, also known as a glutamate-cysteine ligase (GCL), then glycine is added by GSH synthetase.[92] GCL activity is regulated at the translational level and is increased following oxidative stress.[93]

A 2014 study on type 2 diabetic patients found a positive relationship between plasma concentrations of vitamin D and cysteine with GSH.[84] It was found that vitamin D supplementation independently and significantly up-regulates GCL and GR expression. As a result, there are increased levels of GSH in vitamin D-treated cells and significantly lowered ROS levels in cells exposed to both control and high levels of glucose.[94–96] Studies on inflammation in adults and other chronic illnesses like tuberculosis found strong associations of vitamin D concentrations with higher GSH levels leading to the same conclusion that vitamin D up-regulates GCL and GR to increase cellular glutathione formation.[85] The influence of vitamin D on the biosynthesis of cysteine and GSH indicates its role in SARS-CoV-2 infection; it can prevent the interaction between the viral protein with the host cell receptor by maintaining a reducing environment.

7 | VITAMIN D's IMPACT ON THE FUNCTION AND REGULATION OF THIOREDOXIN AND PROTEIN DISULFIDE ISOMERASE

Thioredoxins (Trxs) and protein-disulfide isomerases (PDIs) are enzymes that play a pivotal role in catalyzing protein folding, ensuring the proper function of proteins, and maintaining intracellular redox homeostasis. Because of their role in maintaining the intracellular redox state, these redox enzymes could have an impact on SARS-CoV-2 entry into cells.

7.1 | Thioredoxin

Trxs are redox proteins that act as antioxidants by catalyzing the reduction of disulfides of many proteins through cysteine thiol-disulfide exchange (Figure 4).[97]

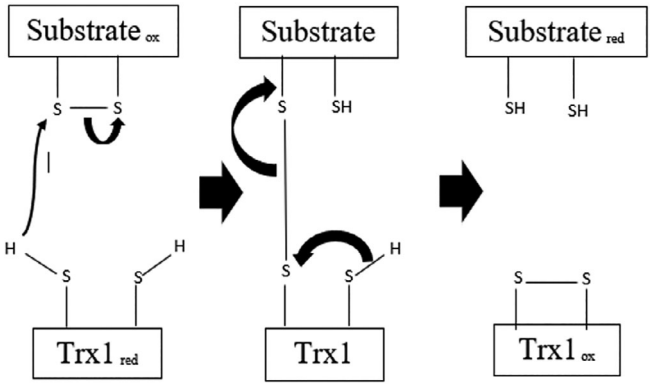

FIGURE 4 Thiol-disulfide exchange reaction catalyzed by thioredoxin 1 (Trx1). The black arrows indicate the flow of electron from Trx1 to substrate. As the Trx1 gets oxidized by reducing the disulfide bond of the substrate, the substrate gets reduced

Trxs act in conjunction with thioredoxin reductase and NADPH. They are very effective in reducing both oxidative and nitrosative stress, and for that reason, they are necessary for survival and present in almost all organisms.[97] There are two main isoforms of thioredoxins in mammals, Trx1 and Trx2, which function in the cytoplasm and mitochondria, respectively. Trx has two cysteine residues in its active site and is involved in a nucleophilic substitution reaction where electrons from Trx get transferred to a substrate protein.[97] The process begins when a substrate protein undergoes a nucleophilic attack on the disulfide bond by the N-terminal cysteine of Trx, creating a mixed disulfide bond involving both the substrate and Trx. After another nucleophilic attack by the C-terminal cysteine of Trx, the intermolecular disulfide bond between substrate and Trx is reduced, which results in the formation of the reduced substrate protein with free thiol groups and oxidized Trx with a disulfide bond (Figure 4). Trx reductase then reduces Trx by using NADPH as an electron donor. The proper functioning of the Trx system, consisting of Trx, NADPH, and thioredoxin reductase,[98] depends on the vitamin D levels as it influences the NADPH production in the cell (*vide supra*). Therefore, vitamin D can regulate the redox status and prevent the severity of the COVID-19 through the Trx system.[8]

7.2 | Protein disulfide isomerase

PDI belongs to a class of oxidoreductases and is the most abundant redox enzyme in the ER lumen.[99,100] PDI has a structure similar to thioredoxin and contains a dithiol-disulfide active site with a redox-active CGHC motif.[99,100] PDI participates in redox signaling and plays several roles within cells, such as serving as a chaperone, facilitating the proper folding of proteins, and playing a role in various disease states.[100,101] The main role of PDI is to catalyze the formation, breakage, or isomerization of disulfide bonds, which is necessary for establishing and maintaining a protein's native structure.[100,101] Much like thioredoxin, when PDI is in the reduced state, the thiol group of active site cysteines attacks the non-native disulfide bonds in the substrate breaking (reducing) the bond.[102] Once the disulfide bond is broken, the substrate cysteine that is unbound to the PDI can interact with another cystine in the substrate, forming a new native disulfide bond (Figure 5). The PDI is released from the substrate upon the formation of the second new disulfide bond.[102]

Several studies have shown that PDI has physiological roles in the diseases such as diabetes, cardiovascular diseases, cancer, neurodegenerative conditions as well as in the entry of pathogen in infectious diseases like HIV-1.[103] The exact role remains unclear but it has been shown that PDI is upregulated into infected cells; overexpression of PDI has been shown to increase the fusion of viral membrane into the host cell in the case of HIV-1.[103] PDI relies on many signals for activation, with vitamin D being one of these signaling molecules. Vitamin D binds to an activation site on PDI, which signals them to activate. Vitamin D signals PDI to activate particularly when they are needed to fight infection.[104] It has been shown that if the VDR site on PDI is disabled, the activity of PDI is greatly reduced.[104]

7.3 | Inhibitory effect of vitamin D and thioredoxin-interacting protein

SARS-CoV-2 infection within patient lungs can be characterized by inflammation, increased intussusceptive angiogenesis, and clots in small blood vessels.[105] In various patients infected with SARS-CoV-2, angiogenesis has shown to cause severe disturbances in blood flow in the lungs, heart, liver, and kidneys.[105] A close association and codependence are seen between inflammation and angiogenesis. This association is primarily seen as inflammation-induced angiogenesis, leading to detrimental effects throughout SARS-CoV-2 infection.[106] In its active form, Trx is known to promote angiogenesis.[107] A vital characteristic of vitamin D and its interaction with thioredoxin can be seen in its ability to stimulate the expression of a thioredoxin inhibitor—thioredoxin-

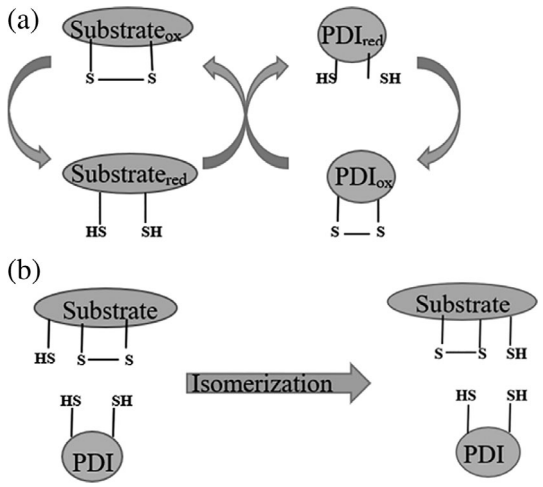

FIGURE 5 Schematic representation of protein disulfide isomerase activity. (a) Disulfide bond formation is catalyzed by PDI. As PDI is reduced, the correct disulfide bonds are formed in the substrate. (b) Disulfide isomerization in the substrate is catalyzed by PDI. Reduced PDI attacks the incorrect disulfide bond in the substrate, and the correct disulfide bond is then formed

interacting protein (TXNIP).[108] TXNIP inactivates the active, reduced thioredoxin by directly binding to the two cysteine residues within the catalytic center of thioredoxin, preventing thioredoxin from producing its biological effects.[109] The effects of this action can be seen specifically in thioredoxin's ability to promote angiogenesis. The inhibitory action of TXNIP directly diminishes the ability of thioredoxin to stimulate angiogenesis, thereby making it a possible candidate for lessening the impact of SARS-CoV-2-induced pulmonary inflammation.

8 | VITAMIN D's ROLE IN MODULATING CELLULAR REDOX STATUS

There has been increasing evidence that vitamin D acts as a reducer of oxidative stress.[13,67,111,112] By performing a meta-analysis of clinical trials, Sepidarkish et al. have demonstrated that the levels of the total antioxidant capacity and GSH increased upon vitamin D supplementation.[110] Vitamin D regulates Nrf2 gene expression, which regulates oxidative stress by modulating antioxidants and redox enzymes.[13] When vitamin D status is adequate, many of the intracellular oxidative stress-related activities are down-regulated.[13,111] Therefore, vitamin D deficiency can lead to higher levels of ROS that could promote disulfide bond formations by oxidizing the cysteine thiols in the S protein of SARS-CoV-2, as well as in the ACE2 receptor. Consequently, these disulfide bonds would promote stronger interactions between the S protein and the ACE2 receptor, and thus increasing the viral infectivity and severity.[8,9] A recent study using mouse models indeed demonstrated that the presence of disulfides within the RBD of the S protein could enhance the viral entry.[10] Therefore, the molecular mechanism of action of vitamin D could be to lower oxidative stress and prevent the fusion of viral protein to the receptor.

9 | CONCLUSIONS

Cytoplasmic conditions are more reduced and regulated, with only~10% of protein cysteines existing as disulfide bonds, compared to the cell surface environment.[79] The extracellular environment lacks an effective redox-homeostasis system, and therefore antioxidant enzymes and LMW thiols are crucial in maintaining the extracellular redox environment.[79] Thiol-disulfide balance affects binding of the SARS-CoV-2 virus with the host cell receptor; when the ACE2 receptor and S protein are in the reduced state, binding is thermodynamically unfavorable. Regulation of oxidative stress has a direct impact on COVID-19 infection. This review on vitamin D elaborated on its role in maintaining the cellular redox status by regulating the expression of antioxidant enzymes and LMW thiols like GSH. In addition, it was observed that vitamin D affects the immune system; it modulates the innate and adaptive immune responses. Taken together, this review has provided a molecular-level understanding of the role of this essential molecule in reducing the risks of viral infections including the COVID-19.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Mobeen Abdrabbo: Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Cole Birch:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Michael Brandt:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Kelsey Cicigoi:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Coffey Coffey:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Connor Dolan:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Hannah DvoraK:** Data curation (equal); funding acquisition (equal); investigation (equal); writing – original draft (equal). **Ava Gehrke:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Audrey Gerzema:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Abby Hansen:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Ethan Henseler:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Alyssa Huelsbeck:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Ben LaBerge:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Caterra Leavens:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Christine Le:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Allison Lindquist:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Rickaela Ludwig:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Jacob Reynolds:** Data curation (equal); formal analysis (equal); investigation

(equal); writing – original draft (equal). **Nathaniel Severson:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Brandon Sherman:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Hunter Sillman:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Michael Smith:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Macey Smith:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Marissa Snortheim:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Levi Svaren:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Emily Vanderpas:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Miles Wackett:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Alec Wozney:** Data curation (equal); formal analysis (equal); investigation (equal); writing – original draft (equal). **Sudeep Bhattacharyya:** Conceptualization (equal); supervision (equal); writing – review and editing (equal). **Sanchita Hati:** Conceptualization (equal); supervision (equal); writing – review and editing (equal).

DATA AVAILABILITY STATEMENT

This review contains no new data; all data are published elsewhere.

ORCID

Sanchita Hati https://orcid.org/0000-0002-7452-0872

REFERENCES

1. Gorbalenya AE, Baker SC, Baric RS, et al. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020;5:536–544.
2. Anon. Available from: https://www.worldometers.info/coronavirus/.
3. Naqvi AAT, Fatima K, Mohammad T, et al. Insights into SARS-CoV-2 genome, structure, evolution, pathogenesis and therapies: Structural genomics approach. Biochim Biophys Acta Mol Basis Dis. 2020;1866(10):165878.
4. Hwang SS, Lim J, Yu Z, et al. MRNA destabilization by BTG1 and BTG2 maintains T cell quiescence. Science. 2020;367:1255–1260.
5. Tang T, Bidon M, Jaimes JA, Whittaker GR, Daniel S. Coronavirus membrane fusion mechanism offers a potential target for antiviral development. Antiviral Res. 2020;178:104792.
6. Touyz RM, Montezano AC. Angiotensin-(1-7) and vascular function. Hypertension. 2018;71:68–69.
7. Lan J, Ge J, Yu J, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature. 2020;581:215–220.
8. Singh J, Dhindsa RS, Misra V, Singh B. SARS-CoV2 infectivity is potentially modulated by host redox status. Comput Struct Biotech J. 2020;18:3705–3711.
9. Hati S, Bhattacharyya S. Impact of thiol-disulfide balance on the binding of Covid-19 spike protein with angiotensin-converting enzyme 2 receptor. ACS Omega. 2020;5:16292–16298.
10. Manček-Keber M, Hafner-Bratkovič I, Lainšček D, et al. Disruption of disulfides within RBD of SARS-CoV-2 spike protein prevents fusion and represents a target for viral entry inhibition by registered drugs. FASEB J. 2021;35:e21651.
11. Schieber M, Chandel NS. ROS function in redox signaling and oxidative stress. Curr Biol. 2014;24:R453–R462.
12. Pizzino G, Irrera N, Cucinotta M, et al. Oxidative stress: Harms and benefits for human health. Oxid Med Cell Longev. 2017;2017:8416763.
13. Ma Q. Role of Nrf2 in oxidative stress and toxicity. Ann Rev Pharmacol Toxicol. 2013;53:401–426.
14. de la Lastra JMP, Andrés-Juan C, Plou FJ, Pérez-Lebeña E. Impact of zinc, glutathione, and polyphenols as antioxidants in the immune response against SARS-CoV-2. Processes. 2021;9(3), 506.
15. Suhail S, Zajac J, Fossum C, et al. Role of oxidative stress on SARS-CoV (SARS) and SARS-CoV-2 (COVID-19) infection: A review. Protein J. 2020;39:644–656.
16. Ansari MGA, Sabico S, Clerici M, et al. Vitamin D supplementation is associated with increased glutathione peroxidase-1 levels in Arab adults with prediabetes. Antioxidants. 2020;9:118.
17. Whittemore PB. COVID-19 fatalities, latitude, sunlight, and vitamin D. Am J Infect Control. 2020;48:1042–1044.
18. Murai IH, Fernandes AL, Sales LP, et al. Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19: A randomized clinical trial. JAMA. 2021;325:1053–1060.
19. Butler-Laporte G, Nakanishi T, Mooser V, et al. Vitamin D and COVID-19 susceptibility and severity in the COVID-19 host genetics initiative: A Mendelian randomization study. PLoS Med. 2021;18:e1003605.
20. Hernández JL, Nan D, Fernandez-Ayala M, et al. Vitamin D status in hospitalized patients with SARS-CoV-2 infection. J Clin Endocrinol Metabol. 2021;106:1343–1353.
21. Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. Association of vitamin D status and other clinical characteristics with COVID-19 test results key points + supplemental content. JAMA Netw Open. 2020;3:2019722.
22. Bendik I, Friedel A, Roos FF, Weber P, Eggersdorfer M. Vitamin D: A critical and essential micronutrient for human health. Front Physiol. 2014;5:1–14.
23. Sirajudeen S, Shah I, al Menhali A. A narrative role of vitamin d and its receptor: With current evidence on the gastric tissues. Intl J Mol Sci. 2019;20:3832.
24. Anandabaskar N, Selvarajan S, Kamalanathan S. Vitamin D in health and disease—An update. J Young Pharm. 2018;10(4):381–387.
25. Bergqvist C, Ezzedine K. Vitamin D and the skin: What should a dermatologist know? Giornale Italiano Dermatologia Venereologia. 2019;154:669–680.
26. Umar M, Sastry K, Chouchane A. Role of vitamin D beyond the skeletal function: A review of the molecular and clinical studies. Intl J Mol Sci. 2018;19:1618.

27. Charoenngam N, Shirvani A, Holick MF. Vitamin D for skeletal and non-skeletal health: What we should know. J Clin Orthopaedics Trauma. 2019;10:1082–1093.
28. Lips P. Vitamin D physiology. Progr Biophys Mol Biol. 2006; 92:4–8.
29. Suwińska K, Kutner A. Crystal and molecular structure of 1,25-dihydroxycholecalciferol. Acta Cryst. 1996;B52:550–554.
30. Hossein-nezhad A, Spira A, Holick MF. Influence of vitamin D status and vitamin D3 supplementation on genome wide expression of white blood cells: A randomized double-blind clinical trial. PLoS ONE. 2013;8:e58725.
31. Zmijewski MA, Carlberg C. Vitamin D receptor(s): In the nucleus but also at membranes? Exp Dermatol. 2020;29: 876–884.
32. Khammissa RAG, Fourie J, Motswaledi MH, Ballyram R, Lemmer J, Feller L. The biological activities of vitamin D and its receptor in relation to calcium and bone homeostasis, cancer, immune and cardiovascular systems, skin biology, and oral health. BioMed Res Intl. 2018;2018:20189276380.
33. Jeon SM, Shin EA. Exploring vitamin D metabolism and function in cancer. Exper Mol Med. 2018;50:20.
34. Veldurthy V, Wei R, Oz L, Dhawan P, Jeon YH, Christakos S. Vitamin D, calcium homeostasis and aging. Bone Res. 2016;4: 16041.
35. Fleet JC. The role of vitamin D in the endocrinology controlling calcium homeostasis. MolCell Endocrin. 2017;453:36–45.
36. Christakos S. Recent advances in our understanding of 1,25-dihydroxyvitamin D 3 regulation of intestinal calcium absorption. Arch Biochem Biophys. 2012;523:73–76.
37. Knöpfel T, Pastor-Arroyo EM, Schnitzbauer U, et al. The intestinal phosphate transporter NaPi-IIb (Slc34a2) is required to protect bone during dietary phosphate restriction. Sci Rep. 2017;7:11018.
38. Díaz GD, Paraskeva C, Thomas MG, Binderup L, Hague A. Apoptosis is induced by the active metabolite of vitamin D3 and its analogue EB1089 in colorectal adenoma and carcinoma cells: Possible implications for prevention and therapy. Cancer Res. 2000;60:2304–2312.
39. McDonnell SL, Baggerly C, French CB, et al. Serum 25-hydroxyvitamin d concentrations ≥40 ng/ml are associated with >65% lower cancer risk: Pooled analysis of randomized trial and prospective cohort study. PLoS ONE. 2016;11: e0152441.
40. Jones G, Strugnell SA, DeLuca HF. Current understanding of the molecular actions of vitamin D. Physiolog Rev. 1998;78: 1193–1231.
41. Verlinden L, Verstuyf A, Convents R, Marcelis S, van Camp M, Bouillon R. Action of 1,25(OH)2D3 on the cell cycle genes, cyclin D1, p21 and p27 in MCF-7 cells. Mol Cell Endocrin. 1998;142:57–65.
42. Berridge MJ. Vitamin D, reactive oxygen species and calcium signalling in ageing and disease. Phil Trans Royal Soc B Biol Sci. 2016;371:20150434.
43. Siddiqui M, Manansala JS, Abdulrahman HA, et al. Immune modulatory effects of vitamin d on viral infections. Nutrients. 2020;12:1–16.
44. Mehta S, Giovannucci E, Mugusi FM, et al. Vitamin D status of HIV-infected women and its association with HIV disease progression, anemia, and mortality. PLoS ONE. 2010;5:e8770.
45. Sudfeld CR, Wang M, Aboud S, Giovannucci EL, Mugusi FM, Fawzi WW. Vitamin D and HIV progression among Tanzanian adults initiating antiretroviral therapy. PLoS ONE. 2012;7:e40036.
46. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. Am J Clin Nutrit. 2010;91:1255–1260.
47. Bitetto D, Fabris C, Fornasiere E, et al. Vitamin D supplementation improves response to antiviral treatment for recurrent hepatitis C. Transplant Intl. 2011;24:43–50.
48. Nimer A, Mouch A. Vitamin D improves viral response in hepatitis C genotype 2-3 naïve patients. World J Gastroenterol. 2012;18(8):800–805.
49. Petta S, Camm̀a C, Scazzone C, et al. Low vitamin d serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. Hepatology. 2010;51:1158–1167.
50. McNally JD, Sampson M, Matheson LA, Hutton B, Little J. Vitamin D receptor (VDR) polymorphisms and severe RSV bronchiolitis: A systematic review and meta-analysis. Pediatric Pulmonol. 2014;49:790–799.
51. Drysdale SB, Prendergast M, Alcazar M, et al. Genetic predisposition of RSV infection-related respiratory morbidity in preterm infants. Eur J Pediatrics. 2014;173:905–912.
52. Puerta-Guardo H, de la Cruz Hernández SI, Rosales VH, Ludert JE, del Angel RM. The 1α,25-dihydroxy-vitamin D3 reduces dengue virus infection in human myelomonocyte (U937) and hepatic (Huh-7) cell lines and cytokine production in the infected monocytes. Antiviral Res. 2012;94:57–61.
53. Jaratsittisin J, Xu B, Sornjai W, et al. Activity of vitamin D receptor agonists against dengue virus. Sci Rep. 2020;10:10835.
54. Malaguarnera L. Vitamin D3 as potential treatment adjuncts for covid-19. Nutrients. 2020;12:3512.
55. Sassi F, Tamone C, D'amelio P. Vitamin D: Nutrient, hormone, and immunomodulator. Nutrients. 2018;10:1656.
56. Martens PJ, Gysemans C, Verstuyf A, Mathieu C. Vitamin D's effect on immune function. Nutrients. 2020;12:1248.
57. Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in COVID-19: The current evidence and treatment strategies. Front Immunol. 2020;11:1708.
58. Cecchini R, Cecchini AL. SARS-CoV-2 infection pathogenesis is related to oxidative stress as a response to aggression. Med Hypotheses. 2020;143:110102.
59. Mangalmurti N, Hunter CA. Cytokine storms: Understanding COVID-19. Immunity. 2020;53:19–25.
60. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. Microbiol Mol Biol Rev. 2012;76:16–32.
61. Schwalfenberg GK. A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency. Mol Nutrit Food Res. 2011;55:96–108.
62. Alhassan Mohammed H, Mirshafiey A, Vahedi H, et al. Immunoregulation of inflammatory and inhibitory cytokines by vitamin D3 in patients with inflammatory bowel diseases. Scand J Immunol. 2017;85:386–394.
63. Kenneth Weir E, Thenappan T, Bhargava M, Chen Y. Does Vitamin D deficiency increase the severity of COVID-19? Clin Med J Royal Coll Physic London. 2020;20:E107–E108.

64. Chernyak BV, Popova EN, Prikhodko AS, Grebenchikov OA, Zinovkina LA, Zinovkin RA. COVID-19 and oxidative stress. Biochemistry (Moscow). 2020;85:1543–1553.
65. Ntyonga-Pono MP. COVID-19 infection and oxidative stress: an under-explored approach for prevention and treatment? Pan African Med J. 2020;35:12.
66. Jain SK, Parsanathan R, Levine SN, Bocchini JA, Holick MF, Vanchiere JA. The potential link between inherited G6PD deficiency, oxidative stress, and vitamin D deficiency and the racial inequities in mortality associated with COVID-19. Free Radic Biol Med. 2020;161:84–91.
67. Wimalawansa SJ. Vitamin D deficiency: Effects on oxidative stress, epigenetics, gene regulation, and aging. Biology. 2019; 8:30.
68. Razzaque MS. The FGF23-Klotho axis: Endocrine regulation of phosphate homeostasis. Nat Rev Endocrin. 2009;5:611–619.
69. Antelmann H, Helmann JD. Thiol-based redox switches and gene regulation. Antiox Redox Signal. 2011;14:1049–1063.
70. Nguyen T, Nioi P, Pickett CB. The Nrf2-antioxidant response element signaling pathway and its activation by oxidative stress. J Biol Chem. 2009;284:13291–13295.
71. McMullan CJ, Borgi L, Curhan GC, Fisher N, Forman JP. The effect of Vitamin D on renin-angiotensin system activation and blood pressure: A randomized control trial. J Hypertens. 2016;35:822–829.
72. Fountain JH, Lappin SL. Physiology, Renin Angiotensin System. 2021 Jul 22. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 29261862.
73. Wen H. Oxidative stress-mediated effects of angiotensin II in the cardiovascular system. World J Hypertens. 2012;2:34–44.
74. Albashir AAD. Renin-angiotensin-aldosterone system (RAAS) inhibitors and coronavirus disease 2019 (COVID-19). South Med J. 2021;114:51–56.
75. Mardani R, Alamdary A, Mousavi Nasab SD, Gholami R, Ahmadi N, Gholami A. Association of vitamin D with the modulation of the disease severity in COVID-19. Virus Res. 2020;289:198148.
76. Li YC. Molecular mechanism of Vitamin D in the cardiovascular system. J Invest Med. 2011;59:868–871.
77. Dikalov SI, Nazarewicz RR. Angiotensin II-induced production of mitochondrial reactive oxygen species: Potential mechanisms and relevance for cardiovascular disease. Antiox Redox Signal. 2013;19:1085–1094.
78. Malek Mahdavi A. A brief review of interplay between vitamin D and angiotensin-converting enzyme 2: Implications for a potential treatment for COVID-19. Rev Med Virol. 2020;30: e2119.
79. Giustarini D, Santucci A, Bartolini D, Galli F, Rossi R. The age-dependent decline of the extracellular thiol-disulfide balance and its role in SARS-CoV-2 infection. Redox Biol. 2021; 41:101902.
80. Couto N, Wood J, Barber J. The role of glutathione reductase and related enzymes on cellular redox homoeostasis network. Free Radic Biol Med. 2016;95:27–42.
81. Borgstahl GEO, Oberley-Deegan RE. Superoxide dismutases (SODs) and SOD mimetics. Antioxidants. 2018;7:156.
82. Bhat M, Ismail A. Vitamin D treatment protects against and reverses oxidative stress induced muscle proteolysis. J Steroid Biochem Mol Biol. 2015;152:171–179.
83. Anderson ME. Glutathione: An overview of biosynthesis and modulation. Chem Biol Interact. 1998;111–112:1–14.
84. Jain SK, Micinski D. Vitamin D upregulates glutamate cysteine ligase and glutathione reductase, and GSH formation, and decreases ROS and MCP-1 and IL-8 secretion in high-glucose exposed U937 monocytes. Biochem Biophys Res Commun. 2013;437:7–11.
85. Jain SK, Parsanathan R, Achari AE, Kanikarla-Marie P, Bocchini JA. Glutathione stimulates vitamin D regulatory and glucose-metabolism genes, lowers oxidative stress and inflammation, and increases 25-hydroxy-vitamin D levels in blood: A novel approach to treat 25-hydroxyvitamin D deficiency. Antioxid Redox Signal. 2018;29:1792–1807.
86. Dzik KP, Kaczor JJ. Mechanisms of vitamin D on skeletal muscle function: oxidative stress, energy metabolism and anabolic state. Eur J Appl Physiol. 2019;119:825–839.
87. Stanton RC. Glucose-6-phosphate dehydrogenase, NADPH, and cell survival. IUBMB Life. 2012;64:362–369.
88. Bao BY, Ting HJ, Hsu JW, Lee YF. Protective role of 1α, 25-dihydroxyvitamin D3 against oxidative stress in nonmalignant human prostate epithelial cells. Int J Cancer. 2008; 122:2699–2706.
89. Parsanathan R, Jain SK. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is linked with cardiovascular disease. Hypertens Res. 2020;43:148–153.
90. Manna P, Jain SK. Vitamin D up-regulates glucose transporter 4 (GLUT4) translocation and glucose utilization mediated by cystathionine-γ-lyase (CSE) activation and H2S formation in 3T3L1 adipocytes. J Biol Chem. 2012;287:42324–42332.
91. Kriebitzsch C, Verlinden L, Eelen G, et al. 1,25-dihydroxyvitamin D 3 influences cellular homocysteine levels in murine preosteoblastic MC3T3-E1 cells by direct regulation of cystathionine β-synthase. J Bone Miner Res. 2011; 26:2991–3000.
92. Krejsa CM, Franklin CC, White CC, Ledbetter JA, Schieven GL, Kavanagh TJ. Rapid activation of glutamate cysteine ligase following oxidative stress. J Biol Chem. 2010;285: 16116–16124.
93. Jain SK, Micinski D, Huning L, Kahlon G, Bass PF, Levine SN. Vitamin D and L-cysteine levels correlate positively with GSH and negatively with insulin resistance levels in the blood of type 2 diabetic patients. Eur J Clin Nutr. 2014; 68:1148–1153.
94. Guha S, Chaurasia S, Roy S. Oxidative stress in the pathogenesis of corneal endothelial dystrophies and other corneal diseases. Reactive Oxygen Species. 2018;6(17):299–310.
95. Singh M, Vaughn C, Sasaninia K, et al. Understanding the relationship between glutathione, TGF-β, and vitamin D in combating *Mycobacterium tuberculosis* infections. J Clin Med. 2020;9:2757.
96. Alvarez JA, Chowdhury R, Jones DP, et al. Vitamin D status is independently associated with plasma glutathione and cysteine thiol/disulphide redox status in adults. Clin Endocrin. 2014;81:458–466.
97. Lee S, Kim SM, Lee RT. Thioredoxin and thioredoxin target proteins: From molecular mechanisms to functional significance. Antiox Redox Signal. 2013;18:1165–1207.
98. Holmgren A, Lu J. Thioredoxin and thioredoxin reductase: Current research with special reference to human disease. Biochem Biophys Res Commun. 2010;396:120–124.

99. Frand AR, Kaiser CA. Ero1p oxidizes protein disulfide isomerase in a pathway for disulfide bond formation in the endoplasmic reticulum. Mol Cell. 1999;4:469–477.
100. Ferrari DM, Söling HD. The protein disulphide-isomerase family: Unravelling a string of folds. Biochem J. 1999;339:1–10.
101. Parakh S, Atkin JD. Novel roles for protein disulphide isomerase in disease states: A double edged sword? Front Cell Devel Biol. 2015;3:30.
102. Klappa P, Ruddock LW, Darby NJ, Freedman RB. The b' domain provides the principal peptide-binding site of protein disulfide isomerase but all domains contribute to binding of misfolded proteins. EMBO J. 1998;17:927–935.
103. Schwaller M, Wilkinson B, Gilbert HF. Reduction-reoxidation cycles contribute to catalysis of disulfide isomerization by protein-disulfide isomerase. J Biol Chem. 2003;278:7154–7159.
104. Hasan Khan R, Khursheed Siddiqui M, Salahuddin P. Protein disulfide isomerase: Structure, mechanism of oxidative protein folding and multiple functional roles. J Biochem Mol Biol Res. 2016;2:173–179.
105. Gezen-Ak D, Atasoy IL, Candaş E, Alaylioglu M, Yllmazer S, Dursun E. Vitamin D receptor regulates amyloid Beta 1-42 production with protein disulfide isomerase A3. ACS Chem Nerosci. 2017;8:2335–2346.
106. Ackermann M, Mentzer SJ, Kolb M, Jonigk D. Inflammation and intussusceptive angiogenesis in COVID-19: Everything in and out of flow. Eur Respirat J. 2020;56:2003147.
107. Jackson JR, Seed MP, Kircher CH, Willoughby DA, Winkler JD. The codependence of angiogenesis and chronic inflammation. FASEB J. 1997;11:457–465.
108. Sherbet GV. Tumour suppression and inhibition of angiogenesis by TXNIP (thioredoxin interacting protein). Molecular Approach to Cancer Management, Academic Press; 2017; p. 101–103.
109. Hamilton JP, Potter JJ, Koganti L, Meltzer SJ, Mezey E. Effects of vitamin D3 stimulation of thioredoxin-interacting protein in hepatocellular carcinoma. Hepatol Res. 2014;44:1357–1366.
110. Yoshihara E, Masaki S, Matsuo Y, Chen Z, Tian H, Yodoi J. Thioredoxin/Txnip: Redoxisome, as a redox switch for the pathogenesis of diseases. Front in Immunol. 2014;4:514.
111. Sepidarkish M, Farsi F, Akbari-Fakhrabadi M, et al. The effect of vitamin D supplementation on oxidative stress parameters: A systematic review and meta-analysis of clinical trials. Pharma Res. 2019;139:141–152.
112. Chen L, Yang R, Qiao W, et al. 1,25-Dihydroxy vitamin D prevents tumorigenesis by inhibiting oxidative stress and inducing tumor cellular senescence in mice. Intl J Cancer. 2018;143:368–382.

How to cite this article: Abdrabbo M, Birch CM, Brandt M, Cicigoi KA, Coffey SJ, Dolan CC, et al. Vitamin D and COVID-19: A review on the role of vitamin D in preventing and reducing the severity of COVID-19 infection. Protein Science. 2021;30:2206–20. https://doi.org/10.1002/pro.4190