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.

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Narrative Review

Rays of immunity: Role of sunshine vitamin in management of COVID-19 infection and associated comorbidities

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SUMMARY

The catastrophic pandemic engendered due to the Novel coronavirus (COVID-19) outbreak which causes severe clinical afflictions on the respiratory system has severely high morbidity and mortality rates. The requirement of novel compounds is at utmost importance due to lack of targeted drug molecule to treat the afflictions and restrict the viral infection and for the usage of prophylactic treatment to avoid the spread of the infection is of utmost importance. Vitamin D is one such naturally available multifunctional molecule, which plays an eminent role in the immune system and instigation of numerous cellular pathways further promoting health benefits and enhancing the human quality of life. This article reviews the current standpoint scenario and future prevalence of vitamin D supplementation in the management of covid-19 patients. Novel findings of Vitamin D suggest that along with regulation of cell growth, neuroprotective and mood-stabilizing effects, it regulates the immune response also modulate cytokine Interleukin-6 (IL-6) by inducing progesterone-induced blocking factor (PIBF), given the IL-6 levels are considerably high in COVID-19 patients which increases the further complications. Vitamin D also have its effect on angiotensin converting enzyme (ACEII) inhibitor through which the COVID-19 virus makes cell entry. Numerous research data elucidate the play of Vitamin D, in complications of COVID-19 including the most common comorbid conditions, neurological manifestations and immunological aspects makes it an ideal molecule for adjuvant therapy. Including Vitamin D as add-on therapy in the management of COVID-19 might aid the arrest of infection and helps fight this arduous epidemic.

1. Introduction

Public health emergency was declared by the world health organization due to the COVID-19 outbreak which claimed millions of lives globally. United States being the worst hit country followed by India and Brazil. These three countries alone accounted for majority of cases and deaths word wide [1].

This infection is comparatively higher in male population than women. Among other variables such as comorbid conditions in which cardiac disorders being highly threatening followed by hypertension [2]. Consequential conditions which are life threatening including unilateral-bilateral pneumonia, pneumothorax, arrhythmia, acute cardiac injury, septic shock, acute respiratory distress syndrome (ARDS), lymphopenia, acute renal injury, abnormal liver function was observed in virus infected [3–6]. SARS-CoV-2 induces cytokine storm syndrome and elevates cytokines such as Interleukin 6-10 (IL6-10), IL1RA, IL1B. Immunological markers like TNFα, IFNγ, MCP-1, MIP-1A, MIP-1B, levels were escalated, because of cumulative repercussion of these conditions acute respiratory distress syndrome is provoked and leads to decreased organ function and, complete organ failure and death [5,7,8]. Various treatment modalities such as corticosteroids and differential antiviral drugs were used in non-serious hospitalized patients [9]. The convulsant plasma therapy exhibited effectiveness and improved the clinical symptoms and lengthened survival in COVID-19 patients, and later on it was pulled back from the treatment regimen [10–13]. Vitamin D is in spotlight for consider amount of time for its notable physiological effects, immunomodulating,

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neuroprotective properties [14]. It is a member of a fat-soluble secosteroids group which are mainly important for the homeostasis of calcium, phosphate and magnesium. Vitamin D2, Vitamin D3 are different active variants of D-vitamin that are metabolised in distinct mechanisms [15]. The vitamin D receptors are involved in crucial role in neurology such as cell growth modulation, mood balancing effects, neuroprotective, and differentiation processes [16], cell proliferation, neuroplasticity, neural-transmission, neural-protection and neurotropism are also evident characters of Vitamin D [15]. Vitamin D might provide a cost-effective path for the management of COVID-19 since it is naturally available as sunshine. There was comparatively less literature available in regarding to the cumulative confrontation of the effect of vitamin D in the co-morbidities associated with COVID-19. This review presents current practical scenario of Vitamin D and its stand point in the COVID-19 and its clinical afflictions.

2. Materials and methods

This narrative review is a compilation of literature found in the bibliographic databases such as google scholar, PubMed and Scopus. The library of National institute of pharmaceutical research and education was also used for the compilation of the literature. The vocables used to retrieve the literature were COVID-19, Interleukins, Vitamin D, calciferol, corona virus, WHO, cytokine storm, and neurological manifestations. The lingual barriers were used as filters for selection of literature and included only articles written and previously converted in to English. Both primary and secondary research literature such as original research, meta-analysis, systemic reviews and peer reviews were also included. The unpublished, incomplete or partially available data was excluded along with literature in different languages. Majority of the literature compiled in this narrative is recently published and the older literature is also included based on relevance and requirement. There was no financial help from any institutions and all the literature is freely downloaded (Table 1).

2.1. COVID-19 and malnutrition

Malnutrition includes both over and under nutrition, vitamin, mineral deficiency and obesity lead to poor health outcomes. Malnutrition has a noteworthy effect in COVID-19, the current pandemic situation has gradually increased the prevalence of malnutrition due to lack of job opportunities and work because of the lockdowns and decreased quality of food [17]. Around 1.9 billion adults are obese and 462 million population are underweight. Deaths associated with under nutrition are around 45% in paediatric population under 5 years of age. Diet related non communicable diseases [NCDs] such as diabetes, hypertension, cardiovascular diseases are linked to malnutrition [18,19]. Co incidentally the population groups with these diseases are at higher risk for COVID-19 infection. Low-mid income countries were likely to increase double burden of malnutrition due of lack of access to the nutrition food [20]. studies suggest that majority of population infected from COVID were severely suffering from malnutrition and minor population were at risk of malnutrition [21,22]. The malnourished patients with COVID-19 infection required prolonged hospitalization compared to non-malnourished patients. The malnutrition was inversely and independently interrelated with the length of hospital stay [18]. Medical nutrition therapy and implementation of nutritional care plan plays a significant role in assessing, preventing, the rate of infection in population who are higher risk such as paediatric, geriatric, neonates and lactating women [23]. Along with malnutrition, trace element deficiency might manipulate the state and course of disease by acting on several cellular mechanisms such as regulation in immune system pathways, regenerative mechanisms, and wound healing [24]. Micro nutrients such as vitamins provide various cellular, physiological and pharmacological effects including instating immune defence, cell repair, proliferation, antioxidant effects which will play a major key role in prevention of infection and can also be used as adjuvant therapy in the management of COVID-19 [25]. This article reviews the importance of a trace element Vitamin D and its significance in the management of COVID-19 and its associated comorbid conditions.

2.2. Hypovitaminosis D

Vitamin D deficiency or hypovitaminosis D is a pressing health predicament that needs to be solved since it increases the risks of many diseases. In the current pandemic situation, immune-

Table 1
Studies on Vitamin D and their correlation with associated comorbidities and outcomes.

S.no.	Correlation	Outcome measured	Reference
01	Vitamin D, MERS-CoV and HBD-2	HBD-2 promoted antiviral activity in MERS-CoV and Vitamin D can induce HBD-2	[55,56]
02	Cathelicidin and antimicrobial activity	Vitamin D proved to have anti-microbial activity against respiratory epithelium.	[25,50]
03	Cathelicidin and tuberculosis	Outcome involved in elimination of tuberculosis bacteria.	[53]
04	Vitamin D and pulmonary fibrosis	High oral intake of Vitamin D reduces Pulmonary fibrosis.	[68]
06	Vitamin D and upper respiratory tract infections	No significant effect of vitamin D was noted	[49]
07	SARS-CoV-2, Vitamin D and ACE-II	SARS-CoV-2 inhibits ACE-II and uses it as entry receptor. Vitamin D regulates and increases ACE-II.	[25,124]
08	Vitamin D and Hepatitis-C virus	Vitamin D constrain Hepatitis −C virus by synergising INF-α	[70]
09	Vitamin D and Hepatitis-B virus	Low Vitamin D levels have high Hepatitis-B viral replication.	[71]
10	Vitamin D and Varicella-zoster virus	High Vitamin D levs had higher Varicella-zoster virus immunoglobulin levels	[74]
11	Vitamin D and HIV	Low Vitamin D levels showed active HIV viral replication and slow restoration of CD4 cells.	[77]
12	Vitamin D H1N1 Influenza	Vitamin D showed effectiveness against H1N1 influenza.	[93]
13	Vitamin D and SARS-CoV-2 positivity	Low vitamin status showed high COVID-19 positivity.	[87,88]
14	Vitamin D, COVID-19 and hospitalization.	Low Vitamin D levels were observed in Hospitalized patients.	[89]
15	Hypovitaminosis-D and COVID-19 severity.	65% of severe covid-19 patients were suffering from hypovitaminosis D	[91]
16	Vitamin D and MCP-1	Increased levels of mcp-1 cytokine were observed in COVID-19 patients.	[94,95]
17	MCP-1, diabetes and Vitamin D	Vitamin D supplementation has lowered MCP-1 levels in diabetic patients	[96]
18	COVID-19, comorbid conditions	Most common comorbid conditions are cardiovascular diseases, hypertension, diabetes.	[2,4]
19	COVID-19 and neurological manifestations.	Most common neurological manifestations are olfactory, gustatory dysfunctions, headache, seizures and impaired consciousness.	[114,115]
20	COVID-19, encephalomyelitis and Vitamin D	Encephalomyelitis is rare comorbid condition of COVID-19 and Vitamin D immuno-inhibitory cellular and humoral reactions.	[127,128]

boosting molecules play a prominent role in maintaining physical and mental health. Vitamin D provides many other health benefits among which regulation of the immune system, body functioning, cell proliferation are major roles. Vitamin D deficiency is considered when the serum/plasma Vitamin D level is below 75 nmol/L (or 30 ng/ml) of concentration [26,27]. Intake of 4000 IU is a proper and safe dosage for a maternal patient to rectify hypovitaminosis D and provide with sufficient nutrients for both newborn infant and the lactating mothers to avoid any further complications of rickets [28]. Around 13% European adults are severely deficient, and ~40% of Europeans are Vitamin D deficient [29]. The regularity of Low Vitamin D in adults worldwide is 97% in India, 80% in Bangladesh, 84% in Pakistan, 74% in Switzerland, and in Malaysia 70% [30]. A population of 14% were suffering from severe Vitamin D deficiency in an analysis of 215 patients where the levels were <50 nmo/L in Spain [31]. Furthermore, countries such as India, Pakistan, and Bangladesh recorded higher number of COVID-19 cases.

Reduced sun exposure and dietary variables are among the top causes for hypovitaminosis D. Solar exposure in winters is less compared to summer, circumvent of sun exposure can also because prolonged days in higher altitudes and high temperatures. In women it is due to application of cosmetics and extensive clothing [32–34]. Hypovitaminosis D in winter was more in women (36%) than men (9%). Physical endurance was also positively influenced by vitamin D [35]. The ubiquity of vitamin D deficiency is 35% in obese population than others among geriatric, and hospitalized patients [36]. The life quality and hypovitaminosis D are directly related to each other where vitamin D insufficiency might have an adverse effect on elderly health [37]. In minority ethnic and black people hypovitaminosis D is primarily due to their pigmentation which reduces the vitamin D production in skin [34,38]. Coincidentally these are the age and ethnic groups who are more affected by among others by COVID-19 [34].

Around 59% of the COVID-19 SARS CoV-2 Infected patients were suffering from hypovitaminosis D at the time of admission in which majority are males (67%) than females (47%) [39] The patients who were treated with vitamin D,B12, magnesium were less likely to need oxygen therapy [40]. Vitamin D3 treated had suggestively abridged the necessity for ICU treatment and able to reduce the sternness of the disease in COVID-19 [41]. Vitamin D exhibited a prominent protective character against influenza A in adolescent population with 1200 IU of dose per diam [42]. A series of meta-analysis studies projected that Vitamin D declines cancer death rate by 16% but there was a null connotation between Vitamin D and Cardiovascular, non-cardiovascular, non-cancer mortality in adult population [43]. It also condenses the risk of acute respiratory infections (ARI) [44,45] in the patients with baseline levels of <25 nmol/L. Vitamin D cuts the rate of Severe or moderate chronic obstructive pulmonary disease (COPD) worsening [46]. Another meta-analysis forecasted that vitamin D was not in correlation with length of hospital stay, ventilation or intensive care unit (ICU) [47]. Vitamin D deficiency in the course of pregnancy might increase the chances of childhood eczema [48].

Better lung function also decreased respiratory infections was observed in adult males compared to women with higher Vitamin D levels, which varied throughout seasons. Forced expiratory volume increased in the adults along with increased levels of Vitamin D [49]. The frequency of Vitamin D insufficiency in patients with Parkinson's disease is comparatively high [50]. Hypovitaminosis D causes osteoporosis and decreased bone mass density and can be treated successfully with vitamin D [51]. Regular consumption of Vitamin D, revamps vitamin standing and also promotes bone mass density, better glucose hemostasis and lipid profile was noted in post-menopausal women [52]. Median dose of 2000 IU which steadied the Vitamin D levels and further warded off the osteoporosis in postmenopausal women within 48 days [53].

2.3. Immunomodulatory and cellular proliferation of vitamin D

In the World of virology, the anti-microbial peptides play prominent role by instigating immune defence against intracellular infectious agents. Vitamin D regulates both adaptive and innate immunity [54]. The notability of vitamin D in treating infectious diseases remains dubious since, Vitamin D regulates immune response to respiratory viruses and decreases COVID-19 menace, influenza and other viral infections [55–57]. Whereas, there were futile results in the case of upper respiratory tract infections [58]. Cathelicidin is one such agent, which induces immune modulatory response to pathogen associated stimuli along with its antimicrobial effect in respiratory epithelium [34,59]. Anti-inflammatory properties of Vitamin D and regulation to T-cell response also induces Cathelicidin antimicrobial peptide (*CAMP*) from human gene and boosts innate immune responses [60]. Induction of Cathelicidin exhibited Vitamin D_3mediated intracellular antimicrobial activity [61].

Addition of vitamin D reduced gene expression in other cytokines, such as TNF alfa and IL6 in alveolar A549 cells, where the pro inflammatory cytokine levels were high due to influenza infection [62,63]. Human beta definism-2 (Hbd-2) promoted antiviral activity in MERS-Cov spike protein by receptor binding domain (RBD). The molecular expression of interferon-gamma & beta, PKR, MxA and RNaseL were escalated when incubated with THP-1 human monocytic cells [64]. Vitamin D induces Human beta defisin-2 (Hbd-2) in mono nuclear cells in peripheral blood [65]. Inflammatory reduction, immune regulation and decreased IL-6 levels were observed after administration of high dose Vitamin D injection [66] (Fig. 1).

The Vitamin D pathway and COVID-19 interconnection was swotted by using Signalling Pathways Project Datasets, there was a significant variation in regulation of molecules associated with Vitamin D pathway. In datasets derived from SARS virus the molecular expression of co receptors of Vitamin D path way such as Fibroblast growth factor-1 (FGFR1-4), CYP24A1, CYP27A1 and retinoic acid receptor (RXRA) were dwindled. Molecular expression of CYP27A1 and FGFR1 were remained low. Increased expression of CYP24A1 were found when the core Vitamin D receptor molecules were analysed, for coalition of SARS-CoV-2 and Vitamin D receptors, in infected unsolidified bronchoalveolar lavage cells of RNA sequencing-based transcriptomic datasets, of human bronchial epithelial cells (NHBE), Non-small cell lung cancer cells (Calu3) and A549 Lung cell lines of human species [67]. The possible correlation between mitogen-activated protein kinase (PAK) and genes modulated by Vitamin D was observed. Since the PAK levels were increased in infected lung cells of SARS-CoV-2. These might have impact upon cytokine signalling, immune regulation and NF-kB pathway. The biotic properties of Vitamin D ensue by either genomic or non-genomic methods, which involves membrane associated rapid response steroid binding receptors (MARRS) and by up regulation and down regulation in expression of cellular genes which enkindle the depletion of Vitamin D expression pathway in infected lung cells of SARS-CoV-2 [67,68].

Angiotensin converting enzyme 2 (ACE2) expression was invigorated by Vitamin D, while SARS CoV-2 downregulates the expression of ACE2 and subjugates it as the entry receptor [34]. Vitamin D inhibits interferon-gamma (IFN-γ), IL-5 and promotes T-cell differentiation, and development by amplifying IL-10 [69]. Down regulation of the expression of major histocompatibility complex-2 (MCH-II) and CD 86 by Vitamin D and promoting the levels of TREG, IL -17A, CD4, IL-10 lymph nodes and spleen of

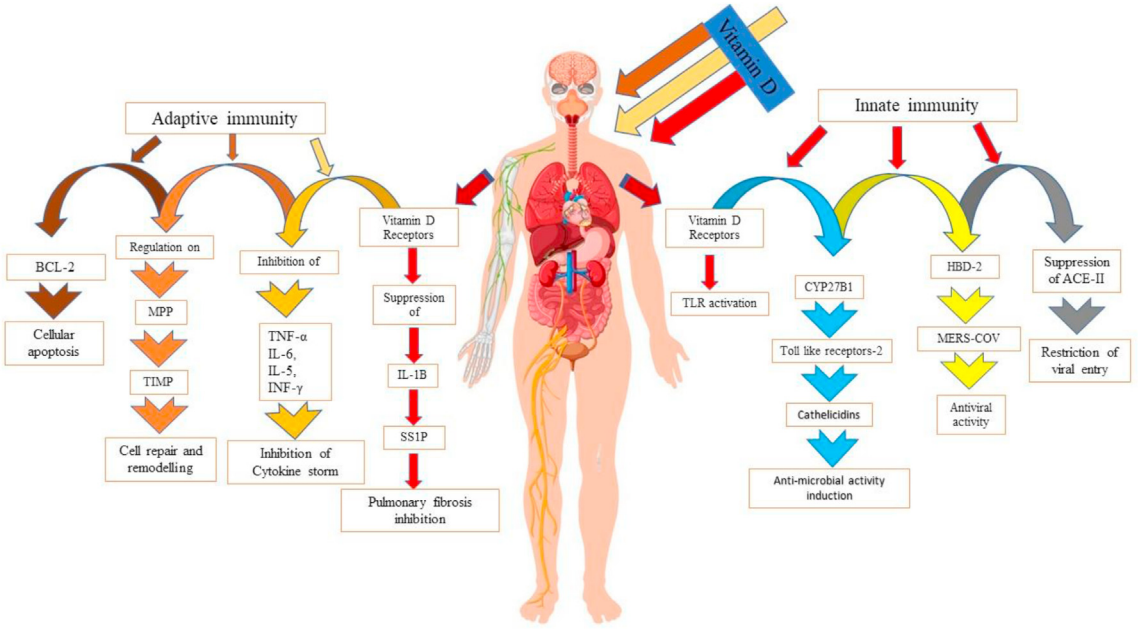

Fig. 1. Diagram showing the regulation of both innate and adaptive immunity, mechanism of antimicrobial effect, inhibition of cytokine storm by using Vitamin D receptors.

encephalomyelitis induced mice was marked [70]. Vitamin D has demonstrated regulatory effects on matrix metalloproteinase (MMP) and tissue inhibitors of metalloproteinases (TIMP) inhibitors these are secreted from the cells and promote cellular remodelling and repair [71]. Activin A was upregulated in human alveolar macrophages after cultured with calcitriol for 24 h [72]. Vitamin D enhances cellular repair and cell proliferation in alveolar epithelial type II cells in lungs and inhibits primary cell apoptosis of AT II cells. It also inhibits TGF-β [73]. Vitamin D minimized serum TNF-alpha levels in Inflammatory bowel disease patients [74].

Vitamin D/Vitamin D receptors prompted anti-inflammatory defense by upholding the integrity of pulmonary epithelial barrier. It also inhibited acute lung infection induced by lipopolysaccharide by restricting the buildup of chemokines [75]. Vitamin D receptors further Inhibits ANG-2 expression in pulmonary endothelial cells and decreases lung injury [76]. Vitamin-D3 can inhibit accumulation, inflammation of activated fibroblasts by supressing expression of IL-1b and SSP1, which expands the area of advanced fibrosis in mice which further stipulates the prevention of interstitial pneumonia. High oral intake of vitamin D inhibits pulmonary fibrosis [77]. The injury found in the oxidative and inflammatory conditions of retinal epithelium and endothelium cells of human has been repaired by adding Vitamin D to the culture. More precisely, the levels of mediated inflammatory cytokines were normalized, along with oxidative stress markers and late apoptosis [78] (Fig. 2).

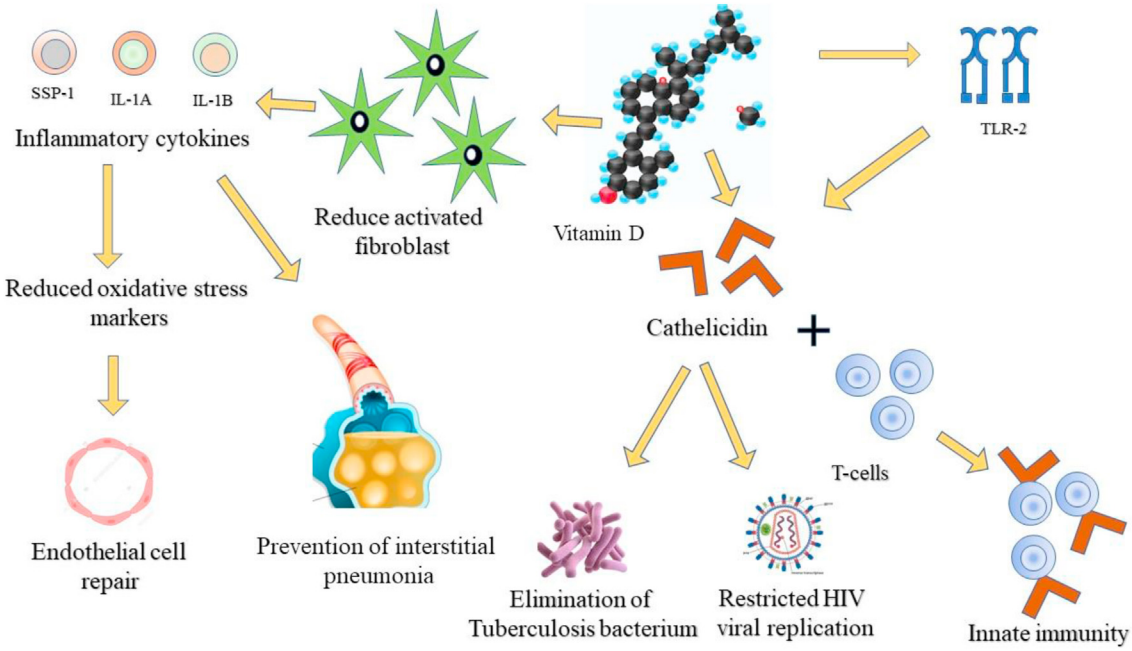

Fig. 2. Diagram showing the Protective effects of Vitamin D in infectious diseases by restricting viral replication, instating innate immunity, endothelial cell repair and interstitial pneumonia prevention.

2.4. Vitamin D and antiviral effect

Vitamin D was explored well for its effects in various viral diseases. Antiviral effect of Vitamin D is explored broadly in numerous viral infections. Calcitriol synergize with interferon-alpha to constrain Hepatitis C virus viral development [79]. In population with congestive heart block (CHB), low Vitamin D serum levels are related to increased hepatitis B virus (HBV) replication. This is a big deviation from chronic hepatitis C, where there has been an absence of association between HCV viral load and Vitamin D serum levels in many previous studies [80]. Multiple sclerosis victims had advanced antibody levels for Epstein–Barr nuclear antigen-1 and cytomegalovirus with vitamin D adequacy (>30mg/nml) [81]. High-dose oral supplementation of vitamin D3 can impact humoral activity in relapsing-remitting multiple sclerosis, immune defences against the latent Epstein-Barr-virus antigen, Epstein-barr nuclear antigen-1 [82]. Increased serum levels of vitamin D has been favourably interrelated with Immunity against Varicella-zoster virus (VGV), Active vitamin D users reported slightly higher levels of VGV-IgG relative to non-active vitamin D users [83]. The serological response was affected positively by vitamin D3 in the strains of influenza virus [84]. Virological response was indefinitely low in hypovitaminosis D and Vitamin D Insufficient patients [85]. Active virus replication was observed in Vitamin D Deficient and insufficient in HIV infected patients. Patients with less values of 25(OH)D were shown to restore the number of CD4 cells more slowly than patients with elevated values. There was also difference in levels of cytokines [86]. Chemokines RANTES and IL-8 transcription induced by H1N1 within epithelial cells is suppressed by calcitriol therapy. Vitamin D decreases autophagy and induces increased apoptosis, it also decreases the levels of IFN-β and IFN-stimulated gene-15, H1N1-induced TNF-alpha [87]. Findings indicate through autophagy- and CAMP-dependent mechanism Vitamin D3 inhibits, Replication of both TB and HIV in human macrophages [88]. In reaction to influenza vaccine, Vit-D supplementation encourages a higher TGFβ plasma level. This supplementation tends to steer the polarization of the lymphocyte into a tolerogenic immune response [89].

2.5. Vitamin D and COVID-19

There is colossal amount of corroboration which justifies the multipurpose properties of Vitamin D supplementation/Vitamin D receptors. A systematic review stated that It is actively explored to use as add-on therapy in the management of numerous infectious diseases [90]. The immune modulatory effects [91], anti-microbial effect [62], functioning of Vitamin D receptors in inhibiting cytokines [70]. The prophylactic effect of Vitamin D on interstitial pneumonia [10,78] and decreases mortality rate in geriatric population [92]. The distinguished interrelation of the serum concentration of Vitamin D and COVID-19 is positively influenced by numerous research and reviews. Numerous studies show positive coalition of Vitamin D and COVID-19 [93]. The countries which are in lower latitude and slighter sunlight exposure such as Spain, Italy have high rates of hypovitaminosis D and confronted inflated COVID-19 morbidity and mortality rates. Countries such as Finland, Norway where Low infection and death rates were observed along with low deficiency of Vitamin D [94].

The notable variance in the measure of Vitamin D in SARS-CoV-2 positive patients (median value of 9.3 ng/mL) when compared to negative patients (median values of 23.1 ng/mL). Furthermore, there was much down fall in the Vitamin D levels when compared in 2019 and 2020 PCR positive patients in age group above 70 years [95]. A study identified an inverted relationship between Vitamin D concentration and the morbidity rate of SARS-CoV-2, where the absolute positivity was 5–7% more in patients with the lowest circulating levels of Vitamin D across central and southern latitudes of US and India. There was an effectual decrease in the risk of SARS-CoV-2 positivity at 55 ng/ml compared to the population with 30–35 ng/ml and there was 54% increased positivity rate in population whose circulating level was <20 ng/ml [96,97]. In a study of 185 patients 64% had Vitamin D levels lower than 20 ng/ml and 22% had less than 12 ng/ml where 50% of total population required hospitalization and observed lesser mean vitamin D status (18.2). Another half did not need hospitalization and had comparatively higher mean vitamin D status, the IL-6 levels were prominently increased in hospitalized patientsdue to COVID-19 infection [98].

In a novel study of feeble geriatric patients who were tested with COVID -19 infection, the bolus vitamin D3 supplementation expressed a clinically relevant defensive effect when taken right before COVID-19. It is also related to decreased severity and improved survival rate [99]. A meta-analysis of 26 studies where 8176 patients took part in revealed that about 65% severe COVID-19 patients were suffering from hypovitaminosis D [100]. COVID-19 prognosis can be dependent on the levels of vitamin D which can further aid in assessing the potential severity of the infection [101]. Calcitriol exhibited effectiveness against H1N1 influenza virus induced in mice by boosting immune response [102]. There was a significant increase in the level's monocyte chemoattractant protein-1 (mcp-1) cytokines in severe COVD-19 patients [103,104]. Daily Vitamin D intake has successfully lowered circulatory MCP-1 levels, in vitamin deficient diabetic population by modulating MCP-1 signalling pathways [105]. Decreased levels of IL-6 was detected in patients with pneumonia after treating with Vitamin D [106]. High-dose of oral supplementation of vitamin D Increased negative for RNA sampling in the proportion of asymptomatic Vitamin D deficient populations with SARS-CoV-2 disease. A substantial decline in inflammatory markers was also observed [91]. Remdesivir, a successful SARS-CoV-2 treatment. Using immunomodulatory agents, in immune system enhancement is often proposed as a possible prophylactic. The combined therapy of these two may be the game changer, but it has not been explored at all [107].

A meta-analysis revealed patients with low serum levels were 1.5 times more prone to be infected with COVID-19. The systematic review concluded no outcome exposed a strong relation between Vitamin D and COVID-19 recovery [108]. Another systematic review found a significant relationship between vitamin D concentration and COVID-19 infection [109]. Low serum vitamin D levels were associated with a high rate of infection, severity and mortality [110]. All these systematic reviews are limited by insufficient data availability, heterogenicity among study types.

An ongoing clinical trial to evaluate the efficacy and safety of Vitamin D in COVID-19 patients. This randomised controlled trial involves up to 6 weeks of the treatment period with 25,000 IU/mL of cholecalciferol. The upcoming results of this trial may provide knowledge that can help to improve the COVID-19 health-related outcomes [111]. Another clinical trial to assess the Vitamin D daily dietary intake and COVID-19 severity among newly diagnosed patients also infection risk reduction among household contacts of newly diagnosed patients [112]. These trials can overcome all the limitations of the above-mentioned systematic reviews.

2.6. Vitamin D in comorbidities of COVID-19

A study concluded that a reported corona virus infection was found in 41 patients admitted to the hospital most of the infected were male with less than half of them having underlying diseases particularly diabetes, hypertension and cardiovascular diseases [4]. The dodgiest co morbid condition being cardiovascular disease followed by chronic respiratory diseases [2]. A published study of

meta-analysis revealed that most prevalent coronary metabolic comorbidities were hypertension, cardiac cerebrovascular disease, accompanied by diabetes [113]. Acute cardiac injury and acute arrhythmia and congestive heart failure (CHF) are among the top cardiac difficulties of COVID-19. A group of 10 out of 138 COVID-19 positive patients had acute heart injury and 23 more experienced acute arrhythmia [114]. Heart failure is one of the chief reasons of COVID-19 disease fatalities. Heart disease accounted for 23% of deaths in a study of 813 patients [115].

Pre-existent comorbidities in older infected patients includes coronary artery disease, hypertension and diabetes. Heart failure can be the outcome of alleviation of these prior conditions, whether diagnosed or unexplained, or subclinical cardiac dysfunction. In specific, diastolic dysfunction can develop cardiac insufficiency caused by high fever, tachycardia, impaired renal function and excessive hydration in geriatric population [116]. Instant inflammatory reaction does not occur due to dysregulation of immune responses, in people with cardiometabolic diseases as the drugs such as ACE inhibitors leads to over expression of ACE2 receptors further related to SARS-CoV-2 virus body entry. This promotes a delayed immune response and induces cytokine storm further increase the complication. Vitamin D receptors can regulate the ACE2 receptors [117]. ACE2 deficiency is also associated with worsening hypertension and cardiac hypertrophy, which is induced by angiotensin II [118].

ACE2 is commonly expressed, controls the fundamental cellular biology of cardiomyocytes, cardio fibroblasts and coronary endothelial cells. In addition, ACE2 deficiency causes patients to be more prone to heart failure due to either inhibition or deletion as a causative outcome for hypertension [119]. The SARSCoV-2 host cell entry is based on the SARS-CoV ACE2 receptor and it can be blocked by cellular serine protease inhibitor, TMPRSS2, used by SARS-CoV-2 for S-protein priming [120]. There was roughly double fold interrelation of COVID-19 mortality with HIV in South Africa, regardless of primary infection or suppressed immunity, subsequent to the episode of COVID-19, and a similar connection between the death of tuberculosis and corona virus infection [121] (Fig. 3).

The histopathological examination indicates the number of aberrations observed with the particular nephrons that infectious virus is expected to victimize. With brush boundary impairment and nonisometric vacuolation, acute tubular necrosis was observed, which could be caused primarily by explicit SARS-CoV-2 virulence. Substantial acute tubular injury and surprising endothelial injury trend, were found with signs of strong parenchymal tubular epithelial and podocyte viral infection in severe lethal COVID-19. Secondary injuries notably cytokine storms, hypoxia, subsequent staph infection, other viruses, fungi, and nephrotoxicity associated with medications may also lead to acute kidney injury [122]. The findings of pre-phase clinical trials have revealed that Vitamin D appears to be a possible regulator of pancreatic β-cell insulin secretion, Ca2+ level. Along with few others genes associated in cytoskeletal organisation, intracellular joints and pancreatic beta cell-growth. Vitamin D receptors also contributed to insulin gene transcription [123]. Numerous reports have publicized that hypovitaminosis D in pancreatic β-cells leads to failure of the glucose mediated insulin secrition. It has also been documented that through vitamin D supplementation, insulin secretion appears to be restored [124].

Calcitriol can directly induce insulin secretion because Vitamin D receptors has been acknowledged in the pancreatic beta-cells of the insulin gene promoter [125]. The findings of several scientific trials have exposed that supplementation of vitamin D has been related to enhancing insulin secretion [33,126]. Vitamin D also exerts anti-coagulant activity by decreasing tissue factor levels and escalates the level of thrombomodulin [127], since COVID-19 is also correlated with coagulation disorders that may further lead to thrombolytic events with COVID-19. Patients frequently reported elevated D-dimer levels and somewhat decreased in thrombocyte count and prothrombin period [54]. (Fig. 4).

2.7. Neurological disorders in COVID-19 and the role of VITAMIN D

The neural manifestations in COVID-19 patients are very much common which includes olfactory dysfunction due to the viral infection. It was reported in a total of 357 patients, (85.6%) mostly at the same time as the occurrence of common or ENT complications, gustatory dysfunctions were identified in a total of 342 patients (88.8 percent), characterized by deficiency taste modalities

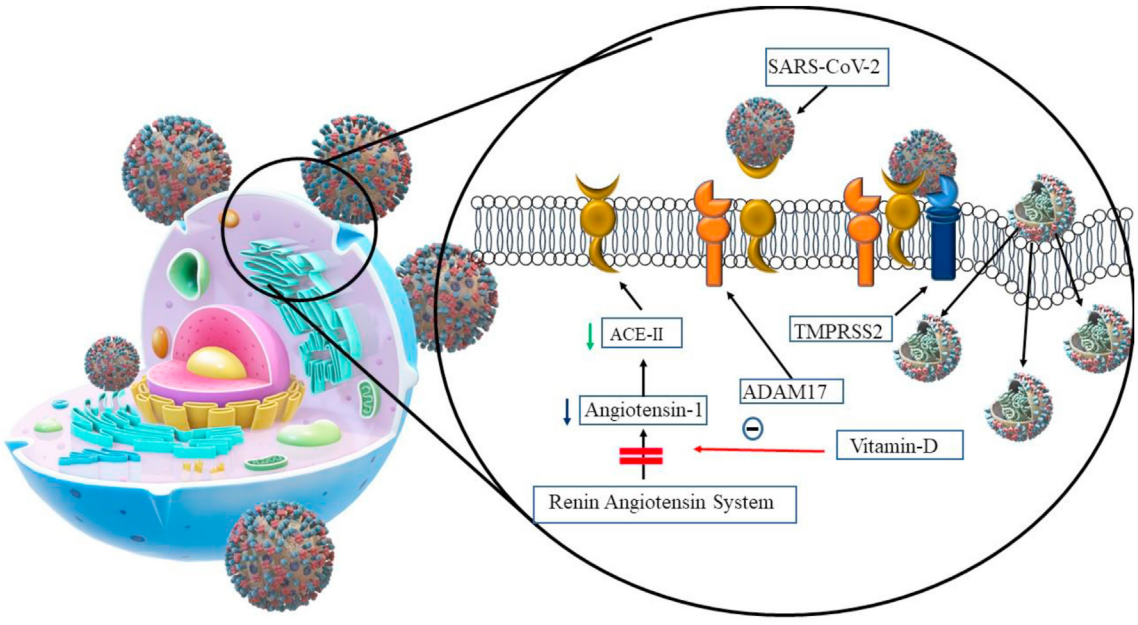

Fig. 3. Diagram showing the Cellular entry of COVID-19 and the role of vitamin D.

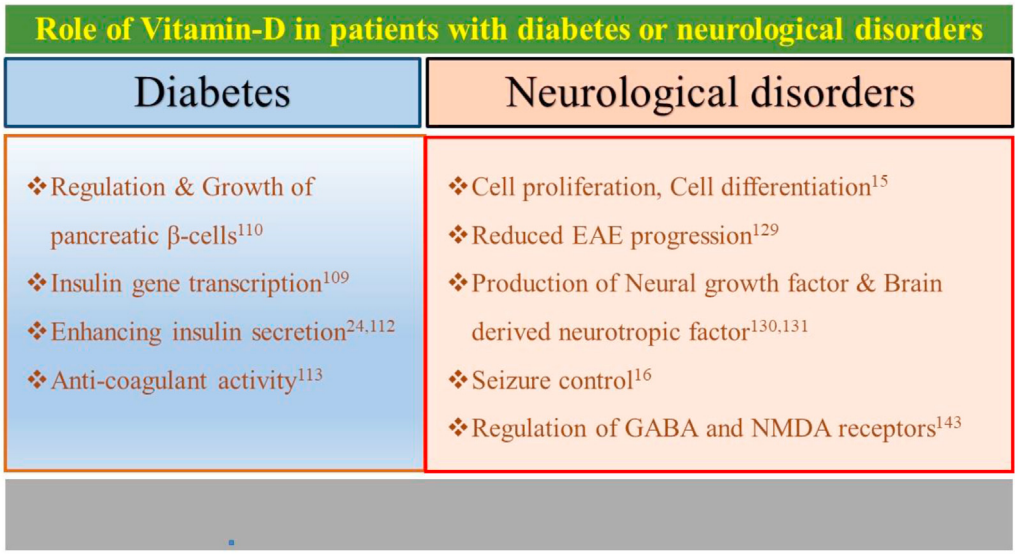

Fig. 4. Diagram Explaining the significant roles of Vitamin-D in major comorbidities of COVID-19.

[128,129]. Status epilepticus was observed in association to SARS, a trace of COVID-19 RNA was found in cerebra spinal fluid and serum samples [130]. Severe acute respiratory syndrome -CoV-2 can affect both the nerve systems, muscles of the skeleton and the respiratory tract. Neurological involvement, which entails acute cerebrovascular infections, altered consciousness, and skeletal muscle damage, is higher in people with serious infection. Accelerated declination of clinical afflictions in extremely infected COVID-19 may be due to neurological episodes like stroke, which would attribute to their high death rate [131].

Few studies were solemnly focused, on the neurological conditions of SARS-CoV-2 has substantial evidence of the happenings [132] A meta-analysis of 409 patients to assess the neurological disorders, headaches being most common followed by dizziness, impaired consciousness, vomiting, seizures, neuralgia, and ataxia were the key physiological adjustments [133]. SARS-CoV-2 is also dependent on ACE2 for cellular tropism and replication very similar to SARS -CoV infection [134]. In many unique brain regions in humans, ACE2 expression was moderately high. The expression of ACE2 in humans is primarily present in both neurons of excitation, moderate ACE2 cells were found in hippocampus and absent in Pre frontal cortex [135]. The associations with ACE2 in different and specific brain sections would give the viral organism the ability to infect the neural network of COVID19 patients if the organism were to cross the blood brain barrier (BBB) over the process of continuous infection [136].

Dopa Decarboxylase (DDC) is a pivotal enzyme that may also have a potential functional interaction between ACE2-mediated angiotensin synthesis [71]. SARS-CoV-2 might also affect the cell populations of neuronal progenitor cells. Since, these cells could be compromised by COVID-19 infection. The regeneration of olfactory activity and other neurological symptoms could be incomplete and late [137]. The expression of ACE2 in various organ systems and exposure to other elements of the renin angiotensin system (RAS) like nicotine imply that nicotinic acetylcholine receptor (nAChR) signalling will facilitate COVID-19 cellular entry. In fact, several of the similar cells that produce ACE2 in the pulmonary organs, liver, blood, and brain are known to have nAChRs [136]. Calcitriol regulates ACE2 and ACE expression [138]. A possible beneficial tactic to countering the expansion of Corona virus-19 mediated ARDS by aiming the imbalanced RAS and ACE2 reduction with vitamin D in COVID-19 infection [139]. Vitamin D also exhibited Seizure control activity [140].

Encephalomyelitis (EAE) is a rare, mostly post-viral, demyelinating condition that is more frequently seen in children, but rarely in adults. It was also observed in patients tested oppositive with COVID-19 infection as a vague comorbid condition. An immunoinhibitory cellular and humoral reaction of Vitamin D3 in vivo was demonstrated in an experimental rat model in the autoimmune encephalomyelitis research [141–143]. Vitamin D3 reversibly prevents EAE progression and that EAE initiation is exacerbated by vitamin D deficiency deliver ample proof that solemnly Vitamin D presence can be a significant feature in deciding the occurrence of MS and that it is a modulator of the immune system which is physiologically significant [133]. Vitamin D influences production of nerve growth factor (NGF), brain derived neurotrophic factor (BNDF) and exhibits a neurotropic effect [133,144,145]. Vitamin D specifically controls the expression of C-Ret, a multifunctional receptor essential for the signalling of Glial Mediated neurotrophic factor in dopaminergic neurons [146]. Since, SARS-CoV has mostly reached and dispersed all over the brain via the olfactory nerve, causing nerve damage [147]. Migration and oligodendrocyte progenitor differentiation and enhanced neural remyelination was stimulated by Vitamin-D to strengthen neural-transmission [148]. Vitamin D shows neuro transmitter effect by increasing dopamine levels [149], abundant studies have accentuated the pivotal place functions of Vitamin D, Vitamin D receptors. In neurology and other multispectral conditions makes it a noteworthy molecule to consider for the prophylactic treatment or for adjuvant therapy. Further research and randomised controlled trials need to be done in this particular perspective.

2.8. Hypercoagulation in COVID-19 & the role of vitamin -D

The effect of vitamin-D in multiple cardiovascular disorders where vitamin -d deficiency is inversely proportional to the economic burden and reduction in overall mortality cause [150,151] followed by hypertension [152], ischemic heart disease and myocardial infraction [153] and various cardio vascular diseases [154]. The anti-thrombotic properties of Vitamin D on various anti-thrombogenic and thrombogenic and coagulation cascade elements have been thoroughly portrayed in previous studies. Where,

Low vitamin D levels have been linked to the emergence of deep venous thromboembolic (DVT) [155] incidents in individuals with ischemic stroke and idiopathic lower-extremity [156]. Similarly, 40% of unprovoked venous thromboembolism cases were due to vitamin-D deficiency where majority are women [157,158]. In obese individuals, a study found a sexually dimorphic influence of vitamin D level correction on proteins implicated in blood coagulation, with men having greater circulating quantities of proteins associated with the blood coagulation pathway than women. Males convert 25-hydroxyvitamin D to the active metabolite 1,25-hydroxyvitamin D at a higher rate than women, as evidenced by protein levels. These characteristics could be attributed to the impact of sex hormone metabolism on vitamin D levels [159]. similarly, Individuals infected with COVID-19 had substantial coagulation dysfunction, with significantly diminished AT values and significantly higher FIB, PT, APTT, INR, FDP, and D-Dimers. COVID-19 victims' coagulation indicators were shown to be strongly linked to indicators of liver function and inflammation, suggesting that coagulation dysfunction could be triggered by inflammatory storm as well as liver injury [160]. Low-density inflammatory band (LDIB) neutrophil population that fluctuates with illness condition throughout time. Such cells formed endogenous neutrophil extracellular traps (NETs), had increased phagocytic capability, and produced more cytokines, and were clinically linked to CD40+ LDIBs. Systemic IL-6, COVID-19 associated coagulopathy (CAC) is caused by the LDIB subgroup, which could be employed as an auxiliary clinical marker to track disease condition and development [159]. In older individuals' neutrophils, 1,25-vitamin D3 suppressed LPS-induced production of macrophage inflammatory protein-1 and VEGF, but not in neonatal neutrophils [161]. D-dimer and TNF- levels. 1,25(OH)2D upregulates the response of an anticoagulant glycoprotein, thrombomodulin, in human peripheral monocytes and downregulates the expression of a critical coagulation factor, tissue factor counteracting the influence of tumour necrosis factor [162]. furtherly the association between haemostatic markers such as von Willebrand factor, D-dimer, highly sensitive C-reactive protein and tissue plasminogen activator was found to be inverse with serum 25(OH)D level [163]. Given the heterogeneity and small number of clinical studies, more study is needed to better understand the haemostatic abnormalities seen in vitamin D3 deficient people, as well as to determine the potential benefits of vitamin D3 supplementation on coagulation and haemostasis.

2.9. Hypocalcemia

Hypocalcaemia is associated with low vitamin D levels and leading to thoracic vertebral fracture among COVID-19 patients. This is a common osteo-metabolic comorbidity among COVID patients, which implies the importance of calcium and vitamin D supplementation to improve health outcomes [164,165]. Hypocalcaemia connected with the osteo-metabolic phenotype increases the risk of infection, disease severity [166]. Another retrospective study concluded hypocalcaemia can be a biological marker, which can be used as a targeted treatment after conducting further research [167]. Altered calcium homeostasis helps viruses to bind with host cells hence calcium became an important element in infectivity and replication [168]. in the study of Severe COVID-19 individuals about 62.6% were found to have suffering from hypocalcaemia. Individuals with significant COVID-19 had a worse prognosis if they had hypocalcaemia. Furthermore, 63.6% of the patients were over the age of 65, with an average age of 68, indicating that elderly persons are more prone to serious COVID-19 [169]. The majority of the participants in the investigation were old and undernourished. Chronic malnutrition causes vitamin D insufficiency, which leads to hypocalcaemia. Furthermore, it can impair calcium absorption in the intestine, resulting in insufficient ingestion and a negative calcium balance. In the plasma, calcium is primarily associated to albumin, hence a reduction in serum albumin will result in hypocalcaemia [170]. Furthermore, COVID19 individuals with hypocalcaemia had markedly elevated levels of CRP, PCT, IL-6, and D-dimer, and hypocalcaemia was significantly associated with these markers, suggesting that individuals with hypocalcaemia have a larger inflammatory response [169]. All the literature suggesting vitamin D and calcium are important components of disease management that might improve COVID-19 health outcomes.

3. Conclusion

This review concludes the possibility of using Vitamin D as adjuvant therapy in corona virus infected patients. Since, plethora of available data on the repute of vitamin D and its stature in therapeutic effects of managing immunomodulatory effects, immune response on influenza [55,56], upper respiratory tract infection [58], antimicrobial effect [34,59], regulation of innate and adaptive immunity [54,60], neurological [16], Hepatitis-B [80], multiple sclerosis [81], varicella-zoster virus [83], and furthermore the expression of cytokine regulation. Its effect on expression of cytokine regulation [63,64]. Vitamin D/Vitamin D receptors also promote cell proliferation, remodeling and repair are notable [68]. Vitamin D regulates ACEII receptors [34] through which SARS-CoV-2 enter in to the body [112]. The effect of Vitamin D on respiratory conditions was also highlighted [77]. The Majority of the world population is suffering from hypovitaminosis D [31] Role of Vitamin D in the comorbidities of COVID-19 is eminent through the physiological pathways, where Vitamin D levels were observed in the COVID-19 patients and it was correlated more in severely infected patients [39]. The possibility of vitamin D using as prophylactic or as adjuvant therapy in COVID-19 management has become a million-dollar question. Since vitamin D is naturally available and even the supplements are inexpensive. Differential combinations of vitamin D along with wide range of antiviral drugs may be a superior treatment option if explored. Furthermore, necessity of studies may bring the curtains down to the question of bit part of Vitamin D in COVID-19. Even though the antiviral activity by using microbial peptides [62] and the immunomodulatory effect by regulating both innate and adaptive immune systems and effect on ACE2 receptors might projects a positive possibility of Vitamin D as adjuvant therapy. Lack of targeted therapy makes it a hard task to treat the infection of COVID-19, supportive therapy, strengthening the immune system, preventive measures and symptomatic treatment are the path to shield from the disease. In this given perspective the indispensable question, whether Vitamin D can be used in the management of COVID-19, needs further exploration of animal to human randomised controlled studies.

Author contribution

V.U.K wrote the first draft of the paper and worked on coding of figures. G.P and R.K responsible for the final content. M.H, K.M, S.D, V.R revised the final draft of the manuscript. All the authors read the manuscript and approved the final manuscript.

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Declaration of competing interest

No conflict of interest.

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