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ARTICLE

Vitamin D and SARS-CoV-2 Infection

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ABSTRACT

The review about the influence of vitamin D (Vit D) on the severity of SARS-CoV-2 infection is presented in this article. It has then been suggested that according to its potential impact on immune response and more particularly on the ACE2 pathway Vit D works as a prevention of severe cases, or in combination with other treatments as necessary supplement to improve recovery. While no benefit has been evidenced in having excess Vit D levels, still Vit D levels very likely affect the severity of SARS-CoV-2 infection and it is, therefore recommended to secure Vit D levels up to suggested values.

KEYWORDS

SARS-CoV-2, Infectivity, Fatality, Vitamin D, Supplementation, Nutrition, Statistic.

INTRODUCTION

Vitamin D (Vit D) is known to protect acute respiratory infections including colds and flu. The protective effects of Vit D supplementation are strong in those who have the lowest Vit D levels and when supplementation is given daily with continuity. Low levels of Vit D were associated with vulnerability to acute respiratory tract infections [1-8]. Vit D status may affect SARS-CoV-2 infection risk and clinical outcomes due to the role of Vit D in the regulation of immunity. Despite the growing body of literature, the subject is still controversial.

One work, based on a basic environmental correlation, suggested early this year that Vit D levels play a major role in SARS-CoV-2 infections. Deficiencies of Vit D were statistically associated with more severe outcomes of SARS-CoV-2 infection including fatality [8]. The general population's low levels of Vit D were claimed to be associated with high numbers of SARS-CoV-2 cases and mortality in a country [8]. The *in vitro* study [9] showed that calcitriol has significant activity against SARS-CoV-2. Other studies were reported from more appropriate clinical settings, however suffering from major limitations. In some cases, significant amount of Vit D was administered, using Vit D as a therapy, more than a nutrient to compensate for a deficit. These works are here to review for a correct historical perspective and to understand the best use of Vit D for SARS-CoV-2 infection.

Environmental studies: Interest towards Vit D followed an environmental work. Population Vit D levels and SARS-CoV-2 fatality were proposed by Ilie *et al.* [8] as proof that Vit D helps with SARS-CoV-2 infection. While correlation is not

the same as causation, the correlation is however also too simple. The work was only based on data of fatalities and general population Vit D levels in selected European countries, attempting to link higher or lower fatalities to higher or lower Vit D levels. People in Italy or Belgium had higher fatalities per million for many other reasons than not simply the deficiency of Vit D vs. northern European countries such as Finland or Norway.

Fig. 1a and Table-1 present the cumulative deaths caused by SARS-CoV-2 per million updated to April 8, 2020, from Ilie *et al.* [8] and updated to October 3, 2020, from [10] vs. the Vit D(25)HD mean in nmol/L from Ilie *et al.* [8]. As shown by the small R^2 , the correlation has minimal statistical value. With about the same 50 Vitamin D(25)HD mean in nmol/L, Germany had 114 fatalities per million and Belgium 865. Similarly, with the higher Vitamin D(25)HD mean in nmol/L of 73.5, Sweden had 583 fatalities per million vs. 114 in Germany.

Countries	Vit D(25)HD mean (nmol/L) [Ref. 8]	Deaths caused by SARS-CoV-2/1 M 8-4-2020 [Ref. 8]	Deaths caused by SARS-CoV-2/1 M 3-10-2020 [Ref. 10]
Island	57.0	18	29
Norway	65.0	19	51
Sweden	73.5	68	583
Finland	67.7	7	62
Denmark	65.0	38	112
UK	47.4	105	622
Ireland	56.4	48	364
Netherlands	59.5	131	375
Belgium	49.3	193	865
Germany	50.1	25	114
France	60.0	167	492
Switzerland	46.0	103	239
Italy	50.0	292	595
Spain	42.5	314	686
Estonia	51.0	18	50
Czech Republic	62.5	9	65

While supplementation of Vit D may certainly help the elderly, the analysis proposed in Ilie *et al.* [8] is statistically insignificant. They have scattered points with $R^2 = 0.29$ from a linear fitting of the original data updated to April 8, 2020 and a smaller $R^2 = 0.13$ from a linear fitting of the data updated to October 3, 2020. The R^2 coefficient of determination is a statistical measure of how well the regression estimates the data points. An R^2 of 1 indicates a perfect fit for the data. An $R^2 = 0.13$ implies that only 13% of the variability is accounted for and the remaining 87% of the variability is unaccounted for.

Fig. 1b is a global map of SARS-CoV-2 fatalities per million (updated December 10, 2020) and Fig. 1c is the population Vit D level. While slightly different maps are available in the literature for the Vit D level, it is immediate to note as the two parameters are mostly uncorrelated. The fatality of SARS-CoV-2 is therefore, not simply explained by the general population Vit D level. Vit D supplementation efficacy against SARS-CoV-2 infection is not proven by a linear correlation at European

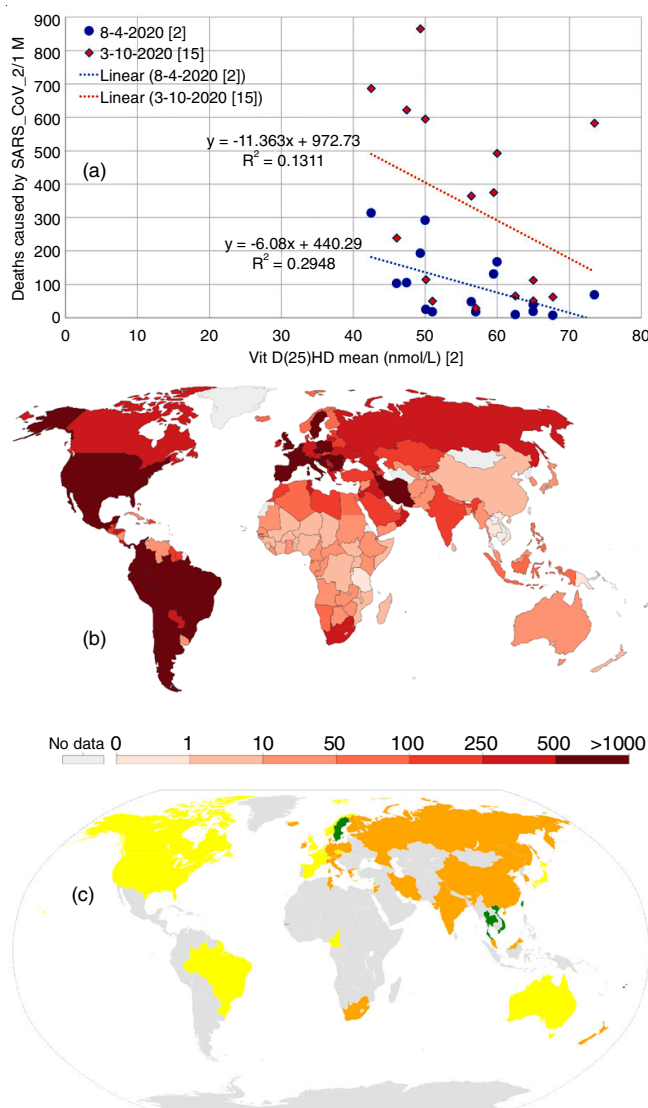


Fig. 1. (a) Cumulative deaths caused by SARS-CoV-2 per million 8-4-2020 from [8] and 3-10-2020 from [10] vs. the Vitamin D(25)HD mean in nmol/L from [8] of selected European countries; (b) Confirmed SARS-CoV-2 deaths per million people across the World updated December 10, 2020. Image from ourworldindata.org. CC-BY. (c) Global Vit D serum levels among adults (nmol/L), 2012 values. Image from commons.wikimedia.org/wiki/File:Vitamin_D_serum_levels_in_adults_world_map.svg. Author RedBurn. Creative Commons Attribution-Share Alike 4.0 International license

nations levels of SARS-CoV-2 fatalities vs. Vitamin D(25)HD levels. Fatalities are correlated to many other parameters, most of them not known.

Despite the work by Ilie *et al.* [8] has been already used 219 times (citation count in Google Scholar of November 1, 2020) as evidence of causation in other works, this work is not proof of correlation nor causation. This type of studies is always bound to be hypothesis generating rather than proof of causation. The updated data still shows the same trend towards increased mortality in countries with lower reported mean serum 25(OH)D and the linear plots still look for correlation across the whole range of serum 25(OH)D concentrations rather than, as correctly pointed out earlier, looking to see whether there is greater mortality with deficiency than sufficiency.

Similar to Ilie *et al.* [8], other works have suggested a correlation between cumulative fatalities of a country and parameters affecting the Vit D level. Panagiotou *et al.* [11] proposes an environmental explanation of fatalities linked to Vit D deficiency at the beginning of the second wave of SARS-CoV-2 infection in Europe based on latitudes but not temperatures. Ali [12] attempt to correlate SARS-CoV-2 mortality rate and sunlight exposure suggesting sunlight exposure has a protective effect. An environmental correlation between SARS-CoV-2 fatalities and latitude, sunlight and Vit D is proposed in [13]. The latitude hypothesis linking Vit D and SARS-CoV-2 is also proposed [14].

Clinical studies: This study includes non-interventional studies as well trials. As it occurred for other treatments related to SARS-CoV-2, almost the totality of the studies is not free of criticism and results are often contradictory. Thus, this part catalogues studies to infer a conclusion by majority of studies.

Correlation between Vit D levels and SARS-CoV-2 fatality may be better assessed in clinical trials and retrospective studies of individual experiences carried out within clinical settings. Even if not proven at all by the oversimplified environmental analyses proposed, it is however very likely that people with insufficient levels of Vit D are those more at risk of severe infection from SARS-CoV-2 and supplementation with Vit D may certainly help them. Vit D generally helps with respiratory tract infections and there is no reason it should not help with the SARS-CoV-2 respiratory tract infection.

Many works in the literature have suggested a correlation between Vit D deficiency and negative outcomes of SARS-CoV-2 infection. About one-half of the works are letters to the editor [15], reviews [16-23] or opinion pieces [24-28]. The other half of the works [29-45], are mostly retrospective studies, of limited statistical significance.

A correlation between low plasma 25 (OH) Vit D level and increased risk of SARS-CoV-2 infection in the Israeli population is proposed [29]. Low serum 25-hydroxyvitamin D (25 [OH] D) levels in patients hospitalized with SARS-CoV-2 infection are associated with greater disease severity [30]. High prevalence of hypovitaminosis D was found in COVID-19 patients with acute respiratory failure, treated in an RICU [31]. Senior adults with Vit D deficiency and COVID-19 may demonstrate worse morbidity outcomes and Vit D status may be a useful prognosticator [32].

The retrospective study of Kaufman *et al.* [33] reports 986 hospitalized patients in the UK. Vit D treatment was associated with a reduced risk of mortality no matter the baseline Vit D status. The retrospective study of Radujkovic *et al.* [34] reports as in the elderly of nurses' homes in France Vitamin D3 supplementation during SARS-CoV-2 infection or started just before SARS-CoV-2 infection was associated with 68% lower mortality and less severe symptoms.

The retrospective study of Israel *et al.* [35] reports 235 hospitalized patients. The study shows a significant association between adequate Vit D levels and the reduction of severity. Another retrospective study of Castillo *et al.* [36] reports of 191,779 patients in the US evidencing an inverse correlation of SARS-CoV-2 severity and circulating Vitamin D(25)HD levels persisting across latitudes, races/ethnicities, gender and

age ranges. Lansiaux *et al.* [37] reported that 185 patients shows an association between Vit D deficiency and severity/mortality. The large observational study by Jolliffe *et al.* [38] reports similar results. Vit D deficiency is associated with SARS-CoV-2 severity.

The way Vitamin D(25)HD treatment for SARS-CoV-2 hospitalized patients reduces ICU admissions [39]. The meta-analysis by Ferder *et al.* [40] shows an association of Vit D supplementation with reduced risk of acute respiratory infections. The positive effects of Vit D supplementation in 33 hospitalized SARS-CoV-2 patients with respiratory failure are reported by Mok *et al.* [41], similarly, the benefits of Vit D supplementation for SARS-CoV-2 infection are discussed by Tan *et al.* [42].

A reduced need for oxygen therapy and ICU admission administering Vit D, magnesium and vitamin B12 to 43 patients vs. the 26 control patients is also reported [43]. The retrospective study of Lau *et al.* [44] analyzed data of 186 hospitalized patients in Belgium correlating Vit D deficiency with the risk for hospitalization for SARS-CoV-2. The analysis of 20 SARS-CoV-2 hospitalized patients as reported by Grant *et al.* [45] also shows ICU patients had low Vit D levels vs. non-ICU patients.

Despite the above generally small and incomplete works are not free of criticism and the medical gold standard clinical trials, with a placebo control group and statistical significance, are missing, still, indications are generally and consistently in favour of supplementation. Regarding risks, we agree with Lewis [25], there is little to be lost and a huge amount to gain by recommending Vit D supplementation.

Conclusions

A proper study about the use of Vit D serum level to limit the severity of SARS-CoV-2 infection should detail how Vit D serum level modulate the immune response and why this could be of interest in the particular situation of SARS-CoV-2 pandemic. Also relevant would be to present how Vit D serum levels may modulate the pathophysiology of SARS-CoV-2 and more particularly its role within the ACE2 pathway. It would have been necessary to discuss the definition of Vit D serum levels for optimal, sub-optimal, moderate and severe deficiency in addition to discuss also that higher optimal values have to be considered for immunomodulation. These studies are not available in the present literature.

What is likely the case, according to its potential impact on immune response and more particularly on the ACE2 pathway, Vit D may be considered supplementation to cover deficiencies is a way to prevent severe cases or in combination with other treatments to permit a better recovery. Definitely Vit D cannot cure SARS-CoV-2 infection. It may only help to limit as much as possible any immune vulnerability, which could negatively impact the course of the infection.

As very well summarized by Mayo Clinic [46], no enough positive data is available to endorse the use of Vit D to prevent infection or to treat SARS-CoV-2 infection, according to the National Institutes of Health and the World Health Organization. From this analysis, while no benefit has been evidenced in having excess Vit D levels, still Vit D levels very likely

affect the severity of SARS-CoV-2 infection and it is therefore recommended to secure Vit D levels up to suggested values.

This result is only partially aligned with the latest advice by National Institute for Health and Care Excellence [47-49]. The recent study by NICE [48] has indeed translated into the new UK government guidance [49] allowing people extremely clinically vulnerable to opt for free 4-month supply of daily vitamin D supplements. However, this recommendation does not address the other factors such as sunshine exposure promoting the necessary physiological levels of Vit D. Vit D supplements are safe. Potential low toxicity is strongly outweighed by potential benefits in protection from SARS-CoV-2.

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