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Vitamin-D deficiency as a predisposing cause for COVID-19 morbidities

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ABSTRACT: The Corona virus disease (COVID-19) mortality is increasing day to day due to the presence of co- morbidities and respiratory failure. The knowledge about the protective risk factors in associations with COVID-19 is still an assumption. Vitamin D protects against acute lung injury through enhanced expression Angiotensin-Converting Enzyme-2 and low levels were associated with upper respiratory tract infections. The increase in COVID-19 mortality rates is due to microvascular thrombosis which leads to respiratory failure and death. Previous literature showed that the protective role of Vitamin D on COVID-19 in various countries, but in a country like India the association with Vitamin D deficiency and COVID-19 mortality rate yet to be ruled out. Hence present review aimed to derive the association between COVID-19 mortality and deficiency of Vitamin D in India. The present brief review enlightened the positive association of vitamin-D deficiency with COVID-19 mortality.

KEY WORDS: COVID-19 mortality, Vitamin D deficiency, Respiratory failure.

I. INTRODUCTION

Vitamin D (Calciferol) is a generic name for a group of fat steroids of which the two major forms are vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol), which undergoes metabolization from the skin by UV rays and convert to its active form i;e Calcitriol, with a pre-existing OH group which undergoes dual hydroxylation in both lungs and kidneys, is derived. Vitamin D is not only essential for maintaining bone health, but it also plays a pivotal role in several other biochemical mechanisms in the body such as immunity, cognitive function, cardiovascular & renal system & mood disorder. Vitamin D contributes to the cardiovascular health by suppressing genes involved in producing the rennin, thus down-regulating the Rennin Angiotensin system (RAS), thereby regulating blood pressure. Vitamin D deficiency is currently a topic of intense interest, as vitamin D deficiency is widely prevalent across all ages, races, geographical regions, and socioeconomic strata. [1] In addition, epidemiologic observations have associated with low vitamin D status with an increased risk of non-musculoskeletal diseases, such as cancer, multiple sclerosis, type 1 diabetes mellitus, type 2 diabetes mellitus and cardiovascular disease. Low vitamin D status is also associated with other non-communicable diseases like diabetes, hypertension and with increased susceptibility to infectious diseases; notably, upper respiratory tract infections. [2, 3] On the other hand, whether low vitamin D levels are a cause or consequence of disease, or vitamin D play protect role on various diseases has remained a point of elevated debate.

Widespread outbreaks of infectious disease, originating as a cluster of mysterious cases of pneumonia in place of Wuhan, China, novel coronavirus disease name as COVID-19. Coronaviruses are basically a large family of viruses which may possibly cause illness in animals or humans. Several clades of coronaviruses are recognized to cause respiratory infections ranging from the common cold to further severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). World Health Organisation (WHO) declared that SARS-Cov-2 a global pandemic. As of now (June 12th 2020), over 2.97 lakh confirmed cases and 8508 deaths attributable to this disease have been reported in India. [4]

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Little is known about the protective factors of COVID-19. Recent studies and meta analysis has reported that vitamin D deficiency is associated with COVID-19 mortality in Spain, Italy and Switzerland. [5-7] Hence with that background of literature the present brief review aimed to enlighten the associations between prevalence of Vitamin D deficiency and COVID-19 mortality rate in India.

II. METHODOLOGY

Overview is based on the literature obtained from the Pub Med database and WHO website using the keywords Vitamin D deficiency, COVID-19 mortality, and Respiratory distress syndrome. The specific keywords related to the pathophysiology of respiratory distress syndrome and COVID-19. The Prevalance of vitamin D deficiency collected from previous epideomological studes. [8-24] Diagnostic cut-offs of levels of serum Vitamin D status mentioned in table 1.

III. DISCUSSION

In this review, data was extracted from previous prevalence based studies and mortality rate of COVID-19 from standard WHO websites. The study hypothesises indicates the association between vitamin-D deficiency and mortality rate due to respiratory failure.

IV. RISK FACTORS FOR VITAMIN D DEFICIENCY AND COVID-19

One of the many risk factors for vitamin D deficiency is in older age with more than 20% of mortality rate, regardless of any country. Recent case reports have reported that those residing at higher latitudes, or with darker skin pigmentation may be particularly affected by COVID-19. Additional to this, at higher risk, is obesity, pre-existing chronic diseases like heart disease or diabetes mellitus and vitamin D deficiency. [25-28] It is already evident that there is a world-wide association between northern latitude and increased Covid19 mortality. Whilst there could be various explanations for this, it supports the hypothesis that sunlight exposure and hence vitamin D status could be impacting on COVID-19 severity. [29]

V. ROLE OF VITAMIN D AND COVID-19

Active vitamin D3 synthesised from bronchoalveolar epithelium along with vitamin D axis i;e cytochrome P450 27 (CYP 27,CYP 24) gets modulated in response to diverse stimuli including cytokines and toll-like receptors (TLR) ligands. It promotes early protection against invading pathogens leading to enhancement of synthesis of antimicrobial peptides such as cathelicidin and other vitamin modulated molecules required for antibacterial and antiviral response. [30] It was observed that there was a significant positive correlation between COVID-19 mortality and prevalence of Vitamin D deficiency in other countries like Spain, Italy and Switzerland. [5]

A role for vitamin D within the reaction to COVID-19 infection will be twofold, which might supports to produce antimicrobial peptides in the respiratory epithelium, hence making infection with the virus and development of COVID-19 signs less likely first. Secondly, might help to lessen the inflammatory reaction to infection with SARS-CoV-2. Any alteration in the regulation of this response, especially of the renin-angiotensin system, is characteristic of COVID-19 and degree of over activation is associated with a weak prognosis. Previous studies identified associations between higher levels of Angiotensin-converting enzyme 2 (ACE2) and improved COVID 19 morbidities outcomes. ACE2 protects against acute lung injury in the alveolar cell of Lung. It was reported that ACE2 directly catalyzes Ang II, thereby lowering its levels. COVID-19 infection may downregulate ACE2, which in turn could lead to excessive accumulation of Ang II. High levels of Ang II may cause ARDS, myocarditis, or cardiac injury (Hanff et al 2020). [31] Calcitriol exerts pronouncedly impacts on ACE2/Ang(1–7)/MasR (an endogenous orphan receptor, Mas) axis with enhanced expression of ACE2. [5, 6]

A R Martineau et al, in 2017 meta-analysis of individual patient data from 11,321 participants in 25 randomised controlled trials showed that vitamin D supplementation protected against acute respiratory tract infections and that patients with very low (<25 nmol/L) serum 25-hydroxyvitamin D concentrations (a marker of vitamin D status) gained the most benefit. [7]

Recent studies were highlighted a crucial supportive role for vitamin D in immune cell function, particularly in modulating the inflammatory response to viral infection.[32, 33] At a cellular level, vitamin D modulates both the adaptive and innate immune system through cytokines and regulation of cell signalling pathways. [34] It was already known that vitamin D receptor (VDR) is present on both T and B immune cells; vitamin D modulates the

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proliferation, inhibition and differentiation of these cells. In experimental models of lipopolysaccharide-induced inflammation, vitamin D is associated with lower concentrations of Interleukin-6 (IL-6), which plays an important role in Covid-19 induced acute respiratory distress syndrome (ARDS). It was reported that Vitamin D reduces lipopolysaccharide-induced lung injury in mice by blocking. Recent research has indicated that vitamin D may have immune supporting properties through modulation of both the adaptive and innate immune system through cytokines and regulation of cell signalling pathways. [35-37]

E Laird et al. opined that optimising vitamin D status to recommendations by national and international public health agencies will certainly have benefits for bone health and as well as potential benefits for Covid-19. There is a strong plausible biological hypothesis and evolving epidemiological data supporting a role for vitamin D in Covid-19. [38]

In 2015, Lykkedegn et al. reported that the beneficial effects of vitamin D for respiratory distress syndrome treatment as well as prevention. In their study substantial evidence of multiple physiological roles through which vitamin D stimulates maturation of lung (fetus), including ATII cell maturation, and alveolarization. It was hypothesis that vitamin D deficiency or insufficiency is a frequent, modifiable risk factor for respiratory distress syndrome. However, further evidence is necessary to determine the relationship with these diseases, particularly for respiratory distress syndrome. [39] With extensive previous epidemiological literature, we opined that vitamin D may play a protective role for SARS-Cov2 infections. The drawback of previous studies made hypothesis between vitamin D deficiency studies and COVID-19 pandemic at two different time points. We don't have randomised controlled trial evidence as of now. Hence the brief review was trying to enlighten the new path for beneficial risk factors of COVID-19, which was useful for further original cohorts in future.

VI. CONCLUSION

The present brief review enlightened that there might be a positive association of vitamin-D deficiency with COVID-19 mortality in India. However, larger multicentric studies should come forward on Vitamin D against COVID 19 patients to strengthen the conclusions of the present review.

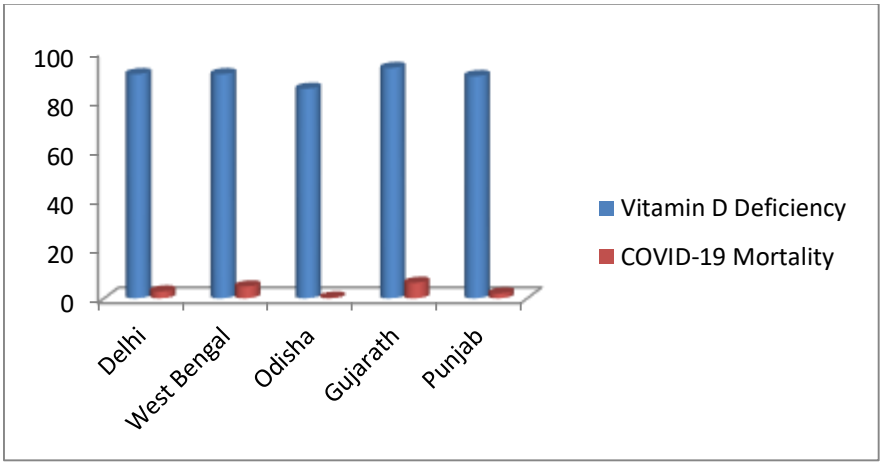

Figure: 1 showed vitamin D deficiency and mortality rate of COVID-19 in India

Table 1: Cut off values for Vitamin D status

Vitamin D status	Vitamin D levels in ng/mL
Deficiency	<20
Insufficiency	21-29
Sufficiency	>30
Toxicity	>150

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