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# COVID-19 infection and metabolic comorbidities: Mitigating role of nutritional sufficiency and drug – nutraceutical combinations of vitamin D

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ABSTRACT

The vulnerability of human health is amplified in recent times with global increase in non-communicable diseases (due to lifestyle changes and environmental insults) and infectious diseases (caused by newer pathogens and drug-resistance strains). Clinical management of diseases is further complicated by disease severity caused by other comorbid factors. Drug-based therapy may not be the sole approach, particularly in scenarios like the COVID-19 pandemic, where there is no specific drug against SARS-CoV-2. Nutritional interventions are significant in armouring human populations in disease prevention, and as adjunctive therapy for disease alleviation. Amidst ongoing clinical trials to determine the efficacy of Vit. D against infections and associated complications, this review examines the pleiotropic benefits of nutritional adequacy of vitamin D (Vit. D) in combating viral infections (COVID-19), its severity and complications due to co-morbidities (obesity, diabetes, stroke and Kawasaki disease), based on research findings and clinical studies. Supplements of Vit. D in combination with other nutrients, and drugs, are suggested as promising preventive-health and adjunct-treatment strategies in the clinical management of viral infections with metabolic comorbidities.

## 1. Introduction

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection 2019, named as COVID-2019 (Coronavirus Disease of 2019) emerged in Wuhan, Hubei province, China in December 2019 and spread across the world due to its high transmissibility and pathogenicity [1]. SARS-CoV-2 is a distinct member of β-coronavirus that includes the acute respiratory syndrome coronavirus (SARS)-CoV, which previously emerged in China in 2002–2003 [2], and the Middle East respiratory syndrome (MERS)-CoV in the Middle East, reported in 2012. The high lethality of CoVs is revealed when they cross the species barrier and infect humans [3]. SARS-CoV-2 can be caused by human-to-human respiratory droplet transmission, close contact with infected patients, and possibly by fecal-oral and aerosol contact [4].

COVID-19 patients often exhibit mild symptoms (cough, fever, fatigue, myalgia) and generally have a good medical prognosis. However, it may be severe in older adults who constitute the main risk group with underlying diseases or comorbidities [5]. Severe COVID-19 is strongly associated with hyper-inflammation, as evidenced by a higher level of C-reactive protein, ferritin, and D-dimers in blood, as well as increased neutrophil to lymphocyte ratio and serum level of several inflammatory chemokines and cytokines [5]. Complications can include shock, acute cardiac or kidney injury [6], acute liver injury, dyspnea, neurological injury, gastrointestinal injury, coagulation impairment [7], organ dysfunction (acute respiratory distress syndrome (ARDS)), and even death [5,8]. The rise in inflammatory cytokines during SARS-CoV-2 infection was reported to cause mild to severe respiratory syndrome, with potentially serious complications and sometimes fatal in children and elderly patients with pulmonary or hypertensive disorders as well as in residents of cities with poor air quality environment [9].

The COVID-19 disease thus turned out be a global health threat with an uncertain trajectory. With no specific treatment available for COVID-19, chemoprevention, vaccination, and repurposing of existing drugs gave hope of controlling the pandemic. Yet, no universal treatment is

*Abbreviations:* ACE2r, angiotensin-converting enzyme 2 receptor; AID, Autoimmune diseases; ARDS, acute respiratory distress syndrome; BMI, body mass index; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; IA, immune activation; IU, international units; KD, Kawasaki Disease; KDSS, Kawasaki disease shock syndrome; mcg, micrograms; NO, nitric oxide; RDA, recommended daily allowance; RAS, renin-angiotensin system; SARS-CoV-2, severe acute respiratory syndrome coronavirus; T2DM, type 2 diabetes mellitus; 24(OH)D, 24-hydroxy vitamin D; VCAM, vascular cell adhesion molecule; VDR, vitamin D receptor; WHO, World Health Organization.

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presently available for COVID-19 management.

Patients with COVID-19 infection were found to have an elevated plasma angiotensin II level, which positively correlated with the extent of lung damage [10], suggesting the connection between COVID-19 and renin-angiotensin system (RAS). The initiation of the infection is due to the invasion of human lung epithelial cells which is caused by the binding of COVID-19 to the angiotensin-converting enzyme 2 receptors (ACE2r). The pharmacological action of the ACE2 is well known for anti-hyperplasia, anti-inflammatory, antioxidant, and anti-fibrotic effects, the degradation of the angiotensin II (Ang II) at lung level by ACE2/Ang1-7/Mas receptor signaling pathway. The toxic over-accumulation of Ang II is prevented due to the degradation of the unwanted Ang II, which provokes acute respiratory distress syndrome which is often seen in COVID-19 infection. Therefore, ACE2 has an antagonistic dual action in viral infection. As compared to females, the expression of ACE2 is lower in males, and also lower in older adults compared to young people, which is congruent with the observed statistics of death of elderly males due to COVID-19 infection [11]. Fig. 1 depicts the general multi-organ complications involving the binding of Ang II with ATR 1 due to multiple causes. This explains some of the multi-organ complications observed in severe COVID-19 cases.

### 1.1. Clinical management of COVID-19: The significant role of nutrition

It has been found that some of the repurposed antiviral therapies - Remdesivir, Lopinavir and Interferon-β1a may act by modulating the immune response and can be used for the effective treatment of SARS CoV-2 as well [12]. The drug repurposing approaches included nucleoside analogues (Abacavir, Galidesivir, Remdesivir), protease inhibitors (Lopinavir, Danoprevir, Ritonavir, Saquinavir), anti-influenza drugs

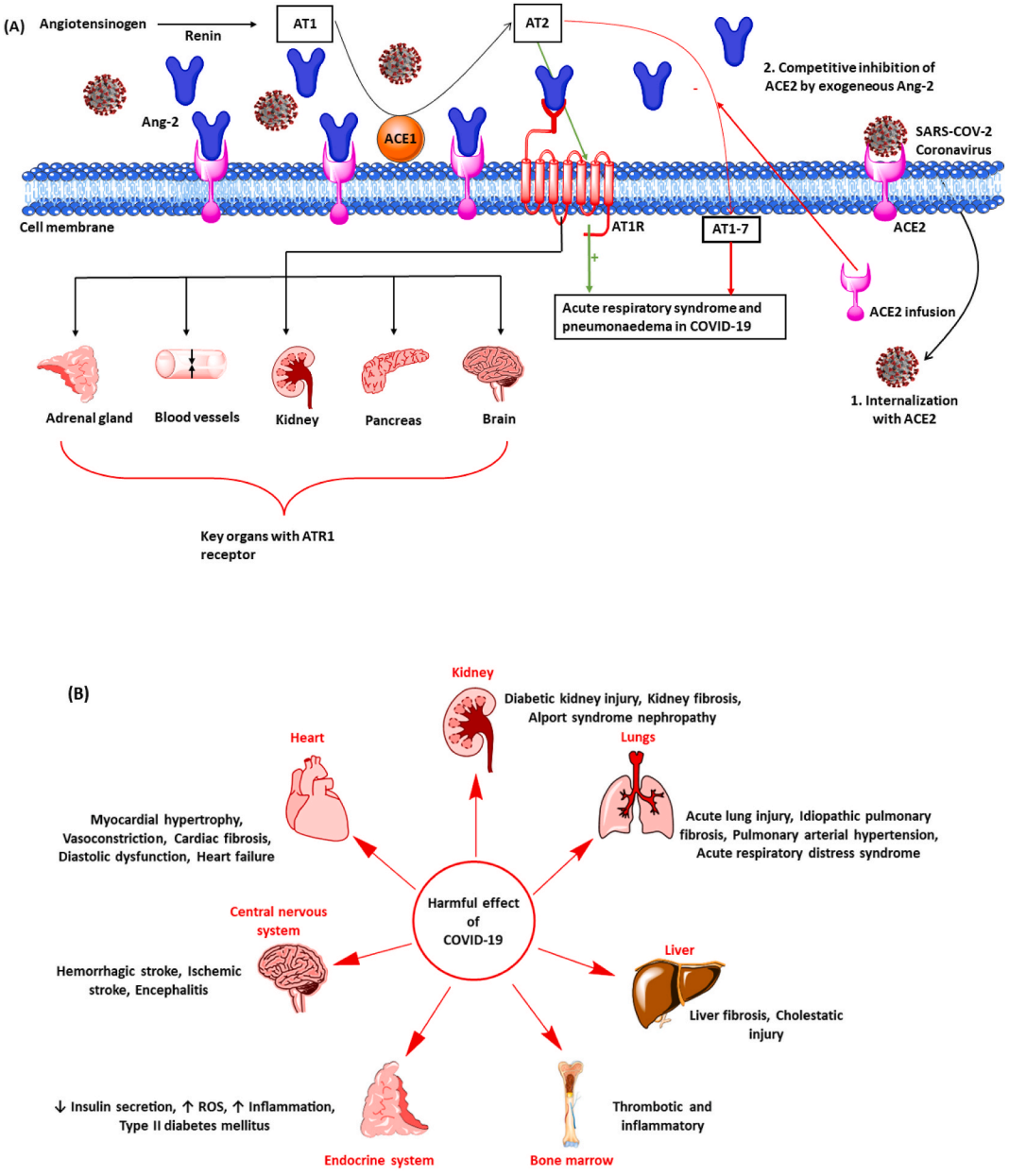


**Fig. 1.** Mechanism of COVID-19 infection and potential for multi-organ complications. A. Schematic representation effect of angiotensin II binding with SARS-COV-2. The Ang II is hypothesized to prevent SARS-COV-2 infection by directly competing with SARS-COV-2 for binding to the ACE2 during the degradation and hydrolysis into angiotensin. The internalization and downregulation of ACE2 results due to the binding of Ang II to the AT1 receptor through an ERK1/2 and p38 MAP kinase pathway. B. Schematic representation of the possible multi-organ complications caused by COVID- 19 induced binding of Ang II with ATR 1.

(Favipiravir, Oseltamivir, Umifenovir), and others (Hydroxychloroquine, Emetin, Sotetsuflavone) [13,14].

In parallel, there have been substantial scientific efforts to promote dietary/nutritional strategies to combat COVID-19 including prevention of the disease and its complications. Several dietary supplements including vitamins, mainly B complex, C, and D have also been considered as effective immune system modulators to aid these therapies [15]. In a detailed review on the potential role of diet in the clinical management of COVID-19, Coelho-Ravagnani et al. pointed out that nearly 31% of the health guidelines emphasized on key nutrients that included vitamins C, A, and D and zinc, for maintaining good immunity [16]. While literature does not conclusively associate dietary supplementation with COVID-19 prevention, the supplements of vitamins C and D, and minerals like zinc and selenium, have shown to exert health benefits to individuals with, or at risk of, respiratory viral infections, or for those with specific nutrient(s) deficiency, owing to their established biochemical, immunological and antioxidant functions [17].

Amidst uncertainties linked with higher doses of Vitamin D to manage COVID-19 infection (or other viral infections) due to possible vitamin toxicity, it is still proposed as a reasonable strategy to at least mitigate the nutrient-deficiency induced vulnerability to infections. Further, Vitamin D deficiency is also correlated with metabolic disorders such as diabetes, obesity and hypertension [17]. Taken together, Vitamin D supplementation to address the nutritional inadequacy in individuals is expected to be beneficial in strengthening immunity alongside co-morbidities, which further exacerbate the clinical manifestations during COVID-19.

Vitamin D is a natural immunomodulator that has been used as an antimicrobial against several pathogens including respiratory viruses [18]. Moreover, clinical trials have shown a strong correlation between vitamin D deficiency and an increased risk of respiratory infections, wherein vitamin D supplementation lowered the risk of complications associated with the respiratory infections [19]. Vitamin D exerts its antiviral effects by upregulating antimicrobial peptides and by producing antiviral cytokines, which interfere with the viral replication cycle [20].

## 2. Vitamin D deficiency *epidemic* & the COVID-19 *pandemic*

Individuals can develop vitamin D deficiency when their intakes are lower than recommended levels, limited exposure to sunlight, inability of the kidneys to convert 25(OH)D to its active form, or inadequate absorption of vitamin D from the digestive tract. People who are allergic to dairy products, or lactose intolerant, and those who consume an ovo-vegetarian or vegan diet may have inadequate Vitamin D levels [21].

There is a world-wide prevalence of low vitamin D status. Prevalence rate of vitamin D deficiency (defined as 25(OH)D <30 nmol/L (or 12 ng/ml)) has been reported to be 5.9% (US) [22], 7.4% (Canada) [23], and 13% (Europe) [24]. The prevalence of 25(OH)D levels <50 nmol/L (or 20 ng/ml) has been estimated to be 24% (US), 37% (Canada), and 40% (Europe) [23–26]. This may vary with factors such as: (a) age, with lower levels in childhood and the elderly, and (b) ethnicity in different regions. A recent south Asian study reported potential genetic factors for Vit. D deficiency in several cohorts of Korean population [27]. Levels of 25(OH)D <30 nmol/L (or 12 ng/ml) in >20% of the population are common in India, Tunisia, Pakistan and Afghanistan [24,26]. A clinical trial from Taiwan reported that prevalence of vitamin D deficiency was 59% and the severe vitamin D deficiency status was 18%, wherein vitamin D deficiency correlated with longer duration of ventilator usage and ICU stay [28].

Vitamin D deficiency is seen in epidemic proportions in many parts of the world, yet is the most undiagnosed and undertreated nutritional deficiency in the world [29]. Vitamin D deficiency has been observed in both countries which are 'sunshine deficient' and 'sunshine sufficient' [30]. For instance, even though India receives abundant sunshine throughout the year, deficiency of vitamin D is emerging as a major nutritional and health burden [31]. It has been estimated that 490 million individuals are vitamin D deficient in India [24,26]. A high prevalence (50-90%) of vitamin D deficiency along with low diet calcium intake has been documented in Indian population [32]. The latest guidelines provided in 2020 by the Indian Council of Medical Research – National Institute of Nutrition (ICMR-NIN) for adequate Vit D intake [33] is represented in Fig. 2.

According to a fact sheet on vitamin D provided by the National Institutes of Health (NIH,USA) [21], the Food and Nutrition Board (FNB) committee established RDAs for vitamin D to indicate daily intakes sufficient to maintain bone health and normal calcium metabolism in healthy people [34]. The RDA and Tolerable Upper Intake Levels (TULs) recommendations for vitamin D intake across age groups, gender and special physiological condition is represented in Fig. 3.

Vitamin D has several mechanisms to reduce the risk of microbial infection and death. A recent review by Rondanelli et al. discussed the role of Vitamin D in reducing the risk of common cold, through the three major mechanisms namely physical barrier, cellular natural immunity, and adaptive immunity [35]. The rationale for the protective role of vitamin D against COVID-19 – mediated complications, is evidenced by the epidemiologic studies connecting vitamin D and various respiratory infections via specific activation of ACE2 and immune mechanisms by Vit. D [36]. The dosages of Vitamin D for an optimal 25(OH)D plasma level of 30–50 ng/mL, was recommended to be a daily supplementation of 400 IU–2000 IU for the general population (as per international guidelines), considering age, sex, body weight, skin colour, time outdoors, and geographic latitude. The recommended dosages generally increase for pregnant and breastfeeding women, obese adults (BMI >30 kg/m2), old-aged people, night workers, and dark-skinned people, as well as patients with a disability or disorder (renal/hepatic/gastrointestinal). Additionally, each nation has developed its own dietary recommendations that is best applicable for its citizens [36]. Table 1 captures the Vit D status and COVID-19 incidence in some of the countries, as per reported studies.

### 2.1. *Potential pathways for conferring COVID-19 protection by vitamin D*

Vitamin D is a prohormone or pseudo-hormone that is biosynthesized by sunlight exposure (UVB radiation at 290-315 nm), and can also be obtained from diet [55]. The catabolic activity of 24-hydroxylase in target tissue plays an important part in regulating both 24-hydroxy vitamin D [24(OH)D; calcidiol], and 1,25(OH)2D (calcitriol) concentration and their availability. A well-known function of calcitriol is to help regulate serum calcium concentrations, which it does in a feedback loop with parathyroid hormone (PTH), which itself has many important functions in the body [55]. Fig. 4 summarizes the biosynthetic pathway of vitamin D and the multifaceted effects of vitamin D that may be helpful in controlling COVID-19 and its complications.

The differential immunomodulatory effects of vitamin D thus enables immune boosting to combat viral infection on one hand, while they also balance or offset the hyperimmune reaction and inflammation through above mechanism. The latter effect favours the prevention of the cytokine storm that was witnessed as a clinical complication in certain COVID-19 affected patients. In a recent review [56], the beneficial effect of calcitriol treatment in avoiding tissue damage in influenza-infected alveolar cells was cited to demonstrate the immune-balancing effects of vitamin D. Vitamin D has been shown to reduce the production of pro-inflammatory factors such as tumour necrosis factor-alpha (TNF-α), IFN-β, CXCL8, and interleukin (IL)-6, thereby reducing the risk of severe inflammatory sequel in COVID-19 patients.

According to several studies, an increased risk of respiratory tract infections was linked to vitamin D insufficiency. As a result, it is believed that this hormone is crucial in lowering the risk of viral infections, including influenza viruses. The processes by which active vitamin D lowers the incidence of the common cold were examined by Grant et al. [57]. Vitamin D initially aids in protecting the different cellular

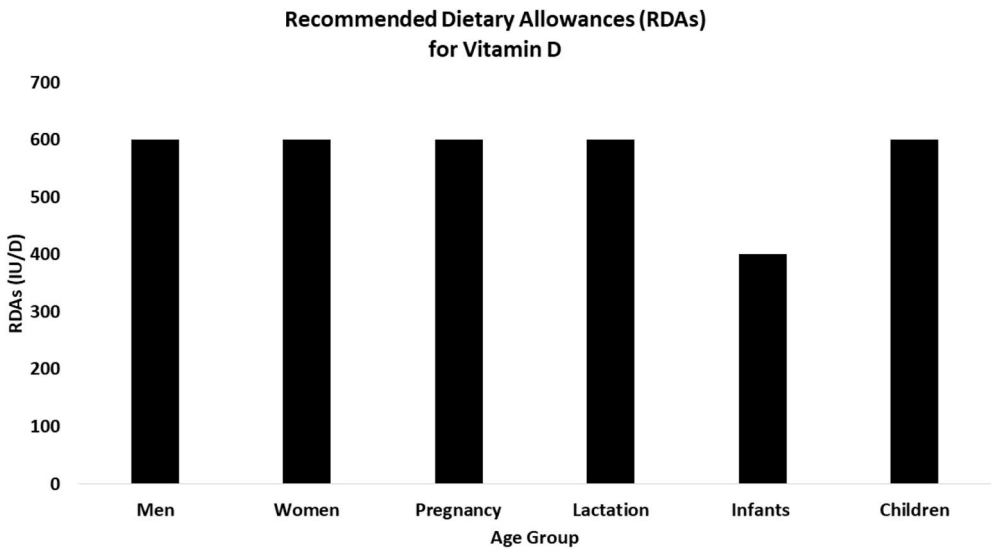


**Fig. 2.** RDA for Vit D according to age groups, gender and special physiological requirements, recommended by ICMR-NIN, 2020. RDAs for vitamin D are listed in both micrograms (mcg) or as international units (IU), where 1 mcg vitamin D is equal to 40 IU.

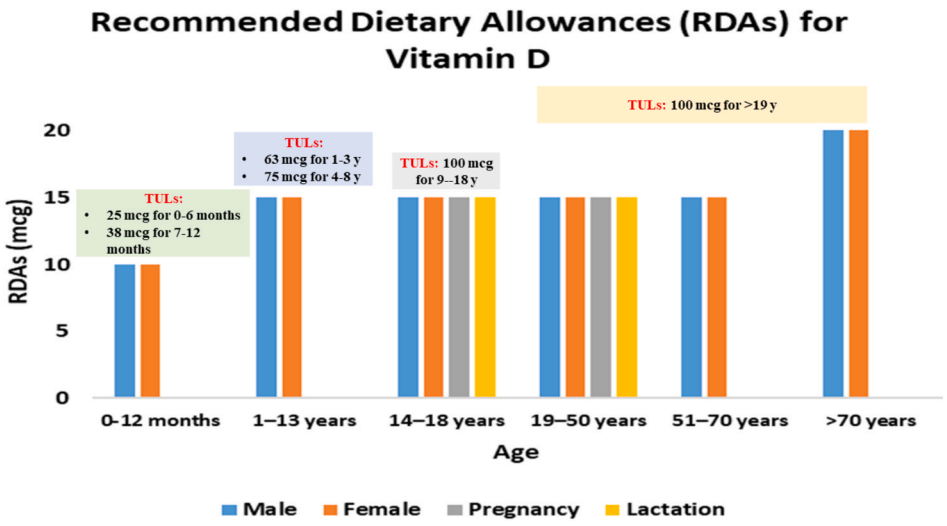


**Fig. 3.** RDA and TULs for Vit D according to age groups, gender and special physiological requirements, recommended by FNB. RDAs for vitamin D are listed in both micrograms (mcg) or as international units (IU), where 1 mcg vitamin D is equal to 40 IU.

junctions against viral assault. In addition, it induces antimicrobial peptides like defensins and cathelicidin, which boosts innate immunity. It also suppresses the cytokine cascade, which lowers the production of pro-inflammatory Th1 cytokines like INF-γ and TNF-α. In addition, active vitamin D decreases the activity of Th1 cells and increases the production of cytokines by Th2 cells, which reduces inflammation [58]. The pleiotropic immune functions of vitamin D has been gaining lot of research interest in order to harness the specific mechanisms for vitamin D based treatment of auto-immune and infectious diseases. The paradoxical involvement of Th1 and Th2 mediated mechanisms involving macrophages and pro-/anti-inflammatory cytokines are being studied from the cell-specific, context-specific, transcriptional factors mediated, and epigenetic aspects [59,60]. In the recent context of COVID-19, Chauss et al. [61] identified an autocrine/paracrine vitamin D loop to prevent the hyperinflammatory effects in COVID-19 patients via transcription factors mediated and epigenetic reprograming of Th1 immune function and its molecular respondents namely IFN-γ and IL-10.

Vitamin D is synthesized by skin exposure to UV light or oral intake of vitamin D and binds to vitamin D binding protein (DBP) in the blood. After being rapidly converted into 25(OH)D by the hepatic 25-hydroxylase CYP2R1, it forms the stable 25(OH)D-DBP complex, which has a long circulating half-life of 480 h. This complex is excreted in urine, reabsorbed by megalin at renal proximal tubule cells, and then converted by the enzyme 1α-hydroxylase CYP27B1 into the active form of vitamin D, 1,25-hydroxyvitamin D (1,25(OH)2D). This activated vitamin D, that is 1,25(OH)2D has a shorter half-life than 25(OH)D due to its lower affinity for DBP. Further, 1-hydroxylase is also affected by other factors, such as parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF23) [62].

Numerous extrarenal cells also express 1-hydroxylase, megalin, and cubilin. As a result, 25(OH)D is taken up into these cells by megalin and cubilin, where it then acts either in an 'autocrine' or in a 'paracrine' manner after being locally transformed into the active form 1,25(OH)2D [63–65]. It should be noted that 1α-hydroxylase in extrarenal tissues is regulated differently than it is in renal tubular tissues. FGF23, for instance, boosts the production of 1-hydroxylase in parathyroid cells, which is the opposite of how it acts on renal proximal tubular cells. Interleukin-1$\beta$, an NF-$\kappa$B activator, promotes the production of 1

**Table 1**
Snapshot of vitamin D deficiency in regions affected by COVID-19.

| Country | Study Population (Number of subjects and age) | Vitamin D status | Prevalence | | | COVID-19 Cases –cumulative Total[a] | References |
|---|---|---|---|---|---|---|---|
| | | | Deficiency (%) | Insufficiency (%) | Sufficiency (%) | | |
| **Brazil** | N = 894; >18 years (mean age 58.15 ± 12.08 years) | 26.06 ± 10.37 ng/ml | – | 28.5 | 43.5 | 21,909,298 | [37–39] |
| | N = 603 (118 M and 485F); 18–90 years | 21.4 ng/mL | 13.8 | – | 76.5 | | |
| **China** | N = 460,537; 1 day to 18 years | 72.18 ± 30.10 nmol/L | 6.69 | 15.92 | 77.39 | 127,018 | [39,40] |
| **France** | N = 892 (463 men,429 women); 18–89 years | Men (24.1 ± 8.2 ng/mL) and women (23.4 ± 8.0 ng/mL | 6.3 | 34.6 | – | 7,030,401 | [39,41] |
| **India** | N = 316 (99 men and 217 premenopausal women); 30–50 years | 9.767.1 ng/ml | 80.1% | – | – | 34,414,186 | [39, 42–44] |
| | N = 3127; age 6-18 years | 9 ng/ml | 11.5 | – | – | | |
| | N = 92 (64 men and 28 non-pregnant/non-lactating women); 18–40 years | 28.35 nmol/l in urban and 32.10 nmol/l in rural populations | 83 | – | – | | |
| **Iran** | N = 993 | 13.75 ng/ml | 85.2 | 9.5 | 5.3 | 6,019,947 | [39, |
| | N = 245; (40-80 years) | 73.0 ± 62.3 nmol/l | – | 5.3 | 37.6 | | 45–47] |
| **Italy** | N = 570; 41–80 years | 18.3 + 8.3 ng/ml | 28 | – | 72 | 4,835,435 | [39,48,49] |
| | N = 700 women; 60–80 years | | 76 | – | – | | |
| **South Africa** | N = 58; 6–18 years | 6–9 y: 49.55<br>10-13 y: 115.6 ± 46.30<br>14-18 y: 36.09 | – | – | – | 2,924,978 | [39,50] |
| **United Kingdom** | N = 449 | 28.7 (10.0–43.8) nmol/L | – | – | – | 9,448,406 | [39,51] |
| **USA** | N = 4962; ≥20 years | 22.9 ± 12.8 ng/mL | 39.92 | – | 60.0 | 46,501, | [39, |
| | N = 20; 65.2 ± 16.2 years | – | – | – | 8 | 534 | 52–54] |
| | N = 499 | | 25 | – | 58 | – | |

Abbreviations: M = male, Y = year, N = number, F = female, nmol/L = nanomoles per litre.
[a] Data as in Nov 2021 from WHO website.

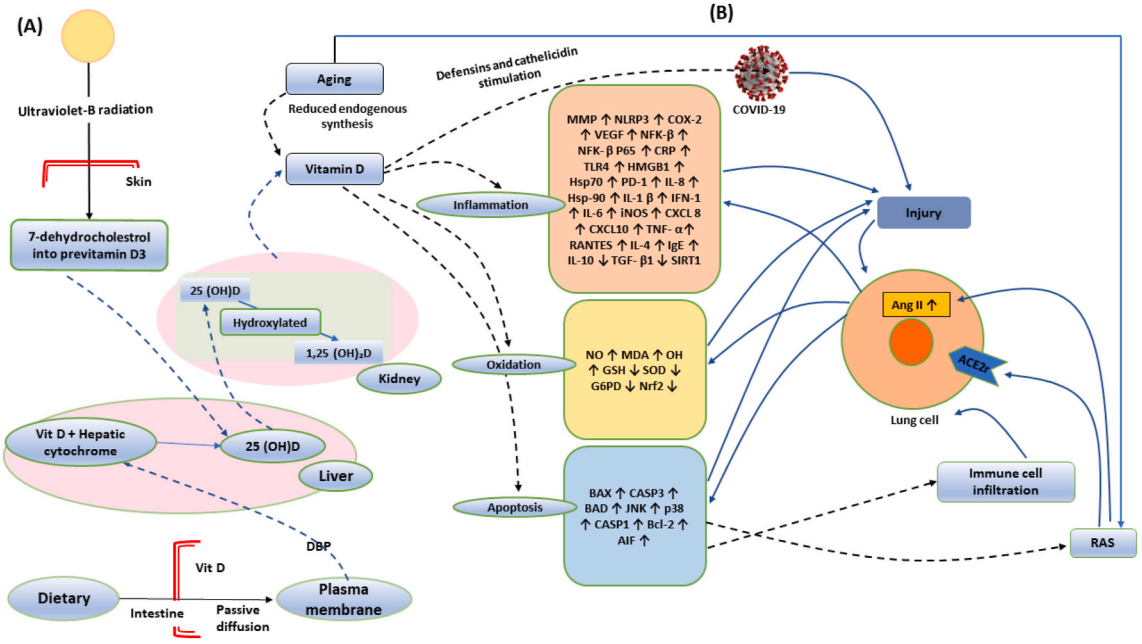


**Fig. 4.** Schematic representation of bioactivation of vitamin D and its role in multiple signaling pathways. (A) The major source of vitamin D is produced in the skin through sunlight-dependent chemical reactions. The exposure of skin to the ultraviolet-B radiation from the sun converts 7-dehydrocholesterol into previtamin D3, which is then converted into calcifediol (25-(OH) D) in the liver and further hydroxylated into 1,25 (OH)2D in the kidney. 1,25 (OH)2D is the biological form of vitamin D. (B) Showing the key signaling pathways of vitamin D for potential protection in COVID-19 lung infection. The solid line indicates the stimulation/induction, while the dashed line indicates inhibition/blocking
Abbreviations: MMP: matrix metalloproteinase; NLRP3: NLR family pyrin domain containing 3; COX2: Cyclooxygenase-2; VEGF: Vascular endothelial growth factor; NKB-β: The nuclear factor NF-κB; CRP: C-reactive protein; TLR4: Toll-Like Receptor 4; HMGB1: High-mobility group box 1; HSP70e: Heat shock protein 70; PD-1: Programmed cell death protein 1; IL-8: Interleukin-8; IL-1 β: interleukin-1β; IFN-1: Interferon type I; iNOS: Inducible nitric oxide synthase; CXCL 8: C-X-C Motif Chemokine Ligand 8; TNF- α: Tumor necrosis factor alpha; RANTES: regulated upon activation, normal T cell expressed and secreted; IgE: immunoglobulin E; SIRT1: Sirtuin 1; NO: nitric oxide; MDA: Malondialdehyde; GSH: Reduced glutathione; SOD: Superoxide dismutases; G6PD: Glucose-6-Phosphate Dehydrogenase; Nrf2: nuclear factor erythroid 2–related factor 2; BAX: Bcl-2-associated X protein; CASP3: Caspase 3; BAD: BCL2 associated agonist of cell death; JNK: c-Jun N-terminal kinase; p38: p38 mitogen-activated protein kinases; CASP1: caspase 1, apoptosis-related cysteine peptidase; Bcl-2: B-cell lymphoma 2; AIF: Apoptosis-inducing factor.

hydroxylase in osteoblasts, whereas PTH and calcium have little effect on it [66,67].

The activation of vitamin D in the body via the above mentioned hydroxylation reactions is critical for the biological action of vitamin D (and VDR). Therefore, alleviating vitamin D insufficiency through supplements need to consider specific conditions where the cardio-reno-vascular disorders may compromise the hydroxylase based vitamin D activation. In this context, synthetic analogues of active form of vitamin D have yielded favourable clinical outcomes when compared with merely vitamin D2/D3 supplementation (Table 2) [68,69].

## 3. COVID-19 and COMORBIDITIES – major cause for disease susceptibility and complications

Pre-existing or comorbid conditions may enhance the susceptibility to COVID-19 infection, and lead to clinical complications. The increased cases of COVID-19-related hospitalizations and deaths in Mexico (particularly young adults) was attributed to chronic diseases associated with poor nutrition and smoking, which strongly pointed to the need for public health interventions to reduce both chronic disease incidence as well as to facilitate infectious disease control [70]. Available literature points to several factors such as age, physical activity, obesity, seasonal change, lower vitamin D absorption, pregnancy, thyroid disorders, long-term corticosteroid use, and ethnicity/race, to have significant bearing on blood 25(OH)D levels [52,71]. As a result, while vitamin D insufficiency has been identified as a key risk factor in the clinical outcomes of COVID-19 patients, it appears that it may also be linked to other underlying risk factors and diseases in these individuals. The nutritional and biochemical role of Vitamin D is recognized beyond its skeletal function, and extends to providing benefit in a number of non-communicable/metabolic disorders as well as infectious diseases [72,73].

**Table 2**
Dietary, nutraceutical supplements, and pharmaceutical sources of vitamins D2 and vitamin D3.

| Sources | Typical vitamin D content | References |
|---|---|---|
| Natural sources | Cod liver oil (34 μg/1 tablespoon)<br>Trout (16.2 μg/3 ounces)<br>Salmon (30 μg/100 g)<br>Mushrooms (9.2 μg/½ cup)<br>Swordfish<br>Milk products (~0.1 μg/100 g)<br>Tuna fish (1.7–18.7 μg/100 g)<br>Beef liver (1.0 μg/3 ounces)<br>Egg yolk (~1.75 μg/100 g)<br>Meat (~0.6 μg/100 g) | [21] |
| Fortified foods | Vitamin D fortified dairy and plant milks (Fortified butter, fortified milk (1.1–2.0 μg/100 g), Fortified yogurts, Fortified cheese (2.6–25.0 μg/100 g))<br>Infant formulas<br>Fortified orange juice<br>Fortified margarine<br>Fortified breakfast cereals | [147,148] |
| Supplements/Drugs | Multi-Vitamin supplements/ nutraceuticals containing Vit D (800 to 1000 IU)<br>D3 vitamin (4000 IU, 60,000 IU)<br>Capsules, chewable tablets, liquids, and drops | [149] |
| Synthetic analogues of active form of vitamin D | Maxacalcitol (22-oxa-1,25(OH)2D3)<br>Calcipotriol (5, 22-ene-26,27-dehydro-1,25(OH)2D3)<br>Dihydrotachysterol (DHT)<br>Paricalcitol (19-norD2)<br>Tacalcitol (8, 1α,24(OH)2D3)<br>Doxercalciferol (1α(OH)D2)<br>Falecalcitriol (26,27-F6-1,25-dihydroxyvitamin D3) | [150] |

In the following few sections, we will discuss the reported comorbidities in relation to COVID-19 infections, along with the independent benefits of vitamin D with respect to the viral infection as well as each comorbid condition.

### 3.1. Link between COVID-19 and stroke

Stroke is the major cause of death all over the world [74], especially in Asia [75]. In the pandemic scenario, older patients infected with COVID-19 along with possible comorbidities of diabetes and hypertension were reportedly susceptible to neurological complications of stroke (mostly ischemic, and few haemorrhagic cases) [76,77]. The cause of the stroke as a comorbid condition for COVID-19 patients could be atherosclerosis, hypertension, and atrial fibrillation [78]. There are epidemiological pointers which indicate that individuals with Vitamin D insufficiency are at a higher risk of diabetes as well as cardiovascular disorders, including stroke [79]. Thus vitamin D has been receiving substantial attention as a potential preventive measure in cardiovascular disease management [80].

In a report from Wuhan, China, around 1875 patients with COVID-19 were hospitalized between January 2020–March 2020, wherein 50 patients had a history of stroke (90% of which were ischemic, and 10% were hemorrhagic) [81]. Another report from Wuhan, China found that out of 214 COVID-19 patients, 36% developed neurological complications. Acute cerebrovascular disease (primarily ischemic stroke) was the dominant complication seen in the infected patients [76]. In a hospital-based report from New York, out of a total of 3556 patients COVID-19 who were hospitalized between March 2020–April 2020, around 32 experienced ischemic strokes. Out of these 32 patients, 14 patients were already suffering from ischemic stroke, and the rest 18 patients developed ischemic stroke during their hospitalization for COVID-19 respiratory symptoms [82].

#### 3.1.1. Dual benefit of Vit D supplementation in COVID-19 patients with stroke

Cardiovascular disorders (CVDs) include stroke (cerebrovascular disease), coronary heart disease, heart failure and other conditions that affect the heart and blood vasculature, wherein the protective role of Vitamin D has been researched for its potential cellular and molecular mechanisms. Reports associate hypovitaminosis D to the pathogenesis of key cardiovascular risk factors such as diabetes mellitus, arterial hypertension, lipid metabolism disorders, as well as the onset of vascular calcifications, intimal thickening, ventricular hypertrophy, and thrombotic process regulation [83,84]. Vitamin D regulates nitric oxide (NO) production, lowers tissue factor and down-regulates the pro-thrombotic plasminogen activator inhibitor 1 and thrombospondin-1, while upregulating thrombomodulin [85]. The effects of this modulation can be seen on the renin-angiotensin system, inflammatory cytokines, glycemic control, vasculature, regulation of PTH levels, and calcium deposition in vascular smooth muscle [86].

Some observational studies also suggested an inverse association between 25-hydroxyvitamin D levels and clinical cardiovascular diseases events [87]. During the winter and in regions with less solar UV-B exposure, when vitamin D levels are known to be at their lowest due to lack of sunshine, higher cardiovascular death rates were reported [88]. Low vitamin D levels (<20 ng/ml) have been independently linked to increased morbidity and mortality [86,89].

### 3.2. Link between COVID-19 and diabetes

In the COVID-19 pandemic, diabetes was one of the leading comorbidities associated with infection severity [90]. Diabetes is characterized by hyperglycemia caused by impaired insulin secretion or action. More than 425 million individuals have diabetes worldwide and is expected to increase to 629 million by 2045 [91]. Diabetes is one of the high-risk factors for mortality of COVID-19 infections [90]. COVID-19 infection

in diabetic patients poses cerebrovascular and cardiovascular complications [92]. Individuals with diabetes are more susceptible to infections [93]. On a comparative note, a two-fold increase in ICU admissions was reported in COVID-19 infected patients with diabetes comorbidity [94].

Susceptibility and complications of COVID-19 infection in patients with diabetes was strongly correlated. For an instance, the outcomes of a small cohort study from Wuhan, China indicated approximately 20% of the COVID-19 patients suffered from diabetes [95]. In a comprehensive study based on clinical findings from nearly 575 hospitals in China, it was evident that the clinical outcomes were poor in COVID-19 patients, and required ICU and ventilator support, when the patients had multiple comorbidities. Here, out of the 1590 patients, the dominant comorbidities were hypertension (16.9%) and diabetes (8.2%) [96]. A study from Italy showed that more than two-thirds of the COVID-19 patients who died, had diabetes as a co-morbid condition [97]. Another hospital-based study from Italy indicated 8.9% prevalence of diabetes among the 146 patients admitted with COVID-19 infection (mean age of 65.3 years) [98]. In a cohort study from New York between March 2020 and April 2020, about 51.9% of patients among the 5279 COVID-19 patients, needed hospitalization, and were associated with different comorbidities such as, cardiovascular disease (70.6%), diabetes (34.7%), and chronic renal disease (21.2%) [99].

All these findings point to (a) the need for risk stratification of severe infection and its complications based on pre-existing comorbidities, and (b) effective management of both the primary infection as well as the comorbidities. For the latter aspect, multi-pronged approach using diet and drug regimen is suggested.

#### 3.2.1. Dual benefit of Vit D supplementation in COVID-19 patients with diabetes

Vitamin D offers a variety of non-skeletal benefits. Vitamin D has been demonstrated to be important in maintaining the function of islet cells. Vitamin D receptor (VDR) targets include the pancreas. It boosts insulin sensitivity as well as insulin synthesis. Low vitamin D levels have been linked to an increased risk of type 2 diabetes mellitus and complications such as diabetic nephropathy [100,101]. Vitamin D receptors (VDR) are expressed in almost all cells of the immune system. Vitamin D is involved in the innate immune response to infections. When pathogens activate VDR, several antimicrobial factors and signalling molecules are activated (including cathelicidin, CD 14, nucleotide oligomerization domain protein 2 (NOD 2) [102]. According to epidemiological studies, vitamin D3 plays a vital role in viral respiratory tract infections (RTIs) and associated acute lung damage [51]. ACE2 is a carboxypeptidase normally involved in the cleavage of Angiotensin I and Angiotensin II and is the main receptor for SAR-COV-2 to infect cells playing a determinant role in viral entry and clearly explaining both the transmissibility and severity of COVID-19 among humans [103]. ACE2 is altered in patients with chronic diseases, due to metabolic alteration, therefore increasing the chance of infection and the severity of this disease in these patients [104].

Type II Diabetes is associated with low 25(OH)D plasma levels [105]. This is frequently linked to a higher risk of metabolic syndrome, hypertension, and heart disease [106]. Insulin resistance, which is commonly associated with low vitamin D levels, could be one of the main causes [107]. The use of metabolic markers in observational and interventional investigations has been well documented. Vitamin D had a beneficial effect on metabolic markers in 10 of 14 intervention studies [108]. Human pancreatic cells are known to have vitamin D receptors, 1-hydroxylase activity, and vitamin D - induced activation of insulin gene transcription, which all offer testimony to vitamin D's participation in insulin secretion and function [109,110]. Higher vitamin D3 levels in the blood are associated with a lower risk of microbiological infections and fatalities from RTIs, including pneumonia and influenza. Normal serum vitamin D3 levels may prevent SARS CoV-2 infection and reduce severity and death [111]. Taken together, Vit D supplementation for COVID-19 patients with diabetes comorbidity would be beneficial.

### 3.3. Link between COVID-19 and obesity (Complications of cytokine storm and thrombosis)

Obesity is a global public health issue that has reached epidemic proportions [112], with annual costs of more than $91 billion. Obesity also plays a role in the development of other chronic diseases, such as cardiometabolic diseases and several types of cancer [113]. It may seem odd that COVID-19 which is a transmissible disease has much closeness with obesity which is a non-communicable disease! Apart from various consequences, obesity decreases lung function, reduces forced expiratory volume, and reduces forced vital capacity [114]. Obesity, like viral infections, causes persistent local and systemic inflammation as well as chronic immune activation (IA), resulting in immune cell dysfunction and reduced immunity. Obesity and inflammation are linked to a variety of non-communicable conditions such as type 2 diabetes, cancer, and atherosclerosis [115].

Obesity, as a result, has been identified as a new risk factor for COVID-19 patients [116]. In addition, compared to lean controls, the prevalence of the disease and the occurrence of complications are higher in obese people. Obesity or obesity-related comorbidities, and severe outcomes of COVID-19 have all been found to be strongly linked [117]. Individuals with a BMI >30 were more likely to be admitted to acute and critical care, compared to those with a BMI <30, according to retrospective studies of adult COVID-19 symptomatic patients [118]. Obese people may have a poor response to diseases, vaccinations, and medicines. Obesity-related immune system dysregulation may potentially lengthen the duration and magnify the magnitude of metabolic stress. It is widely known that immune cells penetrate fat adipose tissue (AT), fueling local inflammation and exacerbating inflammaging. AT causes the release of additional pro-inflammatory mediators in the thorax and abdomen, which can damage lung function even further [119,120]. Following SARS-CoV-2 infection, infiltrating immune cells become activated and contribute to the release of inflammatory mediators. Another major health issue is that the AT may act as a 'viral reservoir', allowing local and systemic inflammation and immunological dysfunction to persist [121]. A cohort study from France found that the patients with severe obesity (BMI >40 kg/m2) with COVID-19 infection are more likely to need invasive mechanical ventilation, independent of age, hypertension, and diabetes [122].

#### 3.3.1. Dual benefit of Vit D supplementation in COVID-19 patients with obesity

ACE is widely distributed in human cells, including adipocytes [123]. ACE2 overexpression and angiotensinogen secretion has been studied in adipocytes in both humans and experimentally induced obesity [124]. The angiotensin type 1 (AT1R) and type 2 (AT2R) receptors may modulate lipid metabolism by upregulating lipogenesis in adipocytes (mediated via ATR2) and by downregulating lipolysis (mediated by AT1R) [125]. Aberrant RAS pathways are implicated in obese patients with hypertension [123].

In a study, obesity (BMI >30 kg/$m^2$) was observed in 47.6% of ICU patients with SARS-CoV-2, and severe obesity (BMI >35 kg/$m^2$) was found in 28.2% patients [122]. In the latter condition, 85.7% needed invasive mechanical ventilation, 50% had hypertension, and 80% of the patients required ventilator support. Obesity is a risk factor for a severe course of the disease. This is supported by a study which showed that when compared to normal weight individuals, overweight patients (BMI 24–27.9 kg/$m^2$) had an 86% higher risk of acquiring pneumonia, while obese patients (BMI >28 kg/$m^2$) had a 142% higher risk of developing pneumonia [126].

A recent review [127] brought out the nexus between hyper-inflammation and underlying chronic inflammation, leading to severe complications such as 'cytokine storm' and thrombosis during COVID-19 infection. It was suggested that the largely undetected chronic inflammatory condition (induced by pre-existing chronic gut/respiratory/systemic inflammation) may predispose the individuals

to hyper-inflammation in the event of a viral infection (COVID-19, influenza), and that this can be mitigated by dietary interventions such as reduction in food that promote chronic inflammation, and those that promote healthy gut microbiome. Other than smoking habit, and environmental pollution related promoters of chronic inflammation, obesity is regarded a potential cause (and consequence) of chronic inflammation, which has been documented to worsen the disease complications in COVID-19 (and other respiratory infections such as pneumonia, influenza, HIN1 infection), based on the immunosuppressed and hyper-inflammatory state in obesity-induced altered innate and adaptive immunity [128]. In another review that discussed several reasons that potentially point out to obesity as a risk factor for COVID-19, the alteration of the physiological microbiota, gut-lung axis and immune response in obesity, was suggested to result in poor anti-viral responses in obese patients [129]. With the growing prevalence of obesity, managing this comorbidity along with a viral infection poses an additional challenge in developing effective treatment.

Considering the protection offered by Vit. D in obesity and viral/respiratory infections independently as outlined above, the supplementation of this vitamin is expected to provide adequate immunity against COVID-19 and such viral infections, and particularly preventing their complications, in obese patients.

### *3.4. COVID-19 and Kawasaki Disease*

Kawasaki Disease (KD) that primarily affects infants and children under five years of age, is an acute and rare self-limiting vasculitis disease, with coronary artery aneurysms as its main complication [130]. In some cases, the patient might have haemodynamic instability, a condition known as Kawasaki disease shock syndrome (KDSS) [131]. In the current COVID-19 scenario, there have been clinical findings from some countries that have reported a small population of children suffering from the Kawasaki disease who were infected with COVID-19. This comorbid condition is clinically significant considering that COVID -19 did not affect the younger population in large numbers – in USA only 1.7% of the population younger than 17 years are affected by COVID-19 [132], and 2% of children in UK [133]. Italy reported a strong connection between the COVID-19 incidence and Kawasaki disease [134]. A recent review also highlighted the association of this viral pandemic with KD and another category of KD-like clinical symptoms in paediatric patients, based on several global reports [135].

In the context of the reviewed metabolic comorbidities here, it is relevant to mention the connect between this autoimmune disorder and metabolic syndrome. Zhang et al. [136] found an association between circulating adipokines (chemerin, omentin-1, adiponectin) and acute Kawasaki Disease, which correlated with early inflammation and lipid disorders seen in Kawasaki disease, that in turn coincides with the risk factors of metabolic syndrome (obesity, diabetes, cardiovascular diseases).

#### *3.4.1. Dual benefit of Vit D supplementation in COVID-19 patients with Kawasaki Disease*

In a study conducted in Italy by Stagi et al. [137], low serum concentrations of 25(OH)-vitamin D were implicated in developing coronary artery complications in children with KD. In another hospital-based study from South Korea on 91 patients with KD [138], vitamin D deficiency was correlated with resistance to intravenous immunoglobulin therapy in KD patients. Here, the anti-inflammatory role of vitamin D was indicated, and consequently, the potential of vitamin D in the prevention and treatment of Kawasaki Disease was suggested. In a population-based German Paediatric Surveillance Study, medical data of nearly 308 patients with KD was analysed that revealed protective effects of vitamin D supplementation (and breastfeeding). Although these interventions could not influence the natural course of the disease, the study reiterated the overall benefit of vitamin D supplementation and breastfeeding [139].

In a clinical study from Japan, Kudo et al. (2012) reported the modulatory effect of Vitamin D in controlling the inflammatory effects of TNF-α induced expression of vascular cell adhesion molecule (VCAM)-1, and IL-8 production, in Kawasaki disease [140]. The role of 25(OH)-vitamin D in mitigating the cardiovascular inflammatory damage is emphasized here, and the potential benefit of ensuring vitamin D sufficiency in this subset of COVID-19 afflicted children with Kawasaki disease. In a very recent clinical trial study (VITAL) consisting of 25871 participants, supplementation of vitamin D (with or without omega 3 fatty acids) for 5 years, resulted in decrease in several autoimmune diseases by 22% [141].

Taken together, these findings point to the beneficial effect of vitamin D supplementation in offsetting the COVID-19 associated complications in patients with autoimmune disorders.

## 4. How can vitamin D be administered (supplements and food sources)?

Commercially, vitamin D2 is produced by ultraviolet irradiation of ergosterol from yeast. Lanolin is used for the production of Vitamin D3 by the ultraviolet irradiation of 7-dehydrocholestrol. Both forms of vitamin D ($D_2$ and $D_3$) are available as vitamin D supplements. Further, for patients with renal diseases, 1,25(OH)2D is particularly indicated, while 25(OH)D is useful when hepatic hydroxylation of vitamin D is impaired.

For improving and maintaining adequate serum 25(OH)D levels, whether the vitamin $D_2$ (ergocalciferol) or vitamin $D_3$ (cholecalciferol) is more efficacious remains uncertain. Several studies have proved equivalence between the two forms [106,142]. However, in other studies, vitamin $D_3$ is more effective than vitamin $D_2$ in raising and maintaining higher serum 25(OH) D levels [143]. Preparations containing only vitamin D are available for those who have no need for supplementations with other vitamins. In addition to these, there are different preparations available that have combinations of vitamin D with other vitamins (multivitamin preparations). Vitamin D is commercially available at various dosage forms including capsules (oil-and water soluble), tablet, concentrates, chewable, and gummy forms, sprays, injections, and oral drops, as the only dosage form available for infants [144].

Fatty fish, red meat, eggs, and wild mushrooms are few food sources naturally high in vitamin D. Fortified foods are another source of dietary vitamin D; for instance, vitamin D is added to milk, infant formula, some bread products, orange juices, cereals, yogurts, and cheese in the United States and Canada [145,146]. The most effective and controlled way to prevent and treat vitamin D deficiency is vitamin D supplementation. Table 2 depicts the various sources of vitamin D and its supplements.

The differential RDA and tolerable upper levels in each age group, as well as certain clinical and geographical circumstances would determine vitamin D intake and supplementation [151]. Thus, RDA of 600-800 IU/day was recommended to maintain adequate level of vitamin D according to a study on North American population [152].

## 5. Vitamin D supplementation in combination with other nutraceuticals or drugs

Hypovitaminosis D predisposes people to diseases/disorders that include metabolic derangements, cellular stresses and immune compromises which in turn leads to a variety of conditions such as metabolic syndrome, aging related issues and susceptibility to infections. Here, the correction of vitamin D deficiency, along with suitable supplementation of other micronutrients and anti-oxidants in combination has been reported to be beneficial [153]. These factors also point towards a protective potential that vitamin D supplementation can exert in the current management of COVID-19 along with comorbidities [111].

### 5.1. Vitamin D supplementation with Glutathione

A viewpoint published recently in the context of present pandemic and available literature hypothesized that glutathione deficiency could potentially increase the disease complications in COVID-19 patients due to increased viral replication, oxidative damage of the lungs and hyper-inflammation [154]. The basis of this conjecture was that the common causes of glutathione depletion/deficiency, such as chronic diseases like diabetes and obesity, cigarette smoking, older age and sex (males) were also risk factors for COVID-19 complications. Another review article [155] also provided mechanistic link for the potential benefits of glutathione on the inflammation caused by imbalance of ACE/ACE2. Future clinical studies are warranted to examine the GSH levels in COVID-19 patients, so that the susceptible populations (comorbidities such as metabolic syndrome, old age) with glutathione deficiency associated diminished antioxidant status are better protected against the adverse inflammatory complications of COVID-19.

### 5.2. Vitamin D supplementation with N-acetyl cysteine

In an interesting work reported by Jain et al. [156], glutathione (an antioxidant tripeptide consisting of glutamate, cysteine, and glycine) was correlated with increased Vitamin D bioavailability, lowered oxidative stress and inflammation. They suggested that supplementing a combination of Vitamin D and L-cysteine (or glutathione precursor), rather than only Vitamin D supplementation, was more beneficial in reaching the required Vitamin D levels, especially in patients who do not respond well to vitamin D supplementation warranting higher supra-physiological dosages. Thus, this approach would also pre-empt very high doses of vitamin D.

### 5.3. Vitamin D supplementation with vitamins C, B12, and minerals zinc, magnesium

It has been recently suggested that supplementation of Vitamin D along with Vitamin C and Zinc can be a strategy to capitalize on the synergies of these nutrients in not only boosting immune defence, but also in maintaining the physical integrity of the biological barriers (through intact tight and adherens junction protein complexes). The breakdown of mucosal epithelial cells can be a gateway for pathogen entry (such as SARS-CoV-2), hence their integrity must be maintained for which these nutrients can contribute in a synergistic manner [157]. When using vitamin D supplements, magnesium supplementation is recommended. Magnesium helps in the activation of vitamin D, which in turn aids in the regulation of calcium and phosphate balance, influencing bone growth and maintenance. Magnesium is required by all enzymes that metabolise vitamin D, as it serves as a cofactor in enzymatic activities in the liver and kidneys. The magnesium dose should be between 250 and 500 mg per day, with twice that amount of calcium [158].

Multiple micronutrients supplementation to protect against infections have been suggested, wherein vitamins C and D, as well as zinc and selenium [159,160], were indicated as the promising candidate micronutrients in conferring immunity. Well-designed clinical studies focusing on optimal dosages, and nutrient combinations, in different populations, would help substantiate the benefits of such micronutrient supplementation as safe and cost-effective approach to managing infections. A combination of vitamin D with magnesium and vitamin B12 tested in older COVID-19 patients was found to significantly reduce the proportion of patients with clinical complications such as requirements of oxygen support and intensive care support [161].

Prasad et al. reported zinc deficiency in malnourished individuals with hepatosplenomegaly, dwarfism, hypogonadism, along with an increased risk of infection, way back in 1963. Now, the multiple biochemical roles of Zinc are well known, ranging from being a catalytic cofactor of several enzymes, to driving cellular processes, RNA and DNA synthesis. While it requires further clinical trials to be conclusive, yet there is ample evidence that links Zinc deficiency with risk of pneumonia in the elderly, prolonged duration of the disease and antimicrobial treatment, and mortality, which in turn points to possible protection from Zinc supplementation [162]. In the context of the present COVID-19 pandemic, Zinc supplementation was suggested as a possible treatment for people with zinc deficiency, who develop severe pneumonia due to COVID-19 [163].

The anti-viral role of Zinc was reviewed by Read et al. [164], where they broadly categorized its anti-viral actions (including corona virus and others) into two aspects: (i) zinc supplementation to improve the anti-viral response and systemic immunity in patients with zinc deficiency, and (ii) zinc treatment in order to directly inhibit viral replication, or infection-related symptoms.

Autoimmune diseases (AID), where immune cells attack self cells and tissues, afflict nearly 5 – 8% of world population, and there is particularly alarming increase in the incidence of type 1 diabetes mellitus, rheumatoid arthritis, multiple sclerosis, Sjogren's syndrome and Crohn's disease. In this context, a comprehensive review and analysis of current literature by Wessels and Rink [165] suggested significant advantage of nutrition-based approaches (prevention and treatment of disease), using vitamin D and Zinc, which would be more cost-effective, and would also offer an alternative strategy of 'balancing', rather than 'suppressing' of the immune system.

### 5.4. Vitamin D in combination with drugs

Using transcriptomic data-based bioinformatics approach, the potential role of Vitamin D in controlling the cytokine storm was suggested through possible mechanisms that include inhibition of pro-inflammatory cytokine production (by blocking TNF induced NFkB1 signaling pathway), and by promoting the anti-viral defences via induction of interferon-stimulating genes through IFN-alpha induced Jak-STAT signaling pathway activation [166]. This study pointed out to the potential combination therapy of Vitamin D with IFN-alpha (the well-known anti-viral treatment) in combating the cytokine storm adverse complication of COVID-19. Another approach to curtail the cytokine storm was suggested by Pinheiro et al. [167] wherein, combination therapy of Vitamin D with a known class of anti-diabetic/anti-hyperglycaemic drugs, dipeptidyl peptidase 4 inhibitors (DPP-4i), seemed promising particularly in COVID-19 patients with comorbid diabetes (and other metabolic syndrome conditions such as cardiovascular diseases).

Manson and Bassuk in their commentary published in the wake of the current COVID-19 pandemic, clearly substantiated vitamin D as an easily modifiable risk factor for protection against COVID-19, and indicated that while several clinical trials are underway to address this, there is no doubt that vitamin D sufficiency is a prudent preventive health measure [168]. On similar lines, another review published in 2020 [169] pointed out the advantages of vitamin D as an inexpensive adjuvant-therapy with relatively lower risks for managing infections and other diseases effectively, at least in vitamin D insufficient/deficient populations. Further they pointed out that larger trials will be required. COVIT and VitCov are recent examples of multicentric controlled clinical trials in France and Switzerland respectively, probing the utility of vitamin D in COVID-19 management [170,171].

Identification of general populations as well as specific categories with high risk of vitamin D deficiency (for instance, critically ill patients) will aid public health measures that can include nutritional and nutraceutical supplements. In a randomized interventional clinical trial in a hospital in India (number of COVID-19 patients recruited: 130, completed: 87 patients), patients received pulse D therapy (daily supplementation of 60,000 IUs of vitamin D) in combination with standard treatment. The study concluded that the vitamin D level was significantly increased in the treated COVID-19 patients from $16 \pm 6$ ng/ml to 80-100 ng/ml with a concomitant reduction in the inflammatory

markers associated with the COVID-19 [172].

A small cohort trial (SHADE) reported that a high oral dosage of vitamin D for seven days increased the vitamin D level significantly from 8.6 to 42.4 ng/ml in COVID-19 patients, along with a considerable reduction in fibrinogen levels, minor reduction in CRP, and early viral clearance [173]. Another trial involving oral administration of high dose of calcifediol decreased the severity of COVID-19, the need for ICU stay, and mortality [174]. Mortality among elderly patients in a nursing home in France who received an oral bolus of vitamin D (80 000 IU) was found to be significantly lower than those who did not receive vitamin D [175]. A large cohort clinical trial of more than 1000 patients enrolled is underway in Cordoba, Spain (COVIDIOL) to test the efficacy of Vit. D intervention in COVID-19 patients [176]. The intervention group is given the best available therapy plus oral calcifediol (0.532 mg = 21,280 IU on day 1, 0.266 mg = 10.640 IU on days 3, 7, 14, 21, and 28), whereas the control group is given only the best available treatment. The endpoints being evaluated are: i) ICU admission and mortality, ii) patients admitted to ICU with ventilator support, and the duration of ventilator support requirement. Such clinical trials will evaluate the protective efficacy of vitamin D as adjunct treatment against COVID-19 (and other viral infections) and associated inflammatory complications.

## 6. Conclusions

Several research reports and clinical trials clearly point to the benefit of alleviating vitamin D insufficiency as a protective measure to combat viral infections including, COVID-19. The devastating inflammatory scenario that was observed in severe COVID-19 infection calls for effective tackling of the inflammatory and oxidative stress parameters. The multifaceted biological actions of vitamin D further support its supplementation in managing pre-existing co-morbidities such as obesity, diabetes, cardiovascular disorders and certain auto-immune disorders. There is growing evidence for combining vitamin D with other nutrients or drugs as adjunct treatment in managing viral infections and their severity. Mentioning Vitamin D as a specific anti-viral nutrient, Calder [73] clearly linked nutritional inadequacy to vulnerability of contracting infections and developing complications during infections, which is a lesson not only for the current COVID-19 pandemic, but also for our future preparedness against infections and non-communicable diseases. In this context, supplementing combinations of vitamin D with other nutrients may be a promising approach.

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## Author contributions

SKM: original draft, data curation and illustrations, formal analysis. MT: data curation and analysis, review and editing. PRD: conceptualization, data curation and analysis, reviewing and editing.

## Author declarations

Authors declare no conflict of interest.

## Authorship statement

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Conception and design of study: Sumit Kumar Mandal; P R Deepa; acquisition of data: Sumit Kumar Mandal; Meghana Tare; P R Deepa; analysis and/or interpretation of data: Sumit Kumar Mandal; Meghana Tare; P R Deepa.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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