Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Gene Reports 24 (2021) 101270

Contents lists available at ScienceDirect

Gene Reports

journal homepage: www.elsevier.com/locate/genrep

Relevance of vitamin D_3 in COVID-19 infection

Falaque Ul Afshan [a], Bushra Nissar [a], Nisar Ahmad Chowdri [b], Bashir Ahmad Ganai [c,*]

[a] Department of Biochemistry, University of Kashmir, Hazratbal, Srinagar, J&K 190006, India
[b] Division of Colorectal Surgery, SKIMS, Soura, Srinagar, J&K 190011, India
[c] Centre For Research and Development, University of Kashmir, Hazratbal, Srinagar, J&K 190006, India

ARTICLE INFO

Keywords:
Vitamin D_3
Hydroxyderivatives
CYP27B1
COVID-19
SARS-CoV-2 virus
Glutathione
L-Cysteine

ABSTRACT

SARS-CoV-2 virus, the main culprit for COVID-19 disaster, has triggered a gust of curiosity both in the mechanism of action of this infection as well as potential risk factors for disease generation and regimentation. The prime focus of the present review, which is basically a narrative one, is in utilizing the current concepts of vitamin D_3 as an agent with myriad functions, one of them being immunocompetence and a promising weapon for both innate and adaptive immunity against COVID-19 infection. Some of the manifestations of SARS-CoV-2 virus such as Acute Respiratory Distress Syndrome (ARDS) overlap with the pathophysiological effects that are overcome due to already established role of vitamin D_3 e.g., amelioration of cytokine outburst. Additionally, the cardiovascular complications due to COVID-19 infection may also be connected to vitamin D_3 levels and the activity of its active forms. Eventually, we summarise the clinical, observational and epidemiological data of the respiratory diseases including COVID-19 disease and try to bring its association with the potential role of vitamin D_3, in particular, the activity of its active forms, circulating levels and its supplementation, against dissemination of this disease.

1. Introduction

December 2019, the world got engulfed by a deadly virus that originated from Wuhan, China creating a global public health crisis. At the time of writing this article, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel virus responsible for coronavirus disease, COVID-19 pandemic had infected over 93.8 million people and had caused over 2.01 million deaths worldwide. In the United States, one of the leading countries hardest hit by this global calamity, there have been over 23.4 million people infected and over 389,000 deaths (https://www.worldometers.info/coronavirus/). SARS-CoV-2 is extraordinarily infectious, affiliated with extremely high rates of morbidity and mortality, and domestic contacts of infected patients and healthcare workers are at particularly greater risk for infection. There is no denying that these numbers will continue to escalate until an effective vaccination (already initiated) or any validated treatment is propagated among the masses (Ahn et al., 2020). Besides, a rigorous research in potential risk factors have highlighted some important contributors to the disease spread which may include: age, obesity, diabetes and ethnicity (Zhou et al., 2020) but the potentiality of the other possible risk factors cannot be undermined as is the case with insufficient vitamin D_3 blood levels (Mitchell, 2020). This can be attributed to the fact that vitamin D_3 plays a pivotal role in the dissemination of immune functions. This function of vitamin D_3 can prove advantageous in warning about the consequences of COVID-19 disease. To support this statement, a newest genomics-directed outline of SARS-CoV-2 targets in human cells highlighted vitamin D_3 as one of the top three scoring molecules that exhibited promising infection alleviation patterns through their influences on gene expression. In particular through binding to the vitamin D_3 response element (VDREs) in the promoter region of target genes and activating or repressing them, vitamin D_3 may theoretically inhibit or mitigate the devastating outcomes of COVID-19 by regulating (a) renin-angiotensin-aldosterone system (RAAS), (b) physical barriers, and (c) innate and adaptive cellular immunity (Grant et al., 2020).

The active form of vitamin D_3 i.e., $1\alpha,25(OH)_2D_3$ is synthesized from vitamin D by a series of steps: the foremost step involves the conversion of substrate 7-dehydrocholesterol (or pro-vitamin D_3) to pre-vitamin D_3 subcutaneously in response to UV light exposure (Holick, 2007) which is then thermo-isomerized to vitamin D_3 in the epidermal basal layers. This form of vitamin D_3, also obtained through the intestinal absorption of

Abbreviations: VDR, vitamin D receptor; ROR, retinoid acid-related orphan receptors; AhR, aryl hydrocarbon receptor; ROS, reactive oxygen species; ARDS, acute respiratory distress syndrome; MERS, Middle East respiratory syndrome; GSH, glutathione; LC, L-cysteine; RCT, Randomised Controlled Trial.

* Corresponding author.
E-mail addresses: afshan@kashmiruniversity.net (F. Ul Afshan), bbcganai@gmail.com (B.A. Ganai).

https://doi.org/10.1016/j.genrep.2021.101270
Received 22 March 2021; Received in revised form 28 May 2021; Accepted 1 July 2021
Available online 7 July 2021

organic foods and supplements, then binds to vitamin D Binding Protein (DBP) in the blood circulation, is transported to liver and hydroxylated by liver mitochondrial and microsomal 25-hydroxylases coded by *CYP27A1* gene (Bikle, 2014). The resultant $25(OH)D_3$ is then again hydroxylated after its transport to kidney by mitochondrial 25-hydroxy vitamin D_3-1α-hydroxylase coded by *CYP27B1* gene to yield $1\alpha,25(OH)_2D_3$ (calcitriol) (Holick, 2007). The production of $1\alpha,25(OH)_2D_3$ from $25(OH)D_3$ is stimulated by parathyroid hormone, and suppressed by Ca^{2+}, P_i and $1\alpha,25(OH)_2D_3$ itself (Deeb et al., 2007). The rate limiting step in catabolism of vitamin D_3 is the degradation of $25(OH)D_3$ and $1\alpha,25(OH)_2D_3$ to $24,25(OH)_2D_3$ and $1\alpha,24,25(OH)_2D_3$ respectively, which takes place via 24-hydroxylation 25-dihydroxyvitamin D 24-hydroxylase which is a cytochrome P450 enzyme encoded by *CYP24A1* gene. These degradation products are finally excreted (Hargrove et al., 2014). $1\alpha,25(OH)_2D_3$ is a key factor disrupted in skeletal and bone disorders (Erben et al., 2002). Vitamin D_3 also has established roles in the prevention of various cancers ranging from the cancers of gastrointestinal tract to breast, lung and prostate cancers (Deeb et al., 2007) and its inadequacy has also been associated with autoimmune disorders which include multiple sclerosis, rheumatoid arthritis, tuberculosis, etc. (Martens et al., 2020). Studies have shown the presence of enzyme 1α-hydroxylase (CYP27B1) in antigen presenting cells (APCs) (dendritic cells and macrophages) which converts the precursor 25-hydroxyvitamin D_3 ($25(OH)D_3$) to the active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3 (Kallas et al., 2010). This immunological response elicited by APCs is a fundamental feature in the above-mentioned immune disorders. However, later reports showed that the expression of CYP27B1 and synthesis of $1\alpha,25(OH)_2D_3$ is the key event in development of APCs even under normal circumstances indicating a direct role of vitamin D_3 in these cells (Hewison et al., 2003). On invasion of pathogens during an infection, body's immune system activates APCs and starts recruiting T cells and neutrophils to the site of infection. In a scenario where vitamin D_3 levels are insufficient to highly deficient such immunological reactions would be debilitated because scanty levels of circulating $25(OH)D_3$ levels would be available to synthesize $1\alpha,25(OH)_2D_3$ to evoke the required immune response (Hewison, 2010). This autocrine/paracrine mechanism is now considered a foundation of the interaction between vitamin D_3 and body's immune system.

2. Hydroxyderivatives of vitamin D_3 metabolism and alternative nuclear receptors

Studies have established novel D_3-hydroxyderivatives of vitamin D_3 metabolism different from $25(OH)D_3$ and $1\alpha,25(OH)_2D_3$. These novel products which include $20(OH)D_3$, $22(OH)D_3$, $20,22(OH)_2D_3$, $20,23(OH)_2D_3$, $1,20(OH)_2D_3$, $1,20,23(OH)_3D_3$, and $17,20,23(OH)_3D_3$ were found to be synthesized by placenta, adrenal glands, and epidermal keratinocytes (Slominski et al., 2014a; Slominski et al., 2015a). The pathways were initiated by steroidogenic enzyme cytochrome P450scc (CYP11A1) and further hydroxylated by CYP27B1 (1α-hydroxylase) (Slominski et al., 2012). The *CYP11A1* gene, only found in vertebrates, converts cholesterol to pregnenolone to initiate de novo steroidogenesis. Recent evidences have suggested the alternative substrates which include cholesterol precursors (7DHC and desmosterol), hydroxycholesterols, plant sterols, ergosterol, lumisterol, and vitamins D_3 and D_2 (Slominski et al., 2015b). They are all closely related to cholesterol in structure. The D_3-hydroxyderivatives of vitamin D_3 are biologically active and are at least as potent as the classical $1\alpha,25(OH)_2D_3$ with antiproliferative, antifibrotic, anti-inflammatory pro-differentiation properties or as adjuvants in cancer therapy (Slominski et al., 2020a). CYP11A1-derived D_3-hydroxyderivatives are also known to exert photoprotective effects. These include induction of intracellular free radical scavenging and DNA damage repair. CYP11A1-derived D_3-hydroxyderivatives, both with and without 1α(OH) group, cause transfer of the VDR from cytosol to nucleus with high potency, however potency was greater with the presence of 1α(OH) group (Slominski et al., 2017).

$1\alpha,25(OH)_2D_3$ exerts most of its pleiotropic phenotypic effects through the binding to its nuclear receptor, vitamin D receptor (VDR) and then heterodimerizing with Retinoid X Receptor (RXR) which is then translocated to nucleus where it binds to the vitamin D response elements (VDRE) present on target genes and influence gene expression (Bikle, 2014). Additionally, $1\alpha,25(OH)_2D_3$ exerts its non-genomic effects through its interaction with $1,25D_3$-membrane-associated, rapid response steroid-binding protein, $1,25D_3$-MARRS (ERp57 or PDIA3), which is an endoplasmic membrane bound protein that plays a role in proper folding of newly synthesized glycoproteins (Slominski et al., 2020a). Recently, in addition to the VDR, alternative nuclear receptors for $1\alpha,25(OH)_2D_3$ have been discovered which include the retinoid acid-related orphan receptors (ROR) α and γ and the Aryl hydrocarbon receptor (AhR) known to activate genomic or nongenomic signal transduction pathways. RORs influence transcription by binding as monomers to ROR-responsive elements (ROREs) in the regulatory regions of target genes in a tissue-specific manner (Slominski et al., 2014b). RORs exhibit critical functions in the regulation of many physiological processes such as embryonic development, differentiation, and in many immune and metabolic pathways. RORs have been implicated in several pathologies including cancer, (auto)immune disease and metabolic syndrome (Slominski et al., 2017). AhR is the major receptor for $20,23(OH)_2D_3$, which also appears to be activated by other CYP11A1-derived vitamin D_3 derivatives, and possibly by $1\alpha,25(OH)_2D_3$ to some extent leading to the subsequent downstream activation of signal transduction pathways in a cell-type-dependent manner (Slominski et al., 2018). The recognition of plentiful endogenously produced alternate hydroxy-metabolites of D_3 that are biologically active, and of potential alternative receptors, may extend an explanation for the pleiotropic and multifarious activities of vitamin D, formerly attributed solely to $1\alpha,25(OH)_2D_3$ and VDR.

3. Anti-microbial activity of vitamin D_3

About three decades ago the anti-microbial role of $1\alpha,25(OH)_2D_3$ was originally unravelled. However, this anti-microbial propensity was acknowledged as a pathway for stimulating anti-bacterial reaction after a study was conducted on *Mycobacterium tuberculi* (Liu et al., 2006). The key concepts are summarised in Fig. 1.

3.1. Cathelicidin

The localized intracellular synthesis of $1\alpha,25(OH)_2D_3$ by monocytes or macrophages stimulates the expression of cathelicidin, an antimicrobial protein and contributes towards intracellular extermination of microbes e.g., *Mycobacterium tuberculi* (Liu et al., *2006*). $1\alpha,25(OH)_2D_3$-VDR-Retinoid X Receptor (RXR) complex binds to the vitamin D response elements on the gene promoter of cathelicidin and increases its expression (Wang et al., 2004). Besides the antimicrobial activity of this protein, cathelicidin exhibits other roles which includes: prompting of a number of proinflammatory cytokines, inducing the chemotaxis of T cells, neutrophils, monocytes and macrophages into the infected epithelial cells and leading to their apoptosis and autophagy as well as clearance of respiratory pathogens (Yuk et al., 2009). It was observed that the competence of immune cells to synthesize cathelicidin closely associated with the circulating levels of $25(OH)D_3$ and thus indicated a high occurrence of diseases like tuberculosis and other respiratory related disorders in individuals with low vitamin D_3 levels (Chan, 2000).

3.2. β-Defensin 2

Vitamin D_3 also induces production of another anti-microbial agent, β-Defensin 2 (DEFβ4) (Wang et al., 2004). This protein like cathelicidin triggers the host defence by instigating the production of chemokines and cytokines that help in rallying the APCs, T cells, NK cells and neutrophils towards the site of infection (Kim et al., 2018). In response to

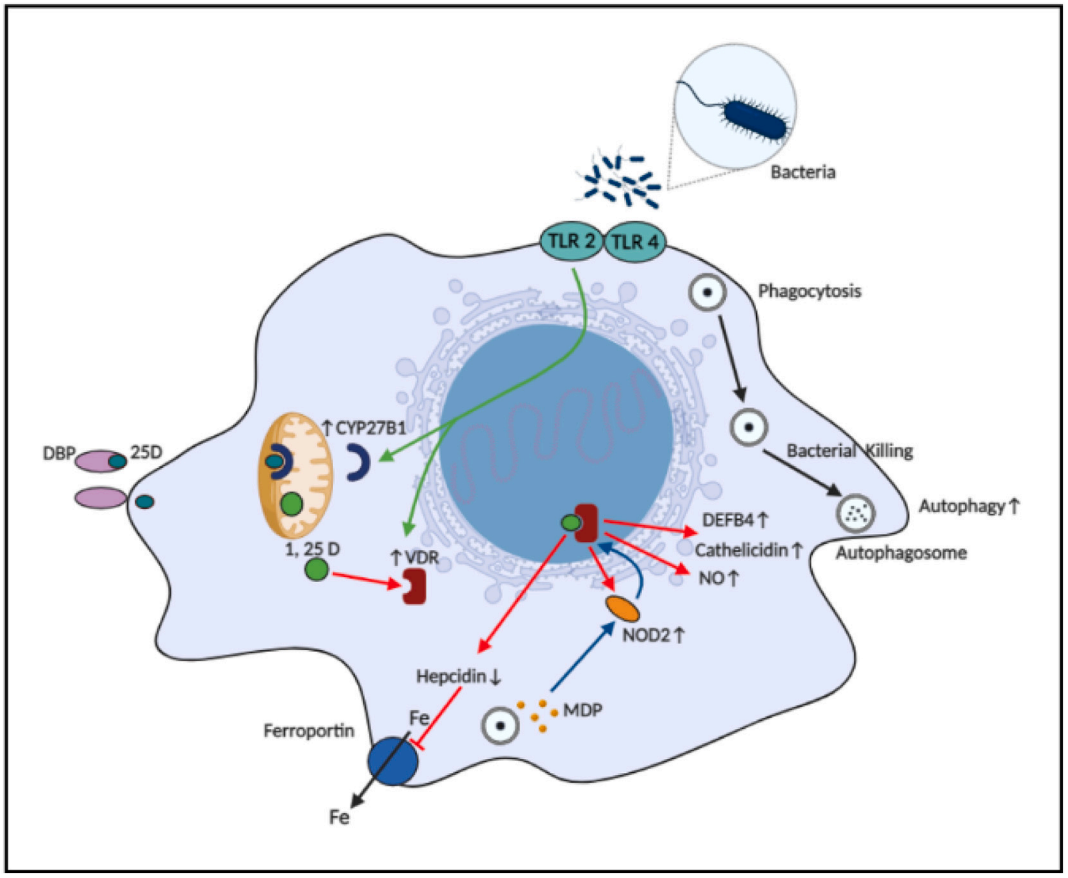

Fig. 1. Antimicrobial actions of vitamin D_3.

pathogenic attack on cells, pattern recognition receptors (PRRs) such as Toll-like receptors (TLR 2 and TLR 4) present on the membrane of these cells (Guo and Thomas, 2017) elicit an immune reaction which leads to the production of cathelicidin and β-Defensin 2 on binding of ligand-VDR receptor complex. Basically, serum 25-hydroxyvitamin D_3 (25$(OH)D_3$) bound to vitamin D binding protein (DBP), present in the blood circulation allows easy intracellular availability of 25$(OH)D_3$ for conversion to 1α,25$(OH)_2D_3$ which later on binds to VDR (Deeb et al., 2007).

3.3. Hepcidin and intracellular iron levels

Intracellular iron is an important factor that promotes the survival of bacteria in host cell environment. Iron is exported via iron transport channels, also known as ferroportin located on the plasma membrane of epithelial cells. Hepcidin, a modulator of iron metabolism is induced due to the bacterial infection and acts by inhibiting the transcellular transport of iron via ferroportin and thus, preventing the decrease in its cellular levels (Ganz, 2006). The induction of 1α,25$(OH)_2D_3$/VDR pathway suppresses the production of hepcidin, preventing the bacterial growth (Bacchetta et al., 2014).

3.4. Other potential targets and maintaining physical barrier

Transcriptional responses to 1α,25$(OH)_2D_3$ include induction of other targets like nucleotide binding oligomerization domain-containing protein 2 (NOD2) (Wang et al., 2010) and nitric oxide (NO) (Gough et al., 2017) indicating broader range of its anti-microbial activity. Vitamin D_3 also upregulates the slaughter of pneumococcus bacteria by inducing neutrophils through the induction of NOD (Subramanian et al., 2017). Besides, vitamin D_3 can also manifest its anti-microbial role independent of the functions related to immune system. For example, in the gastrointestinal tract vitamin D_3 plays a role in stimulating the expression of gap-junction proteins. These proteins are a cornerstone in maintaining physical barrier and prevention of trespass of bacteria from gut into the external environment (Kong et al., 2008). Similar role of vitamin D_3 in providing barrier against microbes as well as induction of antimicrobial actions on immune system has been observed in the lung epithelium (van der Does et al., 2012).

3.5. Activating anti-oxidant processes

Oxidative stress induced DNA damage leads to the generation of reactive oxygen species (ROS) in various inflammatory diseases resulting in damage to many organs and tissues. The role of 1α,25$(OH)_2D_3$ in anti-oxidant defence by activation of several enzymes (as thioredoxin reductase, glutathione reductase, and glutamate–cysteine ligase modifier subunit) as well as directly acting on the production of ROS, in mitochondria and endoplasmic reticulum decreases the intensity of inflammation (Berthelot et al., 2020; Sanz et al., 2020). This activity was demonstrated to help maintain higher levels of vitamin C, an antioxidant which is known to exhibit antimicrobial activity and also proposed as a potential agent against COVID-19 infection (Grant et al., 2020).

4. Anti-viral activity of vitamin D_3

Vitamin D_3 can also induce the anti-viral immunity which is of prime importance nowadays considering the global COVID-19 pandemic. The anti-bacterial responses like stimulation of cathelicidin and β-Defensin 2 are also observed during an immune response to the viral attack thereby preventing the virus entry into host cells and its subsequent multiplication (Barlow et al., 2011). Vitamin D_3 is also responsible for inducing

autophagy as a result of both anti-bacterial and anti-viral activity (Campbell and Spector, 2012a). Autophagy is a mechanism by which cells degrade dysfunctional or damaged cellular organelles, macromolecules and misfolded proteins in lysosomes. This is also one of the ways for host cells of getting rid of viral load. Autophagy leads to the encapsulation of viral particles and degradation in lysosomes and creating a hostile anti-viral schematic event via antigen presentation and adaptive anti-viral responses (Mao et al., 2019). The transcriptional response to $1\alpha,25(OH)_2D_3$ also leads to the stimulation in expression of LC3 protein, an autophagic marker (Yuk et al., 2009), as well as the production of pro-autophagic proteins beclin-1 and PI3K (Wang, 2008) and suppressing the anti-autophagic mTOR pathway (Jang et al., 2014). Vitamin D_3 also promotes intracellular calcium concentrations and NO pathway which again induces the pro-autophagic event of PI3K to accelerate autophagy (Uberti et al., 2014). Autophagy is closely linked to apoptosis and thus could trigger the death of cells. This complex interplay may aid viral replication. Therefore, vitamin D_3 may play a critical role in perpetuating an appropriate equilibrium between autophagy and apoptosis to magnify antiviral responses at the site of infection (Eymoori-Rad et al., 2019). The examples of vitamin D_3-induced autophagy includes decrease in viral activity during HIV-1 infection (Campbell and Spector, 2012b), rotavirus (Tian et al., 2016), influenza A (Khare et al., 2013) and hepatitis C (Abdel-Mohsen et al., 2018). Moreover, during viral infection, $1\alpha,25(OH)_2D_3$ can be produced in the alveolar epithelial cells, which causes an increase in expression of cathelicidin gene (Aygun, 2020). Cathelicidin has direct antiviral activity against enveloped viruses such as influenza, hepatitis B virus and possibly the SARS-CoV-2 (Kara et al., 2020). LL-37, cationic peptide, derived from cleavage of the cathelicidin, after binding to the target virus destroys the envelope of enveloped viruses such as those of the Corona virus family. LL-37 is the only identified member of the cathelicidin family which is expressed by respiratory epithelial cells in humans (Crane-Godreau et al., 2020). The key concepts are summarised in Fig. 2.

5. Vitamin D_3 and immune responses

During antigen presentation, monocytes and macrophages elicit an appropriate adaptive immune response which after sequence of events recruit and activate T and B-cells that perform varied functions pertaining to immune response. For example, activation of dendritic cells during airway breach due to contraction of a certain virus is followed by the triggering of production of specific antibodies for antigen elimination and cytokine secretion which aids in killing of infected cells by T-cells (Holt et al., 2008). The type of immune response depends upon the type of antigen as well as the specific type of T-cells activated due to antigen presentation. Factors like $1\alpha,25(OH)_2D_3$ can influence this process by exerting an anti-inflammatory and inhibitory effects on adaptive immune system. Previous studies have indicated the increased expression of CYP27B1, rate limiting enzyme of $25(OH)D_3$ hydroxylation to $1\alpha,25(OH)_2D_3$, on activation and maturation of dendritic cells (Kallas et al., 2010). Other studies also have reported the induction in expression of Treg cells in dendritic cells on treatment with $1\alpha,25(OH)_2D_3$ (Daniel et al., 2008).

6. VDR regulated innate and adaptive immunity

6.1. *VDR polymorphism and respiratory infection*

Polymorphisms in *VDR* gene influence both innate and adaptive immune responses exerted due to $1\alpha,25(OH)_2D_3$. The well-studied polymorphisms of *VDR* are identified as *Fok* I, Taq I and *Apa* I. In Respiratory Syncytial Virus infection, an enveloped virus infection, a meta-analysis was performed which indicated the increased presence of recessive TT alleles in Fok I in comparison to the CT and CC genotypes and thus a propensity towards contracting this infection. T allele

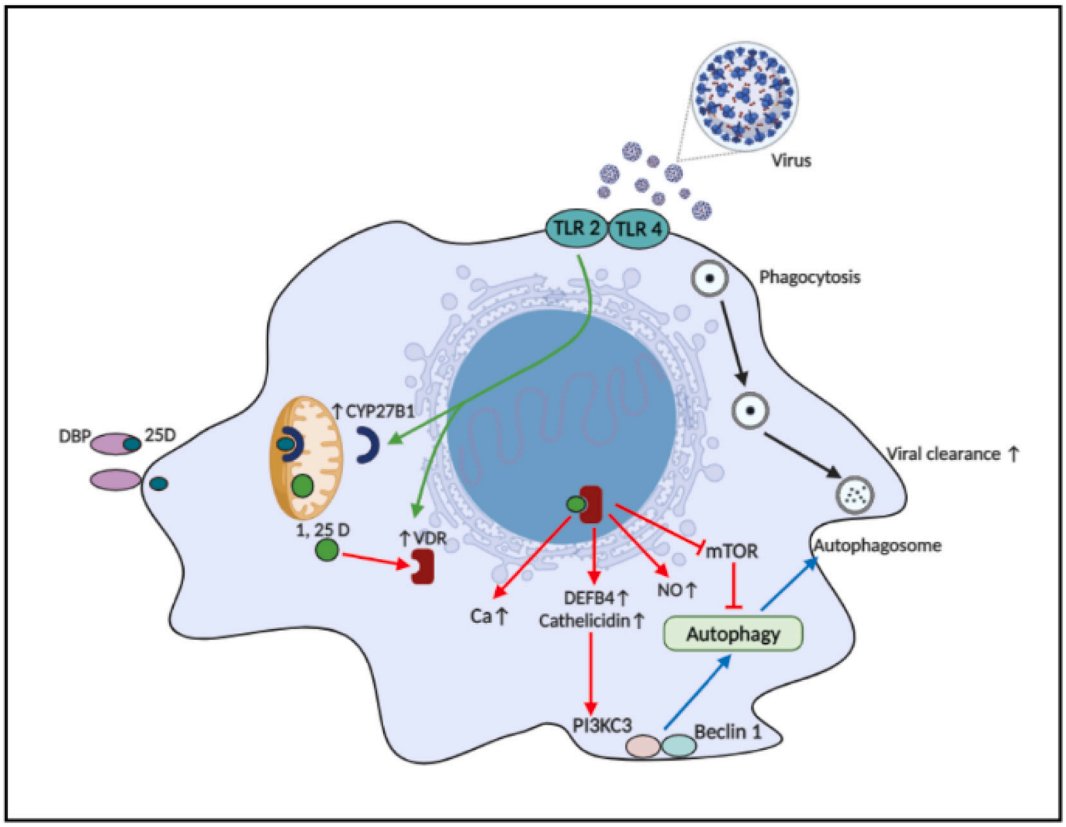

Fig. 2. Autophagy and antiviral actions of vitamin D_3.

reduced the capability of 1α,25(OH)$_2$D$_3$/VDR complex to bind and interact with its responsive target genes that were consistently associated with the higher risk towards Respiratory Syncytial Virus. This overlapping of association of T allele with the incidence of Respiratory Syncytial Virus infection supports the notion that 1α,25(OH)$_2$D$_3$ has a closer association with immune response evoked against viruses (Laplana et al., 2018).

6.2. Lung as a target organ for vitamin D_3

SARS-CoV-2, and the related viruses attack lungs in the most pathetic ways with the potential for severe respiratory complications. Host immune responses in retaliation to this viral attack on lungs lead to the generation of both innate and adaptive immunity (Iwasaki and Medzhitov, 2010). The cells that are principally activated include epithelial cells of the nasopharyngeal tract, alveolar macrophages and dendritic cells. The expression of CYP27B1 and 1α,25(OH)$_2$D$_3$ is high in these cells. Over the past decade, the 1α,25(OH)$_2$D$_3$ inadequacy has been found to be associated with infectious diseases like methicillin-resistant *Staphylococcus aureus* (MRSA) infection, pneumonia, tuberculosis and viral infections like HIV, human papilloma virus, influenza, cytomegalovirus and Hepatitis B and C suggesting a link between low serum 25(OH)D$_3$ levels and faulty antibacterial/antiviral immunity (Aibana et al., 2019; Watkins et al., 2015). Moreover, one of the major revelations of acute SARS-CoV-2 infection is lymphopenia (Tian and Rong, 2020). In studies carried out on mouse models and human cell lines, vitamin D$_3$ exerted its functions in lung tissue and exhibited protective effects on experimental interstitial pneumonitis (Tsujino et al., 2019). Various in vitro studies have indicated that vitamin D$_3$ plays a pivotal role in local "respiratory homeostasis" either by triggering the display of antimicrobial proteins or by directly interfering with the viral replication in respiratory tract (Zdrenghea et al., 2017).

6.3. Abnormal activation of immune system

Corona virus SARS-CoV-2 infection in the COVID-19 patients causes the surge in cytokine production in their pulmonary tract. This uprise in cytokine secretion is the outcome of dysfunctional innate immunity in the host which later leads to uncontrolled production and infiltration of pro-inflammatory cytokines and chemokines with consequential abnormal activation of adaptive immune response which culminates into acute respiratory distress syndrome (ARDS), characterized by widespread inflammation in lungs (Channappanavar and Perlman, 2017). The initial infection causes increased viral replication accompanied by the virus-induced delayed increase in the expression of IFN α and β. Normally, increased IFN α and β expression in dendritic cells would inhibit viral multiplication and accelerate viral clearance (Kohlmeier et al., 2010). However, this delay in their expression causes secretion and accumulation of pro-inflammatory cells (cytokines and chemokines) and thus complicating the problem by dysregulating innate immune responses and increasing the influx of macrophages, neutrophils and monocytes and at the same time predisposing T cells to undergo apoptosis (Channappanavar et al., 2016). This causes destruction of epithelial and endothelial lining of the lung causing vascular leakage and alveolar oedema. Studies have shown that 1α,25(OH)$_2$D$_3$ alleviates this devastating role of abnormal cytokine production by the constitutive expression of CYP27B1 and VDR by airway epithelia and induction of alveolar macrophages to express CYP27B1 and VDR on contracting an infection due to virus or other agents (Hansdottir et al., 2008). Whether the same can be applied to coronaviruses remains a future quest.

7. Vitamin D_3 and COVID-19 related heart diseases

Myocardial infarction, coronary artery disease, thrombosis, arrhythmias and cardiomyopathy became the talk of the town (or globe!) during the ongoing pandemic and scientific data backed the notion that there was a clear-cut association between these cardiovascular complications and present prevalence of COVID-19 (Clerkin et al., 2020). These studies showed that the patients hospitalized for COVID-19 manifested abnormalities during electrocardiography as well as echocardiogram with an increase in cardiac biomarkers (Guo et al., 2020). About 30% of COVID-19 patients also presented with cardiomyopathy (Arentz et al., 2020). 1α,25(OH)$_2$D$_3$ plays a crucial role in the prevention of cholesterol build-up in the arteries by preventing the conversion of macrophages to foam cells (Oh et al., 2009) and enhancing the cholesterol efflux from blood vessels (Yin et al., 2015) and thus may provide protection against arteriosclerosis. Besides, activation of VDR by 1α,25(OH)$_2$D$_3$ can induce endothelial repair through stimulation of vascular endothelial growth factor (VEGF) (Norman and Powell, 2014). This pathway can also induce thrombomodulin expression and NO production and inhibit NF-κB and IL-6 expression and further mitigate the negative effects caused in response to arteriosclerosis (Norman and Powell, 2014). Various risk factors that have been related to morbidity and mortality caused due to COVID-19 are also associated to vitamin D$_3$ inadequacy. Such risk factors include: hypertension (Kunutsor et al., 2013), obesity (Pereira-Santos et al., 2015), diabetes (Song et al., 2013) and kidney diseases (Dusso and Tokumoto, 2011). In mice models with knocked out genes for *CYP27B1* or *VDR,* progression of atherosclerosis, myocardial hypertrophy with upregulation of RAAS, altered vascular function, hypertension and elevated thrombogenicity has been reported (Ni et al., 2014). COVID-19 patients are also at increased risk of similar thrombotic complications however, the mechanisms are yet to be explored. Deficient vitamin D$_3$ levels may be a contributing factor towards this problem as VDR is constitutively expressed in blood vessels (Pilz et al., 2016). In addition, few studies also try to correlate the deficiency of vitamin D$_3$ towards cardio-vascular complications (Khademvatani et al., 2014; Wu and He, 2018), a repercussion in SARS-CoV-2 infection as well.

8. Vitamin D_3 and decreased risk of pulmonary infections

In animal models, vitamin D$_3$ suppressed pulmonary permeability caused due to acute respiratory distress syndrome (ARDS) by regulating RAAS activity and expression of angiotensin-2 converting enzyme (ACE2). This mechanism is of crucial importance since SARS-CoV-2 reportedly exploits ACE2 as a receptor to infect host cells and downregulates its expression. ACE2 is expressed in several organs, which includes the lining of endothelium, intestinal epithelium and pulmonary alveolar epithelium, where it is reported to exert protective effects against inflammation. This downregulation of ACE2 results in inflammatory chain reaction which leads to excess cytokine production also known as the 'cytokine storm', resulting in fatal ARDS and further exacerbating the COVID-19 problem (Annweiler et al., 2020).

Results from a recent meta-analysis have determined the impact of vitamin D$_3$ supplementation on pulmonary tuberculosis to an extent that this could be used as an adjuvant treatment along with the antibiotics (Wu et al., 2018). Observational studies have suggested a close link between low vitamin D$_3$ levels and winter season and an accompanying increase in viral infections such as influenza. During pandemics, same situation arises when more people die in winter season (Cannell et al., 2006). Studies have also demonstrated an inverse correlation between serum 25(OH)D$_3$ levels and respiratory tract infections (Mathyssen et al., 2017). One of the studies inferred a two-fold decreased risk of acute respiratory infections and rapid recovery in patients with highly sufficient levels of serum 25(OH)D$_3$ compared to those with deficient levels (Sabetta et al., 2010). In another retrospective analysis conducted by National Health and Nutrition Examination Survey, serum 25(OH)D$_3$ levels greater than 30 ng/ml correlated with about 60% increase risk for acute respiratory infections (Monlezun et al., 2015). Another thorough meta-analysis evaluating the impact of vitamin D$_3$ supplementation to ameliorate the acute respiratory tract infections indicated a 12% reduced risk of acute respiratory infections with a stronger correlation in

those individuals with serum 25(OH)D_3 levels less than 10 ng/ml than those with levels more than 10 ng/ml (Martineau et al., 2019).

9. Vitamin D_3 and COVID-19 infection-epidemiological evidence

Demographic and ecological studies have provided a substantial data to support the protective role of vitamin D_3 with respect to COVID-19. An analysis was conducted in Europe according to which about 20 European countries with severe vitamin D_3 deficiency were affiliated with an increased rate of incidence as well as mortality in patients with COVID-19 infection (Ilie et al., 2020). A randomized clinical trial of COVID-19 patients suggested highly insufficient levels of serum 25(OH)D_3 in critically ill-patients that were under Intensive Care Unit and a relation with the length of stay and mortality in them (Amrein et al., 2012). This propounds the suggestion that increasing serum vitamin D_3 levels in patients may improve their prognosis. Another study from US depicted a stronger correlation between vitamin D_3 deficiency and poorer clinical outcome in such patients (Daneshkhah et al., 2020). An interesting North to South difference was also indicated by a study in which Northern States of US showed increased number of mortalities with COVID-19 disease in comparison to Southern states (Marik et al., 2020). In a retrospective analysis on about 107 patients from Switzerland tested with COVID-19, the patients with positive RT-PCR for SARS-CoV-2 had a median serum 25(OH)D_3 levels of about 11 ng/ml and those with negative RT-PCR had a median serum 25(OH)D_3 levels of about 24 ng/ml (D'Avolio et al., 2020).

Some more observational studies discerned the correlation between vitamin D_3 levels and COVID-19 cases and mortality. However, the results were not consistent for all investigations. For example, a retrospective study with SARS-CoV-2 infection evaluated serum levels of vitamin D_3 from three hospitals in South Asian countries suggested a significant difference in mean vitamin D_3 levels with mild (78 nmol/l), ordinary (68.5 nmol/l), severe (53 nmol/l) and critical cases of COVID-19 (Alipio, 2020). A cohort observational study in Singapore noted that COVID-19 patients who procured combined oral dosage of vitamin D_3 (1000 IU), Mg (150 mg), and vitamin B12 (500 μg) required oxygen therapy compared to the controls. These patients treated also showed significant protective effects against clinical deterioration even after adjusting for confounders such as age, gender and other comorbidities (Tan et al., 2020). A retrospective study from the main-land of USA which included many COVID-19 cases determined that sunlight and vitamin D_3, with latitude as an indicator, potentially correlated with lowered risks for both COVID-19 cases and fatality (Ali, 2020). A study on Chinese population for analysing the impact of co-morbidities (hypertension and diabetes) in COVID-19 patients exhibited poorer clinical outcome compared to those who had no such comorbidities (Guan et al., 2020). Another study indicated that age, cardiovascular disease and respiratory diseases along with hypertension contributed towards the risk in severe COVID-19 patients compared to non-severe patients (Yang et al., 2020). Additionally, co-infections like bacterial and fungal infections have also been observed to increase this risk (Chen et al., 2020). On the other hand, different results were obtained from another study using UK Biobank data which although suggested the correlation between ethnicity and vitamin D_3 with COVID-19 infection on univariate analysis but after adjustment with potential confounders there was no potential link between vitamin D_3 levels and COVID-19 risk (Hastie et al., 2020).

Spain and Italy, one of the hardest hit countries in the world with COVID-19 pandemic are curiously also highly vitamin D_3 deficient. About 75% of Italian women between the age group of 60–80 years were suffering from hypovitaminosis D_3 (Isaia et al., 2003). Additionally, about 32% of healthy but post-menopausal women also suffered from deficient vitamin D_3 levels during winters and 80% of hospitalized individuals also did the same (Romagnoli et al., 1999). The well-recognized risk factors of COVID-19 infections so far include obesity and diabetes are also related to severely low serum 25(OH)D_3 levels and hence to vitamin D_3 supplementation requirements (Isaia et al., 2003; Formenti et al., 2019). Moreover, this severity of hypovitaminosis D_3 is linked to inflammatory characteristics (Boccardi et al., 2019). A protective feature can be examined of vitamin D_3 supplementation among post-menopausal women to treat their osteoporosis and other bone-related disorders against men who are on no such supplements and thus may be hypothesized to be more prone to this disease (Grant et al., 2020; Degli Esposti et al., 2019).

10. Vitamin D_3 and virulence mechanism of COVID-19 disease

Although it is still not fully characterized, but several molecular mechanisms have been affiliated to the virulence ability and host cell-invasion with respect to COVID-19 which includes dipeptidyl peptidase-4 receptor (DPP-4) or cell adhesion molecule CD26 binding, MDA5 and RIG-I host-recognition evasion, Papain-like protease (PLpro)-mediated replication, and disruption of M-protein mediated type-1 IFN induction. All these cellular mechanisms have been identified in the Covid-MERS virus, a close relative of COVID-19 virus and a causative agent of Middle East respiratory syndrome (MERS) (Skariyachan et al., 2019). Out of these mechanisms, recently human DPP-4/CD26 has also been identified to interact with S1 domain of COVID-19 spike glycoprotein, indicating that it may also be an important factor for COVID-19 infection (Vankadari and Wilce, 2020). Further adding support to this suggestion, the expression of DPP-4/CD26 receptor has shown to be lowered considerably upon amelioration of vitamin D_3 deficiency (Komolmit et al., 2017). Studies have also suggested that augmentation of vitamin D_3 may debilitate some of the destructive downstream immunological responses thought to manifest poorer clinical outcome in COVID-19 infection. This includes a delayed interferon-gamma (IFN-γ) response (Zdrenghea et al., 2017) and continuous interleukin 6 (IL6) upsurge in severely-ill pneumonia patients (Miroliaee et al., 2018) as well as those with COVID-19.

11. Vitamin D_3 recommendation guidelines

Generally, the most widely accepted serum level of 25(OH)D_3 is >30 ng/ml, vitamin D insufficiency is established between 20 and 30 ng/ml and vitamin D_3 deficiency is considered when serum level of 25(OH)D_3 less than 20 ng/ml (Holick, 2007). In 2010, American Academy of Clinical Endocrinology published some guidelines for the management of post-menopausal osteoporosis and one of its recommendations was to ensure sufficiency of vitamin D_3 levels in both children and adults (Watts et al., 2010). Natural food sources are not rich in vitamin D_3 so in order to maintain the adequate levels vitamin D_3 supplementation comes to the rescue. In adults who are over 50 years of age the recommended dosage of vitamin D_3 is 800 to 1000 IU per day (Cosman et al., 2014). Considering the role vitamin D_3 plays in maintaining bone mineral density, cancer prevention, dental health, risk of falls and fractures, hypertension and mortality deficient levels of vitamin D_3 (<20 ng/ml) provide no benefits or exhibit adverse effects while as the adequate levels (≥30 ng/ml) are quite advantageous (Bischoff-Ferrari, 2014). Individuals who are home-bound, indoor workers or patients with intestinal malabsorption usually suffer from vitamin D_3 deficiency. Individuals suffering from obesity are at higher risk of developing vitamin D_3 deficiency because of the property of vitamin D_3 being fat soluble due to which it is easily sequestered by the body fat. In a study involving an oral supplementation of 50,000 IU of vitamin D_3, obese patients were able to raise their vitamin D_3 blood levels only by 50% in comparison to the non-obese individuals (Walsh et al., 2017). For COVID-19 patients, to achieve 25(OH)D_3 levels above 40 ng/ml, a study suggested dosage of 50,000 IU of vitamin D_3 twice a week for the first week and the dose of 50,000 IU for the second and third weeks (Ebadi and Montano-Loza, 2020). The serum response of vitamin D_3 to the given oral dosage is largely varied between the subjects due to differences in anthropometric, demographic and biological variables such as age, ethnicity,

BMI, duration of exposure, seasonal variations, intake of certain medication or drugs, base-line concentration of vitamin D_3, type of vitamin D_3 supplements as well as genetics (Mazahery and von Hurst, 2015; Fabbri et al., 2020) and needs to be considered during determining the preventing role and a potential link of vitamin D_3 in COVID-19.

12. Role of vitamin D_3 and its hydroxy-derivatives against oxidative stress in COVID-19

$1,25(OH)_2D_3$ and non-calcemic CYP11A1 derived vitamin D_3 compounds use several, although partially coinciding, pathways in executing their anti-inflammatory and anti-oxidative activities (Slominski et al., 2020b). While $1,25(OH)_2D_3$ mediates many of its anti-inflammatory and anti-microbial functions via vitamin D receptor (VDR), CYP11A1-derived metabolites also have their own scheme to tackle inflammation. $20(OH)D_3$ and the subsequent hydroxyderivatives act on VDR as "biased agonists". They also act as "inverse agonists" on RORs, RORα and RORγ, transcription factors with important roles in several immune cells and eliciting immune responses (Slominski et al., 2017; Slominski et al., 2014b). Moreover, CYP11A1-derived vitamin D_3 metabolites and classical $1,25(OH)_2D_3$ can act as "agonists" on Aryl hydrocarbon Receptor (AhR), and its secosteroidal signal transduction can be linked to detoxification and anti-oxidative activity or down-regulation of pro-inflammatory responses (Slominski et al., 2018).

As mentioned earlier, leading cause of ARDS is "cytokine storm" with the severe assault to lung alveolar cells causing severe lung injury and in severe cases of COVID-19, other organs and systems are also badly hit. So, the focus of contemporary research studies is to target this cytokine storm from going out of control and preventing the disease from worsening (Slominski et al., 2020b). One of the major manifestations of ARDS is oxidative stress through the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). The pathogenic attack (bacteria, viruses, etc.) stimulates the secretion of cytokines which in turn magnify the production of ROS and RNS. The excessive production of ROS and RNS is perceived by Nuclear factor erythroid 2p45-related factor 2 (NRF-2), a transcription factor which then induces the pathway to counteract oxidative damage (Slominski et al., 2020a). The antioxidant defense system is promoted by the NRF2-Antioxidant Response Element (ARE) signaling pathway by promoting the expression of phase II detoxification enzymes including glutathione reductase (GR), heme oxygenase-1 (HO-1), catalase (CAT), manganese superoxide dismutase (MnSOD), and copper zinc superoxide dismutase (CuZnSOD). NRF-2 loss due to ROS is associated with surge in the levels of pro-inflammatory cytokines and elevated inflammatory responses (Chaiprasongsuk et al., 2019). Both the classical $1,25(OH)_2D_3$ and novel CYP11A1 derived active forms of vitamin D_3 exert anti-inflammatory functions (inhibition of IL-1, IL-6, IL-17, TNFα and INFγ production or other proinflammatory mechanisms) involving downregulation of NF-κB via VDR and Th17 response via inverse agonist action of RORγ (Slominski et al., 2020c; Chaiprasongsuk et al., 2020). These metabolites also cause the activation of NRF-2 and P53 phosphorylation leading to stimulation of antioxidative and DNA repair responses after their translocation to cell nucleus (Chaiprasongsuk et al., 2019). The key concepts are summarised in Fig. 3.

13. Is vitamin D_3 supplementation alone really a solution?

Vitamin D_3 supplementation is not successful in clinical trials even in patients with highly deficient vitamin D_3 levels despite using high dosage of vitamin D_3 and more robust end-point measures. As mentioned earlier low serum concentrations of $25(OH)D_3$ have been associated with increased occurrence of infection, immunological disorders, cancers, obesity, insulin resistance and elevated fasting glucose concentrations and type 2 diabetes (Boucher, 2020; Maretzke et al.,

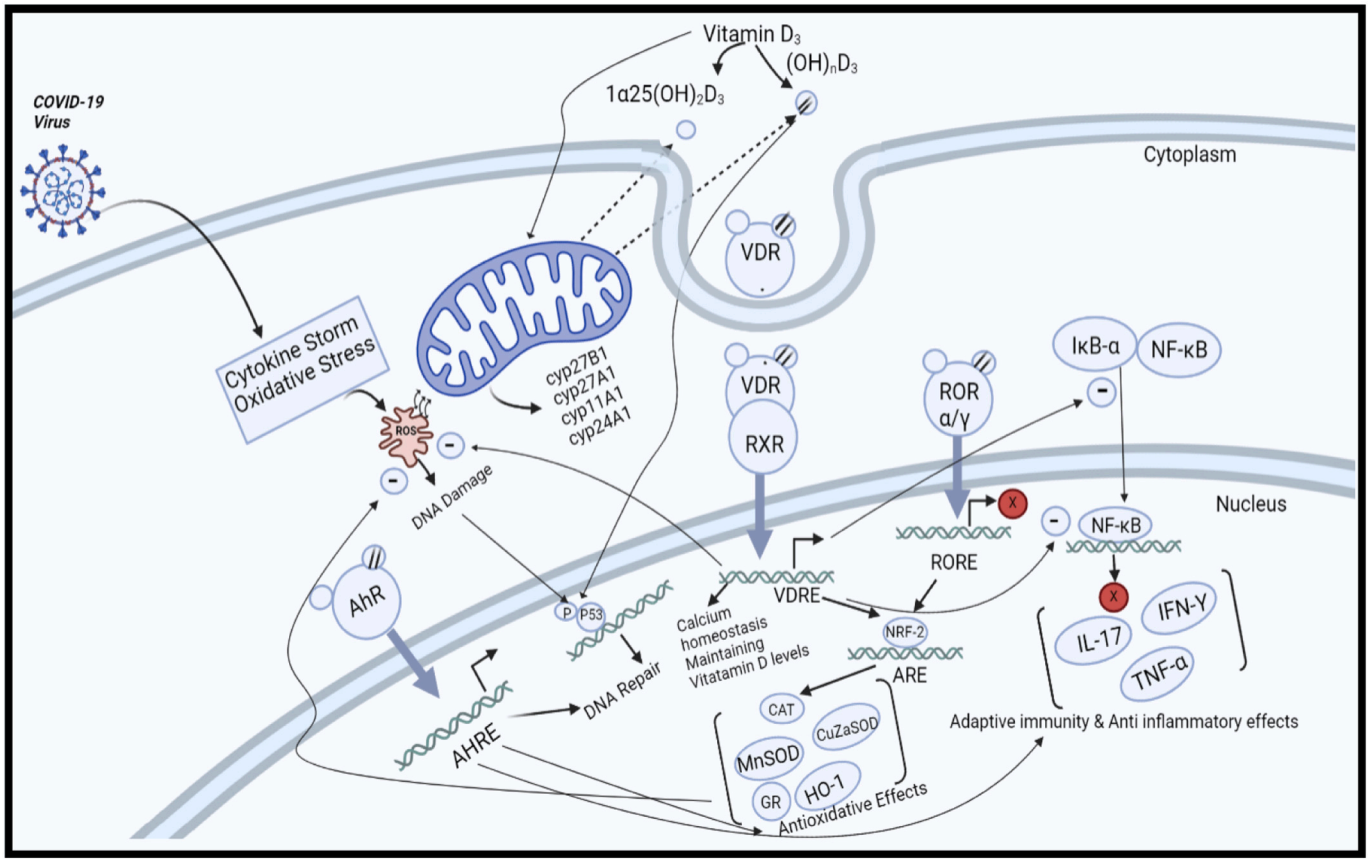

Fig. 3. Vitamin D_3 target receptors activating signal transduction pathways on COVID-19 infection.

2020). Despite the presence of ample epidemiological data, few clinical trials have been conducted to relate vitamin D_3 supplementation with metabolic features like obesity and glucose status and a meta-analysis of such trials indicate considerable heterogeneity in study quality, vitamin D_3 gene polymorphisms, possible confounders, chances of bias, sun-exposure, vitamin D_3 supplementation dosage and duration, vitamin D_3 status of study subjects, use of indirect measures of glucose metabolism and sample size (Maretzke et al., 2020; Mousa et al., 2017). Some clinical trials also have ignored the important parameters like diet and exercise or dietary calcium and vitamin D_3 intake, others did not adjust for potential covariates such as intake of nutritional factors like vitamins (A and K), adiposity or physical activity. Additionally, in a larger and longer clinical trial in which gold-standard methods and higher vitamin D_3 doses in deficient adults were used, no metabolic effects of vitamin D_3 supplementation could be achieved (Boucher, 2020). Many of the Randomised Controlled Trials (RCTs) examining the effect of vitamin D_3 supplementation on insulin secretion and sensitivity have combined calcium with vitamin D_3, which could have confounded the results because calcium concentrations have been indicated to influence both insulin secretion and sensitivity (Mousa et al., 2017). Other RCTs have used methods developed for testing drugs while vitamin D_3 is a nutrient; the recognition of this design defect is important for identifying health benefits from current RCT data and for improving prospective RCT design. Variations in 25(OH)D_3 effect thresholds is another potential confounder of RCT analyses. Bone health, for example, is generally accepted as being maintained when serum 25(OH)D_3 values are at least 50 nmol/l, but higher thresholds of serum 25(OH)D_3 concentration are required for non-skeletal health benefits (Boucher, 2020). All this has led to the difficulty in interpreting the results. Considering these data, it is unlikely that vitamin D_3 supplementation alone has a role in improving metabolic outcomes or risk factors for diseases like type 2 diabetes, cardiovascular disease, or COVID-19 infection.

Glutathione (GSH) is a co-factor of many enzymes, a potent antioxidant, and plays a crucial role as a scavenger of reactive oxygen species, which helps prevent damage to the cellular components and cellular dysfunction. Glutathione deficiency is implicated in the aetiology and pathogenesis of several human diseases including cardiovascular, immune, diseases related to aging, and chronic diseases like diabetes (Jain and Micinski, 2013). Not only this, an imbalance in GSH homeostasis and oxidative stress is an essential component of the inflammation and respiratory distress, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), tuberculosis, neurodegenerative diseases, and several viral infections, including HIV and SIV (Jain and Parsanathan, 2020). GSH deficiency also increases the impairment of the activities of specialized immune cells and thus the body's ability to fight infection. Vitamin D binding protein (VDBP) is a main transporter of vitamin D_3 and 25(OH)D_3 to various tissues and participates in their conversion to 1,25$(OH)_2D_3$. Recent studies have indicated that blood concentrations of VDBP are positively associated to the half-life of circulating 25(OH)D_3, and that blood levels of GSH have a positive relationship with those of VDBP and 25(OH)D_3 in the blood of type 2 diabetic patients (Jain et al., 2016). L-Cysteine (LC) is a precursor of GSH biosynthesis and plays a direct role in posttranslational modification or S-glutathionylation of proteins, and thereby provide protection against oxidative signaling events. Elevated oxidative stress may cause increased LC utilization and subsequently lower LC levels which can be rectified by increasing LC supplementation and improving GSH status. A decrease in oxidative stress can in turn result in the decreased cellular ROS and inhibition of pro-inflammatory cytokines such as TNF-α, MCP-1 and IL-8 secretion by the monocytes (Jain and Micinski, 2013; Jain et al., 2021). According to some studies, GSH deficiency resulted in the downregulation of VDBP and VDR in hepatocytes, as well as 25(OH)D_3 deficiency, which suggests that an improvement in the VDBP and circulating 25(OH)D_3 status may be associated with an improvement in the GSH levels on LC supplementation (Parsanathan and Jain, 2019a). 25(OH)D_3 status is a biomarker of monitoring VD deficiency or inadequacy. Basically, precursor of GSH, such as L-cysteine or *N*-acetylcysteine, boosts the levels of cellular GSH, which upregulates CYP27A1, CYP27B1, and VDR but downregulates CYP24A1. Due to its shorter half-life, GSH replenishment is impaired which is compensated by treatment with L-cysteine as the promising approach (Parsanathan and Jain, 2019b). This suggests a potential role for GSH as an adjuvant therapeutic target for normalizing circulating 25(OH)D_3 status in vulnerable populations where clinical trials involving vitamin D_3 supplementation alone has been unsuccessful. Due to this modern trend of widespread use of vitamin D_3 (VD) supplements by the public attempting to achieve better health, randomized controlled clinical trials conducted have shown that high supraphysiological doses of VD are needed to achieve the required levels of VD in the circulation and that not all subjects respond to vitamin D_3 (VD) supplementation. Therefore, a potential novel therapeutic strategy would be using the combined LC + VD, which could simultaneously antagonize and mitigate cellular oxidative stress and provide lower vascular inflammation (Jain et al., 2018; Parsanathan et al., 2020) and thus provide a better option to achieve better health outcome in various diseases including type 2 diabetes or COVID-19. The cytokine storm in SARS-CoV2 infection has been linked with both diabetes and vitamin D_3 deficiency. There is no previous report in the literature that has examined the potential role/benefit of vitamin D_3 supplementation in boosting cellular GSH levels in case of COVID-19. Thus, a clinical trial examining the ability of vitamin D_3 supplementation to boost circulating GSH levels and lower immune inflammatory or oxidative stress biomarkers is warranted to validate this finding in a COVID-19 patient population (Jain and Parsanathan, 2020). If such trial pertaining to upregulation of the intracellular glutathione redox status and 25(OH)D_3 leads to tangible clinical results, it would provide the basic mechanism that explains the beneficial role of vitamin D_3 in reducing the adverse clinical effects including the 'cytokine storm' one of the most severe consequences of infection with COVID-19 as well as prevent inflammation and impaired immunity in subjects exposed to COVID-19 and in comorbid systemic inflammatory conditions, such as diabetes, obesity, and hypertension all of which are considered significant risk factors for COVID-19 severity.

14. Conclusion

The available clinical data is still at the stage of its infancy considering the disease to be the most recent finding, so it is too early to deduce an established association between vitamin D_3 and COVID-19 infectious disease. Most of the articles published in this regard are circumstantial, associative, less argumentative and undergoing only limited peer-review process. However, large number of recent manuscripts do support the notion that vitamin D_3 deficiency is related to COVID-19 disease. The role that vitamin D_3 plays besides its classical actions in immune cells and non-skeletal target tissues would help in extrapolating its role in the severity of this disease and its clinical outcome. At the time of writing this article clinical trials have already been conducted and many more are under way linking the impact of vitamin D_3 supplementation and 25(OH)D_3 levels on patients with COVID-19 disease. So, until we may find something conclusive it would not be an exaggeration if we state that maintaining the balanced levels of vitamin D_3 is highly recommended considering its diverse benefits in our system.

Funding

Not applicable.

Availability of data and material

Not applicable.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Falaque ul Afshan: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Bushra Nissar:** Writing – review & editing. **Nisar Ahmad Chowdri:** Writing – review & editing. **Bashir Ahmad Ganai:** Supervision.

Declaration of competing interest

The authors confirm that this article content has no conflicts of interest.

Acknowledgement

The authors thank Mr. Umar Yaqoob Batoo, Masters in Computer Applications, University of Kashmir for his valuable inputs during the preparation of the manuscript.

References

Abdel-Mohsen, M.A., El-Braky, A.A.-A., Ghazal, A.A.E., Shamseya, M.M., 2018. Autophagy, apoptosis, vitamin D, and vitamin D receptor in hepatocellular carcinoma associated with hepatitis C virus. Medicine. 97 (12), e0172 https://doi.org/10.1097/MD.0000000000010172.

Ahn, D.G., Shin, H.J., Kim, M.H., Lee, S., Kim, H.S., Myoung, J., Kim, B.T., Kim, S.J., 2020. Current status of epidemiology, diagnosis, therapeutics, and vaccines for novel coronavirus disease 2019 (COVID-19). J. Microbiol. Biotechnol. 30 (3), 313–324. https://doi.org/10.4014/jmb.2003.03011.

Aibana, O., Huang, C.C., Aboud, S., Arnedo-Pena, A., Becerra, M.C., Bellido-Blasco, J.B., Bhosale, R., Calderon, R., Chiang, S., Contreras, C., et al., 2019. Vitamin D status and risk of incident tuberculosis disease: a nested case-control study, systematic review, and individual-participant data meta-analysis. PLoS Med. 16 (9), e1002907 https://doi.org/10.1371/journal.pmed.1002907.

Ali, N., 2020. Role of vitamin D in preventing of COVID-19 infection, progression and severity. J. Infect. Publ. Health. 13 (10), 1373–1380. https://doi.org/10.1016/j.jiph.2020.06.021.

Alipio, M., 2020. Vitamin D supplementation could possibly improve clinical outcomes of patients infected with coronavirus-2019 (COVID-2019). Available at. In: SSRN3571484.

Amrein, K., Schnedl, C., Berghold, A., Pieber, T.R., Dobnig, H., 2012. Correction of vitamin D deficiency in critically ill patients — VITdAL@ICU study protocol of a double-blind, placebo-controlled randomized clinical trial. BMC Endocr. Disord. 12, 27. https://doi.org/10.1186/1472-6823-12-27.

Annweiler, C., Hanotte, B., Grandin de l'Eprevier, C., Sabatier, J.M., Lafaie, L., Célarier, T., 2020. Vitamin D and survival in COVID-19 patients: a quasi-experimental study. J. Steroid Biochem. Mol. Biol. 204, 105771. https://doi.org/10.1016/j.jsbmb.2020.105771.

Arentz, M., Yim, E., Klaff, L., Lokhandwala, S., Riedo, F.X., Chong, M., Lee, M., 2020. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA. 323 (16), 1612–1614. https://doi.org/10.1001/jama.2020.4326.

Aygun, H., 2020. Vitamin D can prevent COVID-19 infection-induced multiple organ damage. Naunyn Schmiedeberg's Arch. Pharmacol. 393 (7), 1157–1160. https://doi.org/10.1007/s00210-020-01911-4.

Bacchetta, J., Zaritsky, J.J., Sea, J.L., Chun, R.F., Lisse, T.S., Zavala, K., Nayak, A., Wesseling Perry, K., Westerman, M., Hollis, B.W., et al., 2014. Suppression of iron-regulatory hepcidin by vitamin D. J. Am. Soc. Nephrol. 25 (3), 564–572. https://doi.org/10.1681/ASN.2013040355.

Barlow, P.G., Svoboda, P., Mackellar, A., Nash, A.A., York, I.A., Pohl, J., Davidson, D.J., Donis, R.O., 2011. Antiviral activity and increased host defense against influenza infection elicited by the human cathelicidin LL-37. PLoS One 6 (10), e25333. https://doi.org/10.1371/journal.pone.0025333.

Berthelot, J.M., Drouet, L., Lioté, F., 2020. Kawasaki-like diseases and thrombotic coagulopathy in COVID-19: delayed over-activation of the STING pathway? Emerg. Microbes Infect. 9 (1), 1514–1522. https://doi.org/10.1080/22221751.2020.1785336.

Bikle, D.D., 2014. Vitamin D metabolism, mechanism of action, and clinical applications. Chem. Biol. 21 (3), 319–329. https://doi.org/10.1016/j.chembiol.2013.12.016.

Bischoff-Ferrari, H.A., 2014. Optimal serum 25-hydroxyvitamin D levels for multiple health outcomes. Adv. Exp. Med. Biol. 810, 500–525. https://doi.org/10.1007/978-1-4939-0437-2_28.

Boccardi, V., Lapenna, M., Gaggi, L., Garaffa, F.M., Croce, M.F., Baroni, M., Ercolani, S., Mecocci, P., Ruggiero, C., 2019. Hypovitaminosis D: a disease marker in hospitalized very old persons at risk of malnutrition. Nutrients. 11 (1), 128. https://doi.org/10.3390/nu11010128.

Boucher, B.J., 2020. Why do so many trials of vitamin D supplementation fail? Endocr. Connect. 9 (9), R195–R206. https://doi.org/10.1530/EC-20-0274.

Campbell, G.R., Spector, S.A., 2012a. Autophagy induction by vitamin D inhibits both Mycobacterium tuberculosis and human immunodeficiency virus type 1. Autophagy. 8 (10), 1523–1525. https://doi.org/10.4161/auto.21154.

Campbell, G.R., Spector, S.A., 2012b. Toll-like receptor 8 ligands activate a vitamin D mediated autophagic response that inhibits human immunodeficiency virus type 1. PLoS Pathog. 8 (11), e1003017 https://doi.org/10.1371/journal.ppat.1003017.

Cannell, J.J., Vieth, R., Umhau, J.C., Holick, M.F., Grant, W.B., Madronich, S., Garland, C.F., Giovannucci, E., 2006. Epidemic influenza and vitamin D. Epidemiol. Infect. 134 (6), 1129–1140. https://doi.org/10.1017/S0950268806007175.

Chaiprasongsuk, A., Janjetovic, Z., Kim, T.K., Jarrett, S.G., D'Orazio, J.A., Holick, M.F., Tang, E.K.Y., Tuckey, R.C., Panich, U., Li, W., Slominski, A.T., 2019. Protective effects of novel derivatives of vitamin D3 and lumisterol against UVB-induced damage in human keratinocytes involve activation of Nrf2 and p53 defense mechanisms. Redox Biol. 24, 101206. https://doi.org/10.1016/j.redox.2019.101206.

Chaiprasongsuk, A., Janjetovic, Z., Kim, T.K., Tuckey, R.C., Li, W., Raman, C., Panich, U., Slominski, A.T., 2020. CYP11A1-derived vitamin D3 products protect against UVB-induced inflammation and promote keratinocytes differentiation. Free Radic. Biol. Med. 155, 87–98. https://doi.org/10.1016/j.freeradbiomed.2020.05.016.

Chan, T.Y., 2000. Vitamin D deficiency and susceptibility to tuberculosis. Calcif. Tissue Int. 66 (6), 476–478. https://doi.org/10.1007/s002230010095.

Channappanavar, R., Perlman, S., 2017. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin. Immunopathol. 39 (5), 529–539. https://doi.org/10.1007/s00281-017-0629-x.

Channappanavar, R., Fehr, A.R., Vijay, R., Mack, M., Zhao, J., Meyerholz, D.K., Perlman, S., 2016. Dysregulated Type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe. 19 (2), 181–193. https://doi.org/10.1016/j.chom.2016.01.007.

Chen, N., Zhou, M., Dong, X., et al., 2020. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 395 (10223), 507–513. https://doi.org/10.1016/S0140-6736(20)30211-7.

Clerkin, K.J., Fried, J.A., Raikhelkar, J., Sayer, G., Griffin, J.M., Masoumi, A., Jain, S.S., Burkhoff, D., Kumaraiah, D., Rabbani, L., et al., 2020. Coronavirus disease 2019 (COVID-19) and cardiovascular disease. Circulation. 141 (20), 1648–1655. https://doi.org/10.1161/CIRCULATIONAHA.120.046941.

Cosman, F., de Beur, S.J., LeBoff, M.S., Lewiecki, E.M., Tanner, B., Randall, S., Lindsay, R., National Osteoporosis Foundation, 2014. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos. Int. 25 (10), 2359–2381. https://doi.org/10.1007/s00198-014-2794-2.

Crane-Godreau, M.A., Clem, K.J., Payne, P., Fiering, S., 2020. Vitamin D deficiency and air pollution exacerbate COVID-19 through suppression of antiviral peptide LL37. Front. Public Health 8, 232. https://doi.org/10.3389/fpubh.2020.00232.

Daneshkhah, A., Agrawal, V., Eshein, A., et al., 2020. The possible role of vitamin D in suppressing cytokine storm and associated mortality in COVID-19 patients. Aging Clin. Exp. Res. 32 (10), 2141–2158. https://doi.org/10.1007/s40520-020-01677-y.

Daniel, C., Sartory, N.A., Zahn, N., Radeke, H.H., Stein, J.M., 2008. Immune modulatory treatment of trinitrobenzene sulfonic acid colitis with calcitriol is associated with a change of a T helper (Th) 1/Th17 to a Th2 and regulatory T cell profile. J. Pharmacol. Exp. Ther. 324 (1), 23–33. https://doi.org/10.1124/jpet.107.127209.

D'Avolio, A., Avataneo, V., Manca, A., Cusato, J., De Nicolò, A., Lucchini, R., Keller, F., Cantù, M., 2020. 25-Hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS CoV-2. Nutrients. 12 (5), 1359. https://doi.org/10.3390/nu12051359.

Deeb, K.K., Trump, D.L., Johnson, C.S., 2007. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. Nat. Rev. Cancer 7 (9), 684–700. https://doi.org/10.1038/nrc2196.

Degli Esposti, L., Girardi, A., Saragoni, S., Sella, S., Andretta, M., Rossini, M., Giannini, S., on the behalf of the Study Group, 2019. Use of antiosteoporotic drugs and calcium/vitamin D in patients with fragility fractures: impact on re-fracture and mortality risk. Endocrine. 64 (2), 367–377. https://doi.org/10.1007/s12020-018-1824-9.

van der Does, A.M., Bergman, P., Agerberth, B., Lindbom, L., 2012. Induction of the human cathelicidin LL-37 as a novel treatment against bacterial infections. J. Leukoc. Biol. 92 (4), 735–742. https://doi.org/10.1189/jlb.0412178.

Dusso, A.S., Tokumoto, M., 2011. Defective renal maintenance of the vitamin D endocrine system impairs vitamin D renoprotection: a downward spiral in kidney disease. Kidney Int. 79 (7), 715–729. https://doi.org/10.1038/ki.2010.543.

Ebadi, M., Montano-Loza, A.J., 2020. Perspective: improving vitamin D status in the management of COVID-19. Eur. J. Clin. Nutr. 74 (6), 856–859. https://doi.org/10.1038/s41430-020-0661-0.

Erben, R.G., Soegiarto, D.W., Weber, K., Zeitz, U., Lieberherr, M., Gniadecki, R., Möller, G., Adamski, J., Balling, R., 2002. Deletion of deoxyribonucleic acid binding domain of the vitamin D receptor abrogates genomic and nongenomic functions of

vitamin D. Mol. Endocrinol. 16 (7), 1524–1537. https://doi.org/10.1210/mend.16.7.0866.
Eymoori-Rad, M., Shokri, F., Salimi, V., Marashi, S.M., 2019. The interplay between vitamin D and viral infections. Rev. Med. Virol. 29 (2), e2032. https://doi.org/10.1002/rmv.2032.
Fabbri, A., Infante, M., Ricordi, C., 2020. Editorial — Vitamin D status: a key modulator of innate immunity and natural defense from acute viral respiratory infections. Eur. Rev. Med. Pharmacol. Sci. 24 (7), 4048–4052. https://doi.org/10.26355/eurrev_202004_20876.
Formenti, A.M., Tecilazich, F., Frara, S., Giubbini, R., De Luca, H., Giustina, A., 2019. Body mass index predicts resistance to active vitamin D in patients with hypoparathyroidism. Endocrine. 66 (3), 699–700. https://doi.org/10.1007/s12020-019-02105-6.
Ganz, T., 2006. Hepcidin—a peptide hormone at the interface of innate immunity and iron metabolism. Curr. Top. Microbiol. Immunol. 306, 183–198.
Gough, M.E., Graviss, E.A., May, E.E., 2017. The dynamic immunomodulatory effects of vitamin D3 during Mycobacterium infection. Innate Immun. 23 (6), 506–523. https://doi.org/10.1177/1753425917719143.
Grant, W.B., Lahore, H., McDonnell, S.L., Baggerly, C.A., French, C.B., Aliano, J.L., Bhattoa, H.P., 2020. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients. 12 (4), 988. https://doi.org/10.3390/nu12040988.
Guan, W.J., Liang, W.H., Zhao, Y., et al., 2020. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur. Respir. J. 55 (5), 2000547. https://doi.org/10.1183/13993003.00547-2020.
Guo, T., Fan, Y., Chen, M., Wu, X., Zhang, L., He, T., Wang, H., Wan, J., Wang, X., Lu, Z., 2020. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 5 (7), 811–818. https://doi.org/10.1001/jamacardio.2020.1017.
Guo, X.J., Thomas, P.G., 2017. New fronts emerge in the influenza cytokine storm. Semin. Immunopathol. 39 (5), 541–550. https://doi.org/10.1007/s00281-017-0636-y.
Hansdottir, S., Monick, M.M., Hinde, S.L., Lovan, N., Look, D.C., Hunninghake, G.W., 2008. Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense. J. Immunol. 181 (10), 7090–7099. https://doi.org/10.4049/jimmunol.181.10.7090.
Hargrove, L., Francis, T., Francis, H., 2014. Vitamin D and GI cancers: shedding some light on dark diseases. Ann. Transl. Med. 2 (1), 9. https://doi.org/10.3978/j.issn.2305-5839.2013.03.04.
Hastie, C.E., Mackay, D.F., Ho, F., Celis-Morales, C.A., Katikireddi, S.V., Niedzwiedz, C. L., Jani, B.D., Welsh, P., Mair, F.S., Gray, S.R., et al., 2020. Corrigendum to "Vitamin D concentrations and COVID-19 infection in UK Biobank" [Diabetes Metabol Syndr: Clin Res Rev 2020;14 (4)561-5]. Diabetes Metab. Syndr. 14 (5), 1315–1316. https://doi.org/10.1016/j.dsx.2020.07.021.
Hewison, M., 2010. Vitamin D and the intracrinology of innate immunity. Mol. Cell. Endocrinol. 321 (2), 103–111. https://doi.org/10.1016/j.mce.2010.02.013.
Hewison, M., Freeman, L., Hughes, S.V., Evans, K.N., Bland, R., Eliopoulos, A.G., Kilby, M.D., Moss, P.A., Chakraverty, R., 2003. Differential regulation of vitamin D receptor and its ligand in human monocyte-derived dendritic cells. J. Immunol. 170 (11), 5382–5390. https://doi.org/10.4049/jimmunol.170.11.5382.
Holick, M.F., 2007. Vitamin D deficiency. N. Engl. J. Med. 357 (3), 266–281. https://doi.org/10.1056/NEJMra070553.
Holt, P.G., Strickland, D.H., Wikstrom, M.E., Jahnsen, F.L., 2008. Regulation of immunological homeostasis in the respiratory tract. Nat. Rev. Immunol. 8 (2), 142–152. https://doi.org/10.1038/nri2236.
Ilie, P.C., Stefanescu, S., Smith, L., 2020. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin. Exp. Res. 32 (7), 1195–1198. https://doi.org/10.1007/s40520-020-01570-8.
Isaia, G., Giorgino, R., Rini, G.B., Bevilacqua, M., Maugeri, D., Adami, S., 2003. Prevalence of hypovitaminosis D in elderly women in Italy: clinical consequences and risk factors. Osteoporos. Int. 14 (7), 577–582. https://doi.org/10.1007/s00198-003-1390-7.
Iwasaki, A., Medzhitov, R., 2010. Regulation of adaptive immunity by the innate immune system. Science. 327 (5963), 291–295. https://doi.org/10.1126/science.1183021.
Jain, S.K., Micinski, D., 2013. 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. 437 (1), 7–11. https://doi.org/10.1016/j.bbrc.2013.06.004.
Jain, S.K., Parsanathan, R., 2020. Can vitamin D and L-cysteine co-supplementation reduce 25(OH)-vitamin D deficiency and the mortality associated with COVID-19 in African Americans? J. Am. Coll. Nutr. 39 (8), 694–699. https://doi.org/10.1080/07315724.2020.1789518.
Jain, S.K., Kanikarla-Marie, P., Warden, C., Micinski, D., 2016. L-Cysteine supplementation upregulates glutathione (GSH) and vitamin D binding protein (VDBP) in hepatocytes cultured in high glucose and in vivo in liver, and increases blood levels of GSH, VDBP, and 25-hydroxy-vitamin D in Zucker diabetic fatty rats. Mol. Nutr. Food Res. 60 (5), 1090–1098. https://doi.org/10.1002/mnfr.201500667.
Jain, S.K., Parsanathan, R., Achari, A.E., Kanikarla-Marie, P., Bocchini Jr., J.A., 2018. 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. 29 (17), 1792–1807. https://doi.org/10.1089/ars.2017.7462.
Jain, S.K., Micinski, D., Parsanathan, R., 2021. L-Cysteine stimulates the effect of vitamin D on inhibition of oxidative stress, IL-8, and MCP-1 secretion in high glucose treated monocytes. J. Am. Coll. Nutr. 40 (4), 327–332. https://doi.org/10.1080/07315724.2020.1850371.
Jang, W., Kim, H.J., Li, H., Jo, K.D., Lee, M.K., Song, S.H., Yang, H.O., 2014. 1,25-Dyhydroxyvitamin D_3 attenuates rotenone-induced neurotoxicity in SH-SY5Y cells through induction of autophagy. Biochem. Biophys. Res. Commun. 451 (1), 142–147. https://doi.org/10.1016/j.bbrc.2014.07.081.
Kallas, M., Green, F., Hewison, M., White, C., Kline, G., 2010. Rare causes of calcitriol-mediated hypercalcemia: a case report and literature review. J. Clin. Endocrinol. Metab. 95 (7), 3111–3117. https://doi.org/10.1210/jc.2009-2673.
Kara, M., Ekiz, T., Ricci, V., Kara, Ö., Chang, K.V., Özçakar, L., 2020. 'Scientific Strabismus' or two related pandemics: coronavirus disease and vitamin D deficiency. Br. J. Nutr. 124 (7), 736–741. https://doi.org/10.1017/S0007114520001749.
Khademvatani, K., Seyyed-Mohammadzad, M.H., Akbari, M., Rezaei, Y., Eskandari, R., Rostamzadeh, A., 2014. The relationship between vitamin D status and idiopathic lower-extremity deep vein thrombosis. Int. J. Gen. Med. 7, 303–309. https://doi.org/10.2147/IJGM.S64812.
Khare, D., Godbole, N.M., Pawar, S.D., Mohan, V., Pandey, G., Gupta, S., Kumar, D., Dhole, T.N., Bodbole, M.M., 2013. Calcitriol [1, 25[OH]2 D3] pre- and post-treatment suppresses inflammatory response to influenza A (H1N1) infection in human lung A549 epithelial cells. Eur. J. Nutr. 52 (4), 1405–1415. https://doi.org/10.1007/s00394-012-0449-7.
Kim, J., Yang, Y.L., Jang, S.H., Jang, Y.S., 2018. Human beta-defensin 2 plays a regulatory role in innate antiviral immunity and is capable of potentiating the induction of antigen-specific immunity. Virol. J. 15 (1), 124. https://doi.org/10.1186/s12985-018-1035-2.
Kohlmeier, J.E., Cookenham, T., Roberts, A.D., Miller, S.C., Woodland, D.L., 2010. Type I interferons regulate cytolytic activity of memory CD8(+) T cells in the lung airways during respiratory virus challenge. Immunity. 33 (1), 96–105. https://doi.org/10.1016/j.immuni.2010.06.016.
Komolmit, P., Charoensuk, K., Thanapirom, K., Suksawatamnuay, S., Thaimai, P., Chirathaworn, C., Poovorawan, Y., 2017. Correction of vitamin D deficiency facilitated suppression of IP-10 and DPP IV levels in patients with chronic hepatitis C: a randomised double-blinded, placebo-control trial. PLoS One 12 (4), e0174608. https://doi.org/10.1371/journal.pone.0174608.
Kong, J., Zhang, Z., Musch, M.W., Ning, G., Sun, J., Hart, J., Bissonnette, M., Li, Y.C., 2008. Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. Am. J. Physiol. Gastrointest. Liver Physiol. 294 (1), G208–G216. https://doi.org/10.1152/ajpgi.00398.2007.
Kunutsor, S.K., Apekey, T.A., Steur, M., 2013. Vitamin D and risk of future hypertension: meta analysis of 283,537 participants. Eur. J. Epidemiol. 28 (3), 205–221. https://doi.org/10.1007/s10654-013-9790-2.
Laplana, M., Royo, J.L., Fibla, J., 2018. Vitamin D receptor polymorphisms and risk of enveloped virus infection: a meta-analysis. Gene. 678, 384–394. https://doi.org/10.1016/j.gene.2018.08.017.
Liu, P.T., Stenger, S., Li, H., Wenzel, L., Tan, B.H., Krutzik, S.R., Ochoa, M.T., Schauber, J., Wu, K., Meinken, C., et al., 2006. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science. 311 (5768), 1770–1773. https://doi.org/10.1126/science.1123933.
Mao, J., Lin, E., He, L., Yu, J., Tan, P., Zhou, Y., 2019. Autophagy and viral infection. Adv. Exp. Med. Biol. 1209, 55–78. https://doi.org/10.1007/978-981-15-0606-2_5.
Maretzke, F., Bechthold, A., Egert, S., Ernst, J.B., Melo van Lent, D., Pilz, S., Reichrath, J., Stangl, G.I., Stehle, P., Volkert, D., Wagner, M., Waizenegger, J., Zittermann, A., Linseisen, J., 2020. Role of vitamin D in preventing and treating selected extraskeletal diseases—an umbrella review. Nutrients 12 (4), 969. https://doi.org/10.3390/nu12040969.
Marik, P.E., Kory, P., Varon, J., 2020. Does vitamin D status impact mortality from SARS-CoV-2 infection? Med. Drug Discov. 6, 100041. https://doi.org/10.1016/j.medidd.2020.100041.
Martens, P.J., Gysemans, C., Verstuyf, A., Mathieu, A.C., 2020. Vitamin D's effect on immune function. Nutrients. 12 (5), 1248. https://doi.org/10.3390/nu12051248.
Martineau, A.R., Jolliffe, D.A., Greenberg, L., Aloia, J.F., Bergman, P., Dubnov-Raz, G., Esposito, S., Ganmaa, D., Ginde, A.A., Goodall, E.C., et al., 2019. Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis. Health Technol. Assess. 23 (2), 1–44. https://doi.org/10.3310/hta23020.
Mathyssen, C., Gayan-Ramirez, G., Bouillon, R., Janssens, W., 2017. Vitamin D supplementation in respiratory diseases: evidence from randomized controlled trials. Pol. Arch. Intern. Med. 127 (11), 775–784. https://doi.org/10.20452/pamw.4134.
Mazahery, H., von Hurst, P.R., 2015. Factors affecting 25-hydroxyvitamin D concentration in response to vitamin D supplementation. Nutrients. 7 (7), 5111–5142. https://doi.org/10.3390/nu7075111.
Miroliaee, A.E., Salamzadeh, J., Shokouhi, S., Sahraei, Z., 2018. The study of vitamin D administration effect on CRP and Interleukin-6 as prognostic biomarkers of ventilator associated pneumonia. J. Crit. Care 44, 300–305. https://doi.org/10.1016/j.jcrc.2017.08.040.
Mitchell, F., 2020. Vitamin-D and COVID-19: do deficient risk a poorer outcome? Lancet Diabetes Endocrinol. 8 (7), 570. https://doi.org/10.1016/S2213-8587(20)30183-2.
Monlezun, D.J., Bittner, E.A., Christopher, K.B., Camargo, C.A., Quraishi, S.A., 2015. Vitamin D status and acute respiratory infection: cross sectional results from the United States National/Health and Nutrition Examination Survey, 2001–2006. Nutrients. 7 (3), 1933–1944. https://doi.org/10.3390/nu7031933.
Mousa, A., Naderpoor, N., de Courten, M.P., Teede, H., Kellow, N., Walker, K., Scragg, R., de Courten, B., 2017. Vitamin D supplementation has no effect on insulin sensitivity or secretion in vitamin D-deficient, overweight or obese adults: a randomized placebo-controlled trial. Am. J. Clin. Nutr. 105 (6), 1372–1381. https://doi.org/10.3945/ajcn.117.152736.
Ni, W., Watts, S.W., Ng, M., Chen, S., Glenn, D.J., Gardner, D.G., 2014. Elimination of vitamin D receptor in vascular endothelial cells alters vascular function.

Hypertension. 64 (6), 1290–1298. https://doi.org/10.1161/HYPERTENSIONAHA.114.03971.
Norman, P.E., Powell, J.T., 2014. Vitamin D and cardiovascular disease. Circ. Res. 114 (2), 379–393. https://doi.org/10.1161/CIRCRESAHA.113.301241.
Oh, J., Weng, S., Felton, S.K., Bhandare, S., Riek, A., Butler, B., Proctor, B.M., Petty, M., Chen, Z., Schechtman, K.B., et al., 2009. 1,25(OH)2 vitamin D inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type 2 diabetes mellitus. Circulation. 120 (8), 687–698. https://doi.org/10.1161/CIRCULATIONAHA.109.856070.
Parsanathan, R., Jain, S.K., 2019a. Glutathione deficiency induces epigenetic alterations of vitamin D metabolism genes in the livers of high-fat diet-fed obese mice. Sci. Rep. 9 (1), 14784. https://doi.org/10.1038/s41598-019-51377-5.
Parsanathan, R., Jain, S.K., 2019b. Glutathione deficiency alters the vitamin D-metabolizing enzymes CYP27B1 and CYP24A1 in human renal proximal tubule epithelial cells and kidney of HFD-fed mice. Free Radic. Biol. Med. 131, 376–381. https://doi.org/10.1016/j.freeradbiomed.2018.12.017.
Parsanathan, R., Achari, A.E., Manna, P., Jain, S.K., 2020. L-Cysteine and vitamin D co-supplementation alleviates markers of musculoskeletal disorders in vitamin D-deficient high-fat diet-fed mice. Nutrients. 12 (11), 3406. https://doi.org/10.3390/nu12113406.
Pereira-Santos, M., Costa, P.R., Assis, A.M., Santos, C.A., Santos, D.B., 2015. Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes. Rev. 16 (4), 341–349. https://doi.org/10.1111/obr.12239.
Pilz, S., Verheyen, N., Grübler, M.R., Tomaschitz, A., März, W., 2016. Vitamin D and cardiovascular disease prevention. Nat. Rev. Cardiol. 13 (7), 404–417. https://doi.org/10.1038/nrcardio.2016.73.
Romagnoli, E., Caravella, P., Scarnecchia, L., Martinez, P., Minisola, S., 1999. Hypovitaminosis D in an Italian population of healthy subjects and hospitalized patients. Br. J. Nutr. 81 (2), 133–137. https://doi.org/10.1017/S0007114599000264.
Sabetta, J.R., DePetrillo, P., Cipriani, R.J., Smardin, J., Burns, L.A., Landry, M.L., 2010. Serum 25 hydroxyvitamin D and the incidence of acute viral respiratory tract infections in healthy adults. PLoS One 5 (6), e11088. https://doi.org/10.1371/journal.pone.0011088.
Sanz, R., Mazzei, L., Santino, N., Ingrasia, M., Manucha, W., 2020. Vitamin D-mitochondria cross-talk could modulate the signaling pathway involved in hypertension development: a translational integrative overview. Clin. Investig. Arterioscler. 32 (4), 144–155. https://doi.org/10.1016/j.arteri.2020.02.002.
Skariyachan, S., Challapilli, S.B., Packirisamy, S., Kumargowda, S.T., Sridhar, V.S., 2019. Recent aspects on the pathogenesis mechanism, animal models and novel therapeutic interventions for Middle East Respiratory Syndrome coronavirus infections. Front Microbiol. 10, 569. https://doi.org/10.3389/fmicb.2019.00569.
Slominski, A.T., Kim, T.K., Shehabi, H.Z., Semak, I., Tang, E.K., Nguyen, M.N., Benson, H. A., Korik, E., Janjetovic, Z., Chen, J., Yates, C.R., Postlethwaite, A., Li, W., Tuckey, R. C., 2012. In vivo evidence for a novel pathway of vitamin D3 metabolism initiated by P450scc and modified by CYP27B1. FASEB J. 26 (9), 3901–3915. https://doi.org/10.1096/fj.12-208975.
Slominski, A.T., Kim, T.K., Shehabi, H.Z., Tang, E.K., Benson, H.A., Semak, I., Lin, Z., Yates, C.R., Wang, J., Li, W., Tuckey, R.C., 2014a. In vivo production of novel vitamin D2 hydroxy-derivatives by human placentas, epidermal keratinocytes, Caco-2 colon cells and the adrenal gland. Mol. Cell. Endocrinol. 383 (1–2), 181–192. https://doi.org/10.1016/j.mce.2013.12.012.
Slominski, A.T., Kim, T.K., Takeda, Y., Janjetovic, Z., Brozyna, A.A., Skobowiat, C., Wang, J., Postlethwaite, A., Li, W., Tuckey, R.C., Jetten, A.M., 2014b. RORα and RORγ are expressed in human skin and serve as receptors for endogenously produced noncalcemic 20-hydroxy- and 20,23-dihydroxyvitamin D. FASEB J. 28 (7), 2775–2789. https://doi.org/10.1096/fj.13-242040.
Slominski, A.T., Kim, T.K., Li, W., Postlethwaite, A., Tieu, E.W., Tang, E.K.Y., Tuckey, R. C., 2015a. Detection of novel CYP11A1-derived secosteroids in the human epidermis and serum and pig adrenal gland. Sci. Rep. 5, 14875. https://doi.org/10.1038/srep14875.
Slominski, A.T., Li, W., Kim, T.K., Semak, I., Wang, J., Zjawiony, J.K., Tuckey, R.C., 2015b. Novel activities of CYP11A1 and their potential physiological significance. J. Steroid Biochem. Mol. Biol. 151, 25–37. https://doi.org/10.1016/j.jsbmb.2014.11.010.
Slominski, A.T., Kim, T.K., Hobrath, J.V., Oak, A.S.W., Tang, E.K.Y., Tieu, E.W., Li, W., Tuckey, R.C., Jetten, A.M., 2017. Endogenously produced nonclassical vitamin D hydroxy-metabolites act as "biased" agonists on VDR and inverse agonists on RORα and RORγ. J. Steroid Biochem. Mol. Biol. 173, 42–56. https://doi.org/10.1016/j.jsbmb.2016.09.024.
Slominski, A.T., Kim, T.K., Janjetovic, Z., Brożyna, A.A., Żmijewski, M.A., Xu, H., Sutter, T.R., Tuckey, R.C., Jetten, A.M., Crossman, D.K., 2018. Differential and overlapping effects of 20,23(OH)2D3 and 1,25(OH)2D3 on gene expression in human epidermal keratinocytes: identification of AhR as an alternative receptor for 20,23(OH)2D3. Int. J. Mol. Sci. 19 (10), 3072. https://doi.org/10.3390/ijms19103072.
Slominski, A.T., Chaiprasongsuk, A., Janjetovic, Z., Kim, T.K., Stefan, J., Slominski, R.M., Hanumanthu, V.S., Raman, C., Qayyum, S., Song, Y., Song, Y., Panich, U., Crossman, D.K., Athar, M., Holick, M.F., Jetten, A.M., Zmijewski, M.A., Zmijewski, J., Tuckey, R.C., 2020a. Photoprotective properties of vitamin D and lumisterol hydroxyderivatives. Cell Biochem. Biophys. 78 (2), 165–180. https://doi.org/10.1007/s12013-020-00913-6.
Slominski, A.T., Slominski, R.M., Goepfert, P.A., Kim, T.K., Holick, M.F., Jetten, A.M., Raman, C., 2020c. Reply to Jakovac and to Rocha et al.: can vitamin D prevent or manage COVID-19 illness? Am. J. Physiol. Endocrinol. Metab. 319 (2), E455–E457. https://doi.org/10.1152/ajpendo.00348.2020.
Slominski, R.M., Stefan, J., Athar, M., Holick, M.F., Jetten, A.M., Raman, C., Slominski, A.T., 2020b. COVID-19 and vitamin D: a lesson from the skin. Exp. Dermatol. 29 (9), 885–890. https://doi.org/10.1111/exd.14170.
Song, Y., Wang, L., Pittas, A.G., Del Gobbo, L.C., Zhang, C., Manson, J.E., Hu, F.B., 2013. Blood 25 hydroxy vitamin D levels and incident type 2 diabetes: a meta-analysis of prospective studies. Diabetes Care 36 (5), 1422–1428. https://doi.org/10.2337/dc12-0962.
Subramanian, K., Bergman, P., Henriques-Normark, B., 2017. Vitamin D promotes pneumococcal killing and modulates inflammatory responses in primary human neutrophils. J. Innate Immun. 9 (4), 375–386. https://doi.org/10.1159/000455969.
Tan, C.W., Ho, L.P., Kalimuddin, S., Cherng, B.P.Z., Teh, Y.E., Thien, S.Y., Wong, H.M., Tern, P.J.W., Chandran, M., Chay, J.W.M., Nagarajan, C., Sultana, R., Low, J.G.H., Ng, H.J., 2020. Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B12 in combination on progression to severe outcomes in older patients with coronavirus (COVID-19). Nutrition 79–80. https://doi.org/10.1016/j.nut.2020.111017, 111017.
Tian, G., Liang, X., Chen, D., Mao, X., Yu, J., Zheng, P., He, J., Huang, Z., Yu, B., 2016. Vitamin D3 supplementation alleviates rotavirus infection in pigs and IPEC-J2 cells via regulating the autophagy signaling pathway. J. Steroid Biochem. Mol. Biol. 163, 157–163. https://doi.org/10.1016/j.jsbmb.2016.05.004.
Tian, Y., Rong, L., 2020. Letter: Covid-19, and vitamin D. Authors' reply. Aliment. Pharmacol. Ther. 51 (10), 995–996. https://doi.org/10.1111/apt.15764.
Tsujino, I., Ushikoshi-Nakayama, R., Yamazaki, T., Matsumoto, N., Saito, I., 2019. Pulmonary activation of vitamin D3 and preventive effect against interstitial pneumonia. J. Clin. Biochem. Nutr. 65 (3), 245–251. https://doi.org/10.3164/jcbn.19-48.
Uberti, F., Lattuada, D., Morsanuto, V., Nava, U., Bolis, G., Vacca, G., Squarzanti, D.F., Cisari, C., Molinari, C., 2014. Vitamin D protects human endothelial cells from oxidative stress through the autophagic and survival pathways. J. Clin. Endocrinol. Metab. 99 (4), 1367–1374. https://doi.org/10.1210/jc.2013-2103.
Vankadari, N., Wilce, J.A., 2020. Emerging Wuhan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. Emerg. Microbes Infect. 9 (1), 601–604. https://doi.org/10.1080/22221751.2020.1739565.
Walsh, J.S., Bowles, S., Evans, A.L., 2017. Vitamin D in obesity. Curr. Opin. Endocrinol. Diabetes Obes. 24 (6), 389–394. https://doi.org/10.1097/MED.0000000000000371.
Wang, J., 2008. Beclin 1 bridges autophagy, apoptosis and differentiation. Autophagy. 4 (7), 947–948. https://doi.org/10.4161/auto.6787.
Wang, T.T., Nestel, F.P., Bourdeau, V., Nagai, Y., Wang, Q., Liao, J., Tavera-Mendoza, L., Lin, R., Hanrahan, J.W., Mader, S., et al., 2004. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. J. Immunol. 173 (5), 2909–2912. https://doi.org/10.4049/jimmunol.173.5.2909.
Wang, T.T., Dabbas, B., Laperriere, D., Bitton, A.J., Soualhine, H., Taverta-Mendoza, L.E., Dionne, S., Servant, M.J., Bitton, A., Seidman, E.G., et al., 2010. Direct and indirect induction by 1,25 dihydroxyvitamin D3 of the NOD2/CARD15-defensin beta2 innate immune pathway defective in Crohn disease. J. Biol. Chem. 285 (4), 2227–2231. https://doi.org/10.1074/jbc.C109.071225.
Watkins, R.R., Lemonovich, T.L., Salata, R.A., 2015. An update on the association of vitamin D deficiency with common infectious diseases. Can. J. Physiol. Pharmacol. 93 (5), 363–368. https://doi.org/10.1139/cjpp-2014-0352.
Watts, N.B., Bilezikian, J.P., Camacho, P.M., et al., 2010. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of postmenopausal osteoporosis: executive summary of recommendations. Endocr. Pract. 16 (6), 1016–1019. https://doi.org/10.4158/ep.16.6.1016.
Wu, H.X., Xiong, X.F., Zhu, M., Wei, J., Zhuo, K.Q., Cheng, D.Y., 2018. Effects of vitamin D supplementation on the outcomes of patients with pulmonary tuberculosis: a systematic review and meta-analysis. BMC Pulm. Med. 18 (1), 108. https://doi.org/10.1186/s12890-018-0677-6.
Wu, W.X., He, D.R., 2018. Low vitamin D levels are associated with the development of deep venous thromboembolic events in patients with ischemic stroke. Clin. Appl. Thromb. Hemost. 24 (9_suppl), 69S–75S. https://doi.org/10.1177/1076029618786574.
Yang, J., Zheng, Y., Gou, X., Pu, K., Chen, Z., Guo, Q., Ji, R., Wang, H., Wang, Y., Zhou, Y., 2020. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int. J. Infect. Dis. 94, 91–95. https://doi.org/10.1016/j.ijid.2020.03.017.
Yin, K., You, Y., Swier, V., Tang, L., Radwan, M.M., Pandya, A.N., Agrawal, D.K., 2015. Vitamin D protects against atherosclerosis via regulation of cholesterol efflux and macrophage polarization in hypercholesterolemic swine. Arterioscler. Thromb. Vasc. Biol. 35 (11), 2432–2442. https://doi.org/10.1161/ATVBAHA.115.306132.
Yuk, J.M., Shin, D.M., Lee, H.M., Yang, C.S., Jin, H.S., Kim, K.K., Lee, Z.W., Lee, S.H., Kim, J.M., Jo, E.K., 2009. Vitamin D3 induces autophagy in human monocytes/macrophages via cathelicidin. Cell Host Microbe 6 (3), 231–243. https://doi.org/10.1016/j.chom.2009.08.004.
Zdrenghea, M.T., Makrinioti, H., Bagacean, C., Bush, A., Johnston, S.L., Stanciu, L.A., 2017. Vitamin D modulation of innate immune responses to respiratory viral infections. Rev. Med. Virol. 27 (1) https://doi.org/10.1002/rmv.1909.
Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., et al., 2020. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 395 (10229), 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3.