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Review Article

Does Vitamin D Serum Levels Affect The Risk of Covid 19 and its Clinical Outcomes? A Review of Literature

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Abstract: *Background*: SARS-COV-2 has brought untold hardship, economic meltdown, mystery and deaths to the world and has been declared a global pandemic by the WHO. The aim of this study is to review evidence that either support or refute the hypothesis that some level of relationships exists between vitamin D serum level and the risk of COVID-19 disease as well as its clinical outcome. *Materials and Methods:* A Pubmed/Medline, Google scholar, JSTOR, and AJOL search was performed in May 2020 for studies that links COVID-19 to serum levels of vitamin D. Search terms used include a combination of vitamin D, ascorbic acid, 25-hydroxycholecalciferol, corona virus, COVID-19, and SARS-COV-2. *Results and Discussion:* A total of 79 articles were identified (mostly from Pubmed / Medline and Google scholar) after removal of duplicates, out of which 7(5.9%) articles met the inclusion criteria. 85% of the studies reported that a link exist between Vitamin D levels and risk of COVID-19 infection and also, that being positive for COVID-19 was associated with deficiency or lower levels of vitamin D. Critical cases of COVID-19 and its associated mortality was linked to deficiency or lower serum levels of vitamin D in some studies. Age, sex and ethnicity are important factors that determine the outcome of these relationships. *Conclusion:* This study adds to body of evidence that the risk of COVID-19 and its clinical outcome is associated with the vitamin D levels of the subjects. There is a need to include serum Vitamin D testing parameter among COVID-19 patients in their treatment centers across the globe and in Nigeria in particular.
Keywords: COVID-19, SARS-COV-2, Coronavirus, Vitamin D, Ascorbic acid, 25-hydroxycholecalciferol.

INTRODUCTION

Since COVID-19 disease which was caused by SARS-CoV-2 virus was declared a global pandemic by World Health Organization (WHO) in March 2020, efforts had been made towards saving lives and halting the spread of the virus. SARS-CoV-2 virus reported to have originated in Wuhan, Hubei province in China in December 2019 causes severe acute respiratory syndrome (Jakovac H. 2020) and as of 30th May 2020 had caused 364, 891deaths worldwide with 5,899,866 infections (ECDPC. 2020) making SARS-CoV-2 virus highly contagious with high mortality rate when compared to other corona viruses like severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV). Though SARS-CoV-2 virus had been sequenced (Zhou, P. *et al.,* 2020; & Zhu, N. *et al.,* 2020) lots of studies are still required to better understand the pathogenecity, modes of transmission, treatment and management of COVID-19. Worst still, there are enormous variations in the reported case fatality rate between countries and

between regions in the same country (Marik, P. E. *et al.,* 2020) and though several reasons have been given to explain the unfortunate trend, vitamin D status was postulated to possibly have influence in the risk of dying from COVID-19 (Marik, P. E. *et al.,* 2020). Interestingly, even before the advent of COVID-19 disease, studies had documented the protective roles of vitamin D against acute viral respiratory tract infections (Cannell, J. J. *et al.,* 2006; & Martineau, A. R. *et al.,* 2017) while others showed that vitamin D has antiviral effects which can interfere directly with viral replications and also act in immunomodulatory and anti-inflammatory way (Teymoori-Rad, M. *et al.,* 2019). However, there seemed to be an increase in focus by researchers to link the protective roles and antiviral activities of vitamin D to the variations seen in reported COVID-19 case fatalities between countries and regions. Despite all these attempts, the number of studies is still grossly insufficient to make a conclusion. The present study thus, systematically reviews all the available studies which investigated this relationship for better understanding and guide.

METHODOLOGY

In May 2020, a literature search was performed on studies that reported the importance of Vitamin D (25-hydroxycholecalciferol) in COVID-19 subjects using Pubmed/Medline, Google scholar, JSTOR, and AJOL databases. Key words included a combination of the following: Vitamin D, 25-hydroxycholecalciferol, corona virus, COVID-19, and SARS-COV-2. Only studies reported in English which must be an original research article and must address the relationship between vitamin D levels in COVID-19 subjects. Review articles, newsletters, commentaries, editorials and articles written in any language that is not English were excluded from the study. At the stage of titles, titles that did not address issue of COVID-19 and vitamin D were excluded. At the abstract stage, studies that were review articles, newsletters, commentaries, editorials, and did not link Vitamin D levels to COVID-19 outcomes were not included in this study. During full text review, the authors excluded studies if all the condition listed for excluding articles in abstract stage were missed due to incomplete information in the abstract but found in the full text. Though full text articles are normally used in systematic reviews, one abstract (Lau, F. H. *et al.,* 2019) was indeed added to this work due to its uniqueness and completeness. All publications were retrieved online while data extraction was carried out for each paper highlighting the following: name of first author and year of publication, study design, study location, major findings, comments and recommendation. The search strategy are provided in figure 1.
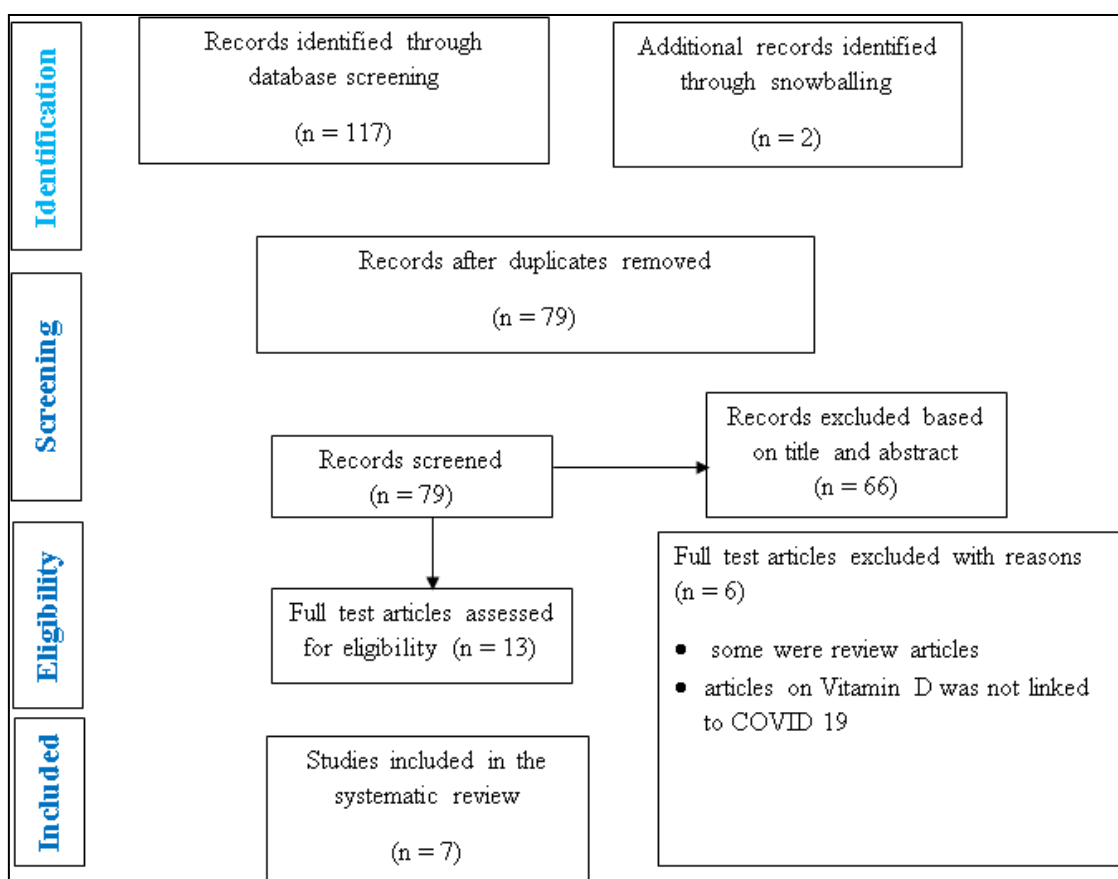

Figure 1. Flow diagram for the selection of studies on Vitamin D and COVID-19

RESULTS

Following a thorough search of the four databases, a total of 117 articles were identified (mostly from Pubmed/Medline and Google scholar) which was reduced to 79 following removal of duplicates. At the end a total of 7(5.9%) articles (Lau, F. H. *et al.,* 2020; D'Avolio, A. *et al.,* 2020; Alipio, M. 2020; Raharusun, P. *et al.,* 2020; De Smet, D. *et al.,* 2020; Hastie, C. E. *et al.,* 2020 & Meltzer, D. O. *et al.,* 2020) met the inclusion criteria and were systematically reviewed. All the seven studies were done in year 2020 and are retrospective in design.

Vitamin D and COVID-19 infection

Six out of the seven studies (85%) reported that a link exist between Vitamin D level and risk of COVID-19 infection and also, that being positive for COVID-19 was associated with deficiency or lower levels of vitamin D (Lau, F. H. *et al.,* 2020; D'Avolio, A. *et al.,* 2020; Alipio, M. 2020; Raharusun, P. *et al.,* 2020; De Smet, D. *et al.,* 2020; & Meltzer, D. O. *et al.,* 2020).

Vitamin D levels were lowest in critical cases of COVID-19 (11) just as it was associated with COVID-19 clinical outcomes and mortality (Alipio, M. 2020; & Raharusun, P. *et al.,* 2020). Majority of the COVID-19 cases with insufficient and deficient vitamin D status died (Raharusun, P. *et al.,* 2020).

The relationship which exists between vitamin D and COVID-19 infection and its clinical outcome was found to be dependent on the age and sex of the patients (Lau, F. H. *et al.,* 2020; D'Avolio, A. *et al.,* 2020; P. *et al.,* 2020; De Smet, D. *et al.,* 2020; & Meltzer, D. O. *et al.,* 2020).

Table 1: General characteristics of the studies reviewed

REFERENCE	STUDY DESIGN	STUDY POPULATION	LOCATION	YEAR OF STUDY
Grant WB *et al.,* 2020	Retrospective	20 COVID-19 positive patients	New Orlean (US)	2020
Hastie CE *et al,* 2020	Retrospective cohort	107 COVID-19 positive patients	Switzerland	2020
Ilie PC *et al.,* 2020	Retrospective	212 COVID-19 positive patients	NA	2020
Jakovac H *et al.,* 2020	Retrospective Cohort	780 COVID-19 positive patients	Indonesia	2020
Lau FH *et al.,* 2020	Retrospective observational	186 COVID-19 patients + 2717 age/season matched controls	West Flanders (Belgium)	2020
Lips P *et al.,* 2020	Retrospective cohort	348,598 UK Biobank participants out of which 449 had confirmed COVID-19 infection	United Kingdom	2020
MacLaughlin J *et al.,* 2020	Retrospective cohort	4314 patients tested for COVID-19 of which 499 had a previous vitamin D level a year before unknown	Chicago (US)	2020

Table 2: Identified major findings in reviewed studies

REFERENCE	MAJOR FINDINGS	COMMENT	RECOMMENDATION
Grant WB *et al.,* 2020	• 86.6% of COVID-19 ICU subjects presented with VDI in comparison to 57% of floor subjects • 100% of ICU subjects less than 75 years old had VDI	VDI is highly prevalent in severe COVID-19 patients	Prospective, randomized controlled studies of VDI in COVID-19 patients
Hastie CE *et al,* 2020	• Positive COVID-19 patients vitamin D levels are significantly lower (11.1ng/ml) compared with the negative controls (24.6ng/ml) • The findings were age dependent as Vitamin D levels were significantly different in patients 70 years and above	Vitamin D supplementation might be a useful measure to reduce the risk of infection	Randomized controlled trial and large population studies to confirm preliminary observations
Ilie PC *et al.,*	• Mean serum vitamin D is 23.8ng/ml	Vitamin D supplementation could	Randomized controlled trials and large population studies to

2020	• Serum vitamin level was lowest in critical cases but highest in mild cases • Serum vitamin D levels was significantly associated with clinical outcomes • Majority of the COVID-19 patients had insufficient vitamin D status, most of which were not severe	possibly improve clinical outcomes of patients infected with COVID-19.	evaluate these observations.
Jakovac H *et al.,* 2020	• Majority of the COVID-19 cases with insufficient and deficient Vitamin D status died. • The odds of death was higher in older and male cases with pre-existing condition and below normal Vitamin D levels • When controlling for age, sex, and comorbidity, Vitamin D status is strongly associated with COVID-19 mortality.	When controlling for age, sex and co morbidity, vitamin D status is strongly associated with COVID-19 mortality outcome of cases	Randomized controlled trials are warranted to investigate the role of vitamin D supplementation on COVID-19 outcomes and to establish the underlying mechanisms
Lau FH *et al.,* 2020	• COVID-19 patients had lower median of vitamin D (18.6ng/ml) as against the control with median value of 21.5ng/ml with p value of 0.0016 • COVID-19 patients had higher vitamin D deficiency rates (58.6%) against the control group (45.2%) with p value of 0.0005 • The finding was sex dependent as males COVID-19 patients had markedly higher deficiency rates than male control (67.0% versus 49.2%, p value=0.0006) • No stage dependent vitamin D variations was seen in Female COVID-19 patients	• Vitamin D deficiency is a prevalent risk factor for severe COVID-19. • Vitamin D supplementati on might be an inexpensive and safe mitigation for the SARS-CoV-2 pandemic.	NA
Lips P *et al.,* 2020	• Vitamin D was associated with COVID-19 infection univariably (OR=0.99,	The finding do not support a potential link between Vitamin D level and risk of	NA

	P value = 0.013) but not after adjustment for confounders (OR=1.00, P value=0.208)	COVID-19 infection
MacLaughlin J *et al.,* 2020	• Being vitamin D deficient is associated with testing positive for COVID 19 • Testing positive for COVID 19 was associated with increasing age and ethnicity • Vitamin deficiency decrease with increasing vitamin D dose • Vitamin D dose was not significantly associated with testing positive for COVID 19	Vitamin D deficiency that is not sufficiently treated is associated with COVID-19 risk	Testing and treatment for vitamin D deficiency to address COVID-19 warrant aggressive pursuit and study.

KEY: VDI= vitamin D insufficiency, ICU= intensive care unit, NA=not available

DISCUSSION

From this study, evidence exists that potential relationships exist between vitamin D levels and risk of COVID-19 infection as well as its clinical outcomes. Critical cases of COVID-19 and its associated mortality was linked to deficiency or lower serum levels of vitamin D in those subjects. A similar systematic review on vitamin D levels in countries and regions that recorded high case fatality with COVID-19 also reported strong association between mean levels of vitamin D in those countries and the number of COVID-19 infection as well as the associated mortality caused by the infection (Ilie, P. C. *et al.,* 2020). The potential protection of vitamin D from negative consequences of COVID-19 infection as well as its role in the prevention of COVID-19 infection was explained to be responsible for the association observed (Ilie, P. C. *et al.,* 2020). Vitamin D deficiency has been defined as a serum 25(OH) D level lower than 30 nMol/L (Lips, P. *et al.,* 2019). Vitamin D performs numerous functions in the body and the infection with the COVID 19 virus and development of symptoms are less likely due to the ability of vitamin D to support the production of antimicrobial peptides in the respiratory epithelium. Also, ability of vitamin D to interact with angiotensin-convertin enzyme 2 (ACE2) in the renin-angiotensin system by promoting the gene that regulates the ACE2 helps to reduce the inflammatory response to SARS-COV-2 infection (Mitchell, F. 2020). Similarly, in support of the evidence generated in this study, a large meta-analysis of randomized controlled trials reported that vitamin D supplementation reduced the risk of acute respiratory tract infections (Martineau, A. R. e al 2017; & Bergman, P. *et al.,* 2013). Interestingly, reports from randomized controlled trials equally reported that high dose vitamin D has no benefit even in critically ill

patients who were deficient of vitamin D (Early high-dose vitamin 2019).

The present study identified that the relationship between the COVID-19 and vitamin D serum levels are age and sex dependent as male COVID-19 patients and those above 70 years of age were found to have markedly higher deficiency rates. This is because the ability of the skin to produce vitamin D_3 decreases with age (MacLaughlin, J., & Holick, M. F. 1985). The increase in chronic diseases with age could also account for the increase mortality from COVID-19.

Many governments are beginning to recognize the importance of vitamin D in ameliorating the COVID-19 infection especially among the older people due to their poor outcome and have directed that people take vitamin D supplements during this pandemic (MacLaughlin, J., & Holick, M. F. 1985; & Grant, W. B. *et al.,* 2020) with other supplements such as Vitamin C (23), other multivitamins and exercise. ther multivitamins, and exercise. However, the need to conduct a trial on this hypothesis has also been noted by authors" with various comments and recommendations as contained in table 2.

CONCLUSION

This study has provided more evidence supporting the existence of relationships between vitamin D levels and the COVID-19 risk and clinical outcomes. The associations is dependent on the age and sex of the patient as males and patients more than 70 years of age and above have higher deficiency rates of vitamin D and are more prone to mortality associated with COVID-19. Though there are documented evidences of protective roles of Vitamin D in acute

respiratory diseases, randomize clinical trials are still required to evaluate this observations especially with regards to COVID-19 infection globally and in Nigeria in particular.

It is therefore imperative to add serum vitamin D tests among the parameters run on COVID-19 patients in the treatment centers in Nigeria and across the globe. However, since most of these studies are observational in nature, randomized clinical trials and large population studies are still required to evaluate these observations towards better use of Vitamin D in the management of COVID-19.

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