Vitamin D Supplementation Could Potentially Reduce Risk of COVID-19 Infections and Deaths

Jing Qin Tay[1], Ajay L Mahajan[2], and M Julie Thornton[2]

[1]Bradford Teaching Hospitals NHS Foundation Trust
[2]University of Bradford

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Abstract

Vitamin D has long been known to be a major regulator for both the endocrine and the immune system. With the advent of COVID-19 pandemic, there has been a growing interest in looking at the feasibility of using vitamin D as a preventative and therapeutic option in the management of the disease. A low serum level of vitamin D is linked to higher incidence of respiratory tract infection and disease progression. Vitamin D supplementation has proven to be effective in enhancing the immune system, strengthen lung epithelial barrier, and prevention of unchecked inflammatory response. Previous studies on the roles of vitamin D in managing influenza and other enveloped virus infection could shed light on the possible roles of vitamin D in the current pandemic. More randomised controlled trials are needed to explore the effects of vitamin D supplementation on COVID-19 infection.

Review Criteria:

Papers published in the MEDLINE and EMBASE databases were reviewed for evidence relating viral and respiratory tract infections to vitamin D deficiency; the effects of vitamin D supplementation on the immune and inflammatory responses; and ongoing trials on the use of vitamin D in managing COVID-19 illness. The findings were discussed and dose recommendation for vitamin D supplements summarised.

Message for the Clinic:

Vitamin D could be a readily accessible and cost-effective adjuvant therapy for COVID-19 that deserves further research.

Introduction

The outbreak of COVID-19 started at Wuhan City of China in December 2019. It has spread at a remarkable speed to countries all around the world. There is now a race to find an effective vaccine and therapy. COVID-19 is an enveloped, single-stranded, positive-sense RNA virus, which belongs to the coronavirus family. The crown-like appearance of COVID-19 is due to the presence of spike glycoproteins on the surface envelope(1). It is the seventh member of the coronavirus family that is able to infect humans(2). This virus is phylogenetically related to previously known severe acute respiratory syndrome coronavirus (SARS-CoV)

and the Middle East respiratory syndrome coronavirus (MERS-CoV)(3). Symptoms associated with COVID-19 are fever, persistent dry cough, breathlessness and lethargy; with a minority of patients suffering from headache, haemoptysis, diarrhoea, erythematous rash and urticaria(4-6). Severe cases of COVID-19 may progress to pneumonia, acute respiratory distress syndrome (ARDS) and multi organ failure(4). In terms of mortality rate, COVID-19 ranked the third in the family of coronavirus related death, compared to MERS-CoV with a reported mortality rate of 37% and SARS-CoV of 10%(5). To date, there are over four millions confirmed cases of COVID-19, with a fatality rate of just over 300,000(7). At present, there is no definitive therapy for COVID-19. Most of the therapeutic options come from previous experience in managing SARS and MERS epidemics. Different regimes have been proposed, including the use of type 1 interferon (IFN-I), hydroxychloroquine, Ritonavir/lopinavir, Remdesivir, and neutralising antibodies (Nabs)(8).While waiting for the development of an effective vaccine, there has been ongoing research looking at alternatives that may help in the management of COVID-19 patients. Vitamin C, vitamin D, and Zinc have all been investigated as potential adjuvant therapies(9, 10).

Vitamin D in particular, has been in the spotlight recently. The prevalence of vitamin D deficiency is increasing, with some studies labelling it as a pandemic(11, 12). There is now an abundance of evidence in the literature highlighting the consequences of vitamin D deficiency, and its association with a variety of acute and chronic illnesses including autoimmune disease, cardiovascular disease, cancers, diabetes mellitus and neurological disorders(13, 14). Traditionally, vitamin D is known as the "sunshine vitamin", sunlight being the main source. 7-dehydrocholesterol in the skin is converted to cholecalciferol. It then undergoes further hydroxylation in the liver and kidney before becoming the biological active form, 1,25-dihydroxyvitaminD ($1,25(OH)_2D$), also known as calcitriol(15). $1,25(OH)_2D$ activates the vitamin D receptor (VDR), which is a nuclear receptor, to exert its functions. It is now known that VDR is highly expressed in most cell types, suggesting the myriad of regulatory roles vitamin D plays in maintaining healthy functioning of our body(16) (Figure 1). In particular, there is strong evidence supporting the role of vitamin D in regulating the immune system(17).

Unfortunately, sunlight alone is a not a reliable source of vitamin D, especially among those living at high latitudes, ethnicity with darker skin colour and the institutionalised population(18). In high human density habitations, a lack of open spaces and high pollution has led to a decrease in direct sunlight exposure(18). To counteract this problem, vitamin D supplementation has been recommended. Research studies have shown that vitamin D supplement is effective in raising serum level of vitamin D(19, 20). Vitamin D supplement helps to strengthen the immune response and plays a vital role in respiratory illness prevention, among its many other health benefits(17, 21). This paper discusses the roles of vitamin D in reducing the risk of viral infections and mitigating the severity of disease progression. More importantly this paper investigates the feasibility of using vitamin D as an adjuvant therapy in alleviating some of the symptoms associated with pneumonia and acute respiratory distress syndrome (ARDS) that lead to a poorer outcome among COVID-19 patients. This paper also discusses whether vitamin D could play any role in reversing disease progression and the prevention of COVID-19 in the general population.

Methods

We conducted a review of the evidence relating viral and respiratory tract infections to vitamin D deficiency. We searched for papers investigating the effects of vitamin D supplementation on the immune and inflammatory responses. Finally, we reviewed all articles related to COVID-19 and registered trials on the use of vitamin D in managing COVID-19 illness. All relevant entries on MEDLINE and EMBASE databases up to May 2020 were included in the discussion.

Vitamin D Reduces Risks of Viral Infection by Enhancing The Immune Response and Maintaining Integrity of Epithelial Barriers

Vitamin D is a fat-soluble steroid hormone(22). Vitamin D modulates both the innate and adaptive immune response(23-26). In the context of disease prevention, vitamin D enhances macrophage activation, phagocytic response and production of antimicrobial peptides to stimulate the innate immune response(17, 27). It is known that vitamin D can suppress the infectiveness of a variety of enveloped virus such as the Ebola, Epstein-Barr and Hepatitis C viruses(28).Vitamin D's anti-viral mechanism is mainly attributable to its effects in the upregulation of anti-microbial peptides such as cathelicidins (LL37) and human beta defensins 2(28). Cathelicidins and defensins act by perturbing the cell envelope of the virus, binding lipopolysaccharide residues of commensal bacteria, and inhibiting viral adhesion and entry(29-33). Lymphocytes, macrophages and dendritic cells all express the necessary enzymes that can metabolise vitamin D to its biological active form(34, 35). They are also important target cells for vitamin D as VDR is highly expressed in these cell types(35, 36). By regulating both T and B cells maturation and proliferation, it plays a pivotal role in mounting an immune response against viruses(34). Vitamin D also protects the integrity of epithelial cells lining the respiratory tract and stimulates epithelial repair, thereby alleviating lung injury associated with pneumonia that commonly complicates COVID-19 infection(37-39).

Vitamin D deficiency is common among acquired immune deficiency syndrome (AIDS) patients(40). Research study on a group of AIDS patients showed an increased mortality rate in patients who are vitamin D deficient(41, 42). The HIV virus mainly targets cluster of differentiation 4 (CD4) found on the surface of immune cells such as T helper cells, monocytes, macrophages and dendritic cells(43). The HIV virus damages and destroys these infected cells, causing a gradual depletion in CD4 positive cells, leading to immunological failure(43). There are studies which showed that vitamin D has a positive impact on improving the CD4 count in HIV patients(44). A longitudinal study in 2018 concluded that a high serum level of 25(OH)D is associated with increased CD4 count and reduces infection severity in HIV patients(45). This suggests that vitamin D supplements can enhance the recovery of human immune system. Even in AIDS patients, vitamin D supplementation has been shown to increase the level of circulating vitamin D and therefore lower the risks of bone disease and inflammation(40, 46). The use of vitamin D supplementation in HIV patients have been reported to increase the immune response against pathogens, improve immunologic recovery during combination antiretroviral therapy and reduce levels of inflammation(47, 48). Furthermore, vitamin D supplementation has been shown to reduce HIV and Hepatitis C susceptibility by inhibiting viral entry into human cells(49-52). With regards to COVID-19, vitamin D supplementation has been shown to reduce human dipeptidyl peptidase-4 receptor (DPP-4/CD26) expression(53). As DDP-4/CD26 is a receptor that interacts with the S1 domain of the COVID-19 spike glycoprotein for cell entry, vitamin D supplementation could potentially reduce the virulence of COVID-19 in humans(54, 55).

Vitamin D Reduces Risk of Respiratory Tract Infection

COVID-19 infection shows similar properties to the Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS)(2). However, from an epidemiology perspective, COVID-19 is far more contagious than SARS-CoV and MERS-CoV, with confirmed cases far exceeding the latter two combined(2, 56). COVID-19 involves respiratory tract illness ranging from mild, moderate to severe forms(57).

Research has shown that vitamin D deficiency is a predisposing factor in respiratory tract infection (RTI)(58). RTI affect the majority of the world population. It is also the one of the main causes for hospital admission as it can progress into moderate to severe pneumonia(59, 60). One of the main predisposing factors for developing RTI is partial or full impairment of the immune system. Vitamin D is recognised to regulate innate and adaptive immune system by stimulating the production of antimicrobial peptides in the event of viral or bacterial infections(28). Several studies have concluded a positive correlation between low serum level of vitamin D with a higher incidence and severity of lower respiratory infection in both adults and

children(61-65). There are also studies which showed that vitamin D supplement helps to lower the rate of development of lower respiratory tract infection, especially in winter when there is a scarcity of sunlight(66, 67). However, there are some studies which showed no beneficial effects of short-term bolus doses of vitamin D supplement on the incidence and resolution of pneumonia(68-70). The mixed findings may be explained by different ages at study enrolment and severity of pneumonia, with children at the younger extreme of age having not fully developed immune system associated with poorer outcomes(61). A large European study has also shown that correcting serum level of 25(OH)D has beneficial effects on prevention of RTI and reducing disease severity in adults(71). A randomised controlled trial in Japan looking at the effects of vitamin D supplement on prevention of seasonal influenza A showed that taking 1200 international units (IU) of vitamin D per day has a 58% relative risk reduction of influenza A incidence in school children compared to the placebo group(72).

Epidemiological and observational studies have linked vitamin D deficiency with the spread of RTI and other infectious diseases(63, 73-76). It has been seen that vitamin D deficiency is common among children below the age of five, which coincides with the prevalence of lower respiratory tract infection (LRTI), respiratory syncytial virus (RSV), and related human metapneumovirus (hMPV) infections(77). Reviews of serum vitamin D levels among the paediatric population in America shows a correlation between low serum vitamin D with LRTI and RSV severity(78). Another large scale study of the paediatric population in Middle Eastern countries further showed that children who have a low serum level of vitamin D are usually tested positive for RSV infection(79). There are studies which suggested that vitamin D deficiency is an important predisposing factor for developing community-acquired pneumonia and stroke-associated pneumonia (SAP)(80). A low serum level of vitamin D is associated with poorer disease progression in all types of acquired pneumonia including viral pneumonia, streptococcal pneumonia, and Legionella pneumonia(81). Granulomatosis with polyangiitis is an autoimmune disease characterised by vasculitis that primarily affects the respiratory tract and the kidneys. Vitamin D deficiency has been shown to be an important risk factor for RTI in this group of patients(82). The effects of vitamin D on lung immunity and respiratory diseases are well established(83).

Vitamin D Prevents the Maladaptive Cycle of Local Inflammation and Secondary Injury that Leads to Poorer Outcomes

A recent large-scale epidemiological study suggested a possible link between vitamin D deficiency and the severity of COVID-19 cases among patients in the USA, France and the United Kingdom(84). This study correlated the low serum level of vitamin D with a higher C-reactive protein (CRP) level in COVID-19 patients based on previous findings(85, 86). In fact, multiple observational and intervention studies have suggested the beneficial effects of vitamin D on reducing circulating CRP and pro-inflammatory cytokines(86-90). This has a beneficial impact in lowering a heightened inflammation state that is associated with poorer outcomes(91-93). Vitamin D also modulates the renin-angiotensin cascade(94). A high expression of angiotensin converting enzyme (ACE) and angiotensin II, coupled with reduced expression of angiotensin converting enzyme 2 (ACE2) are common features in a pro-inflammatory state in acute respiratory distress syndrome (ARDS). Vitamin D reduces the susceptibility to acute lung injury (ALI) by inhibiting renin thereby angiotensin II biosynthesis(95-98). This may have a protective effect in preventing a “cytokine storm” that is often implicated in severe COVID-19 cases(84, 99).

Vitamin D also enhances the production of interleukin-10 (IL-10), a cytokine with potent anti-inflammatory properties(100). Increasing IL-10 favours the proliferation and differentiation of T helper cell 2 (Th2) and T regulator (T reg) cells over T helper cell 1 (Th1) and T helper cell 17 (Th 17) (101, 102). This could have an effect in promoting tolerance and controlling an exacerbated immune response(41). Furthermore, vitamin D supplementation reduces the expression of pro-inflammatory cytokines and increases the expression of anti-inflammatory cytokines by macrophages, by enhancing expression of MAPK phosphatase-1 and suppressing p38 activation(103-105). A persistent immune activation leads to an increased mortality in HIV patient. Vitamin D protects against the development of immune reconstitution inflammatory syndrome events in

HIV patients, likely through downregulating CD38 expression on the surface of memory $CD8^+$ T cells(106, 107). Vitamin D also decreases the expression of major histocompatibility complex (MHC) class II and their co-stimulatory molecules such as CD80, thereby decreasing T cell activation with persistent antigen presentation(108). It could be posited that these anti-inflammatory properties of vitamin D could have beneficial impacts on patients suffering from severe form of COVID-19.

In animal studies, it has been shown that vitamin D can reduce the severity of coronavirus illness such as the enteropathogenic porcine epidemic diarrhoea virus (PEDV)(109). Adding 155.5μg/kg diet 25(OH)D to the feed given to weaned pigs can have a protective effect on PEDV-induced inflammation and alleviate damage to the intestinal tracts(109). This is achieved by regulating autophagy, enhancing cathelicidins production and inhibiting jejuna mucosa interleukin-6 (IL-6) and interleukin-8 (IL-8) mRNA expression, hence lessening the severity of damage(109-111). The VDR-knockout mice model has demonstrated that vitamin D has protective effects on the integrity of epithelial cells lining the respiratory tract, by reducing lipopolysaccharides-induced acute lung injury(112). These animal studies suggest that active vitamin D could be effective in reducing the severity of acute lung injury and suppress a heightened inflammatory state in COVID-19 patients.

Dose recommendation for vitamin D supplements

Unfortunately, there is no consensus on the optimal dose of vitamin D supplementation for managing viral diseases or RTI. A previous study has reported that in children suffering from recurrent respiratory tract infection, giving vitamin D supplements could reduce the number of disease occurrences in a year, with no noticeable adverse side effects, suggesting that vitamin D supplementation could be an effective adjuvant therapy in managing RTI(113). Doses ranging from 800 IU to 100,000 IU per day have been suggested(114). When using a bolus schedule, the effects seems to be smaller(115-117). Vitamin D has been shown to be beneficial in the prevention and treatment of influenza(118). Research conducted in Japan has reported that taking 1200 IU per day of vitamin D supplement could reduce the risk of contracting influenza by six fold(72). In terms of recommending dosage of vitamin D as an adjuvant therapy for influenza, it has been shown that there is a lower incidence of influenza among patients whose serum level of vitamin D is above 40ng/mL(118, 119). Besides that, by giving 50,000IU of vitamin D_3 supplement once daily or 10,000IU of vitamin D three times a day, significantly reduced the severity of symptoms in patients who suffer from influenza after a period of seventy-two hours(120).

Vitamin D supplementation should ideally be guided by serum levels of vitamin D to avoid untoward effects. Recent trials challenged whether serum vitamin D levels of [?]30 ng/mL promote human health(121). A study by Quraishi et al (2013) found that people with vitamin D levels of less than 30 ng/ml were 56% more likely to develop community acquired pneumonia than those with levels of 30 ng/ml or higher(80). A recent paper by Grant *et al* (2020) suggested taking 10,000 IU per day of vitamin D_3 for a few weeks as a loading dose, followed by 5000 IU per day as a maintenance dose, in order to raise serum vitamin D level above 40–60 ng/mL(122). Indeed, a dose of up to 4000 IU or 100 micrograms per day has been cited as a safe dose by several studies(123, 124). Public Health England (PHE) has recently recommended taking 10 micrograms of vitamin D per day as a supplement during the lockdown period(125). More randomised controlled trials and large population studies should be conducted to evaluate these recommendations(122).

Conclusion

In conclusion, the impacts of COVID 19 and its strain on the healthcare system are huge. The mortality rate is especially high in vulnerable populations that are vitamin D deficient. The situation is likely to be worse with the introduction of emergency lockdown measures that confines the population indoors. Vitamin D deficiency is prevalent among the U.K. population, with crude incidence rate increased from 0.29 per 1000

person-year in 2005 to 16.08 per 1000 person-year in 2015(126). It affects one in five people in the U.K. according to a national survey(127). In the northern hemisphere, Vitamin D deficiency is often worse over the months from October to March when there is less sunlight in the day, corresponding to a peak in the spread of COVID-19. To date there are ongoing clinical trials in the U.S. and Spain involving COVID-19 patients to establish whether taking vitamin D can help in attenuating disease progression(9). The use of vitamin D as a readily accessible and cost-effective strategy to reduce the incidence and severity of disease in COVID-19 patients is an option that deserves further consideration.

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Figure Legend

Figure 1: The metabolic pathway of vitamin D synthesis and the tissue specific cellular response it mediates that may reduce COVID-19 severity. CYP2R1, CYP27A1, and CYP27B1 are the cytochrome enzymes involve in the hydroxylation processes of cholecalciferol to the active form of vitamin D, $1,25(OH)_2D$. $1,25(OH)_2D$ then binds to VDR which forms a heterodimer with retinoid X receptor (RXR). Interaction of the heterodimer with the vitamin D response element (VDRE) leads to downstream target gene regulation.