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Role of vitamin D supplementation for prevention and control of covid-19: A review article

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Abstract
COVID-19 is a novel respiratory disease which is caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), broke out in the end of winter season in 2019 in China and became a pandemic. Characteristically there is rapid local spread and very high systemic inflammatory response in the patients. Apart from high morbidity and mortality there has been tremendous social and financial impact in the entire world. A possibility exists that maintaining vitamin D sufficiency can increase the antimicrobial activity in the respiratory lining epithelium and inhibit the exaggerated cytokine inflammatory cascade thereby promoting repair of the respiratory epithelium. To date, no definitive treatment or preventive measure is available for COVID-19 other than symptomatic and supportive care.

By various mechanisms vitamin D is antimicrobial, immuno-modulatory and anti-inflammatory. These beneficial effects can be utilized as a measure for providing protection to the community at large in outbreak situations, when the population is susceptible. There is a high possibility that vitamin D supplementation in population at risk as well the cases of COVID-19 has a key role in prevention and control.

Hence, it is believed that oral vitamin D may be helpful in population at risk and cases to prevent and control COVID-19, during and prior to the development of active disease for boosting favorable immune response and relevant trials must be conducted to test this hypothesis.

Keywords: Coronavirus, COVID-19, respiratory tract infections, SARS CoV2, Vitamin D

1. Introduction

COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) has been declared as a public health emergency of international concern by WHO [1]. It is a rapidly spreading disease involving the upper and lower respiratory tract, and has high morbidity and mortality. There is an urgent need to prevent and control the disease while no vaccine or cure is available. COVID-19 is caused by a novel virus and there is limited information about the natural history of the disease. Host defense mechanisms are known to play critical role in disease prevention and control. Researchers have suggested that vitamin D has a potential role in the prevention of respiratory tract infections by regulating the immune response. [2, 3] However the mechanisms involved in respiratory tract protection is yet not fully understood. In a recent meta-analysis, low levels of vitamin D is shown to be associated with increased incidence of acute respiratory tract infections. [2, 3] However the mechanisms involved in respiratory tract protection is yet not fully understood.

Most recently researchers from different countries found negative correlation between mean level of vitamin D with number of COVID- 19 cases and mortality and suggested intervention with vitamin D in them for better outcome. [4, 5] In this article, we attempt to explore different mechanisms by which vitamin D can improve immune functions and inflammation in various microbial infections. Hence, the authors made an attempt to review the available studies on various infective disorders to explore the potential role of vitamin D supplementation in prevention and control of COVID-19.

Methodology

The available relevant evidence / research articles were searched on various search engines

like PubMed, Medline, EMBASE, Google Scholar, and other databases to access relevant and the recent information. The main focus of the search were vitamin D deficiency, infectious diseases, infections, microbes, virus, immune cells, coronavirus respiratory infections, etc. and reviewed. Articles in English were included. The information so collected from the reviewed articles was collated, interpreted, summarized and analyzed to know whether or how vitamin D supplementation can benefit in COVID-19.

Results and Discussion

1. Immuno-modulatory and antimicrobial effects of Vitamin D

Humans have elaborate immune defense system including physical barriers, specialized immune cells, antibodies and biochemical molecules with sole purpose to attack pathogenic microbial organisms. There is a complex interaction between pathogens, innate immune cells and acquired immune cells to generate the pathophysiological response to the microbes. Vitamin D is an important nutrient playing a key role in regulation of immunity in almost every step of immune response.

Vitamin D influences more than 200 human genes responsible for skeletal and extra skeletal effects, which may be impaired when vitamin levels are insufficient. In 1980, research community demonstrated vitamin D receptors (VDR) located on immune cells including activated B and T cells [6-8]. Further shown that VDR are located on major T cell lineages and on macrophage / monocytes in the blood [9]. Recent studies have also shown vitamin D to be an inhibitor of dendritic cell maturation [10-11].

Studies have shown that lack of vitamin D can affect immune function against microbes in many ways. Even among relatively healthy individuals, vitamin D deficiency has been hypothesized to have a link with respiratory tract infections. In the study, researchers showed that 1, 25$(OH)_2$ D is a direct regulator of anti-microbial peptide gene expression, inducing cathelicidin and defensin β_2, anti-microbial peptides (AMP) in monocytes, neutrophils and human cell lines. They demonstrated that 1,25$(OH)_2$ D, alongwith LPS, synergistically induce AMP expression in neutrophils. [12, 13] The above mentioned paragraph denote that many proteins and cytokines are released during immunomodulation. These proteins have antimicrobial action. Therefore we believe a possible local and systemic effect of adequate vitamin D to fight a pathogen. Many authors support this in their research work [14].

Early evidence from reports about tuberculosis treatment with cod liver oil containing vitamin D suggested it to stimulate the innate immunity to increase the phagocytic capabilities of the innate immune cells and also activates the transcription of antimicrobial peptides such as defensin B and cathelicidin [14]. The main action of vitamin D on activated macrophages is suppression of proinflammatory cytokine production and elevation of their phagocytic ability [15]. In support of this, Chandra *et al.*, explained the shift in macrophage phenotype as an effect of vitamin D on phagocytic potential of macrophages [15].

In a recent study researchers revealed the role of vitamin D directed against COVID-19. [4] Additionally the antimicrobial peptides such as defensin and cathelicidin function like endogenous antibiotics which specifically kill the invading pathogen [16]. Cells producing these peptides are the components of the innate immune response for rapid first line defense [17]. These peptides are not only from neutrophils, macrophages and natural killer cells but also respiratory lining cells and are shown to contribute for defense against respiratory diseases [18-19].

Another mechanism suggested is impaired oxidative burst function in lack of vitamin D and the compromised release of lysosomal enzymes, acid phosphatase and H_2O_2 release which have important antimicrobial functions [20-21]. Most importantly research findings have shown that administration of vitamin D significantly triggers expression of antimicrobial peptides (AMP) in human monocytes, neutrophils and other human cell lines [22-24]. It has also been found that AMP has broad spectrum action and have been shown to inactivate influenza virus as well [25-27].

Similar reports to suggests the initial host response to the pathogen or damage by foreign bodies is challenged by the immune system. To support this, SefHansdottir *et al.* demonstrated that primary respiratory epithelial cells convert inactive vitamin D to active form. This activates vitamin D responsive genes that produce proteins important for innate immunity [5, 28].

However, in many studies, adequate vitamin D levels had been found to be associated with susceptibility to microbial infections. This has been attributed to VDR polymorphism [5, 28]. Vitamin D has been shown to induce T cell differentiation to modulate adaptive immune response favorably [29]. Activation of adaptive immune response to release IL – 1 β and TNF - α amplies the inflammatory response by stimulating release of nuclear factor kappa B (NF- κB) and activation of MAPK [30].

2. Anti-inflammatory effect of Vitamin D

Modulation of inflammatory processes with adequate vitamin D levels are shown in vitro and in vivo studies. [31, 32] It is known that activation of immune system is accompanied by cytokine release. Inflammatory cytokines TNF – α, IL-1β, IL – 6, and IL-12 are released at the early stage of innate immune response [33].

Vitamin D down-regulates these pro-inflammatory cytokines and promotes anti-inflammatory effects for tissue repair through regulating inflammation via modulating NF-κB [31, 33]. Vitamin D also reduces expression of pro-inflammatory cytokines by macrophages and at the same time it promotes expression of anti-inflammatory cytokines [34-36].

In a recent study in tuberculosis, it was shown that NF-κB activity is inhibited by vitamin D supplementation. Sufficient vitamin D causes increased degradation of NF-κB resulting in decrease in its activity [37-38].

Studies have demonstrated that vitamin D upregulates Th2 activity while downregulates Th1 promoting anti-inflammatory effects [39-41]. However this effect of vitamin D on T helper cells differentiation may be through its effect on dendritic cells by decreasing cytokines such as IL – 12 and TNF – alpha and with increased IL-10 levels [29, 42].

Increased leukocyte count and plasma pro-inflammatory cytokines level, along with abnormal respiratory findings are revealed as most likely characteristics of COVID-19. High erythrocyte sedimentation rate and D-dimer may also be observed in COVID-19 infections. According to the researches available, very high cytokines and chemokines levels had been seen among COVID-19 patients. High

levels of pro-inflammatory cytokines may be seen in some severe COVID-19 cases particularly those admitted in intensive care units [43]. This pathogenesis of SARS-CoV-2 warrants use of agents to prevent or manage such deadly stages in the disease. Beneficial effects of vitamin D as explained above are in line with the pathogenesis of COVID-19.

In an exhaustive literature review vitamin D supplementation has been shown to have potential antimicrobial effects against diseases like tuberculosis where immune function is usually compromised [44]. Also low serum vitamin D has been related with HIV / AIDS morbidity and mortality [45]. Similarly vitamin D supplementation is likely to have beneficial role in covid-19. List of infections in which vitamin D supplementation has a role are shown in Table 1. Most of these infections are acute and respiratory. This justifies to a large extent that supplementation of vitamin D for other acute respiratory infections like SARS-CoV-2 as a preventive and control measure.

Table 1: List of infections showing improved outcome with vitamin D supplementation

Serial no.	Infections
1.	Mycobacterium tuberculosis [44-49]
2.	Salmonella typhi [50]
3.	Pseudomonas aeruginosa [49]
4.	H1N1 viral infection [49]
5.	HIV [45, 49, 51]
6.	Respiratory Syncytial Virus [33, 49]
7.	Rhinovirus [33, 49, 52]
8.	Influenza virus [33, 49, 53-54]

Conclusion and recommendations

Vitamin D has antimicrobial, immuno-modulatory and anti-inflammatory roles in infectious diseases which can be utilized as a measure of providing protection to the community at large in outbreak situations when the population is susceptible. There is a high possibility that vitamin D supplementation in population at risk as well as cases of COVID-19 has a key role in preventing progression to moderate and severe disease and its control. Vitamin D sufficiency / supplementation may turn out to be an effective strategy in prevention and control of COVID-19. It is recommended that relevant trials must be conducted to test the hypothesis.

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