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SHORT COMMUNICATION

Revisiting the role of vitamin D levels in the prevention of COVID-19 infection and mortality in European countries post infections peak

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Abstract

Various studies are underway to identify protective variables for the COVID-19 pandemic. We hypothesized that if indeed the vitamin D levels would be protective in the European population, as recently proposed, the correlation would become more robust when the countries had passed the infection peak as on May 12 2020, compared to April 8 2020, when the majority had not. Comparative analysis of data from the mentioned stages indicated a significant increase in negative correlation of vitamin D levels with COVID-19 cases per million population in later stage ($r(20)$: −0.5504; $R^2 = 0.3029$; p value: 0.0119 vs $r(20)$: −0.4435; $R^2 = 0.1967$; p value: 0.0501), whereas the correlation with deaths per million population became insignificant ($r(20)$: −0.3935; $R^2 = 0.1549$; p value: 0.0860 vs r(20): −0.4378; $R^2 = 0.1917$; p value: 0.0535). Considering divergence of vitamin D levels from the mean in subgroups, e.g. children, women, aged, dedicated exploratory studies with carefully chosen matched target groups is advisable.

Keywords COVID-19 · SARS-CoV-2 · Correlation · Vitamin D · Europe

Introduction

The COVID-19 pandemic caused by the novel coronavirus SARS-CoV-2 has taken the world by surprise. The spread of COVID-19 (SARS-CoV-2) has been rapid with significant tolls in comparison to earlier coronavirus pandemic/outbreaks. It has already infected more than 4.25 million and killed about 287 thousand people by 12th May 2020 [1]. The severity of COVID-19 and its spread has been muted in African, Asian, and South American countries. Recently, a peer-review publication had negatively correlated the serum vitamin D level in European countries with reported COVID-19 infection cases and deaths per million populations [2]. Vitamin D is known to exert a positive effect on the immunity and general health of individuals [3]. It has been indicated to protect from other acute respiratory tract infections and the adverse outcomes [4, 5]. It has been proposed to do that through a multitude of effects including increasing the oxygen-carrying capacity of the blood, modulating the immune system, expediting the recovery from acute lung injury and modulation of renin-angiotensin system including the ACE2 [6], the receptor of SARS-CoV-2 [7].

The association of vitamin D levels with COVID-19 incidence and severity had been investigated recently [2]. A protective correlation with mean vitamin D levels in select European countries had been suggested using COVID-19 data from April 8, 2020 when all countries were not at the same stage of the current wave of infections [1]. We hypothesized if indeed such a protective correlation exists it would become more robust with the passage of time when all countries reach a similar stage of the COVID-19 pandemic. The primary aim of this study was to reevaluate the protective effect of vitamin D levels on the European population. The secondary aim was to ascertain if it had any impact on the number of cases. Our analysis of the countries indicated a significant negative correlation between vitamin D levels with COVID-19 cases but an insignificant negative correlation with adverse disease outcome (mortality).

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Material and methods

The countries of Europe with comparable UV exposure and dietary intake were chosen for the analysis for decreasing the effect of confounding variables as expected in such studies as done previously [2]. The data about COVID-19 cases per million of population and deaths per million of the population (Table 1) were obtained for 8th April and 12th May 2020 from worldwide coronavirus pandemic data portal at https://www.worldometers.info/coronavirus/ [1]. The data for mean serum vitamin D levels were from a previous publication [2]. The Microsoft excel was used for making basic statistic calculations (linear regression analysis—calculation of best-fit trend line for data, the *R*-squared value (R^2); and Pearson correlation coefficient).

Results

For the countries studied, we observed a stronger negative correlation between vitamin D levels and COVID-19 cases post COVID-19 infections peak on 12 May 2020, as compared to that observed on 8 April 2020 (Table 2). However, the negative correlation with deaths per million population seemed to be insignificant. Please see Table 2 for comparative correlation (linear regression) at different stages of pandemic and Fig. 1 for exponential correlative inference ($R^2 = 0.3751$).

Discussion

Vitamin D has been known to affect the immune system and decrease the severity of respiratory tract infections [4–6]. Recent correlative analysis investigating the effect of mean serum levels on the COVID-19 occurrence/cases and deaths in European countries had indicated a tenuous negative (protective) covariation [2]. The level of significance

Table 1 COVID-19 cases and deaths at two different stages of the current wave of infections in European countries

Countries	Vitamin D level mean (nmol/L)	8 April 2020 (Most countries before peak)		12 May 2020 (All countries post peak)	
		Cases/million population	Deaths/million population	Cases/million population	Deaths/million population
Iceland	57	4736	18	5278	29
Norway	65	1123	19	1500	41
Sweden	73.5	834	68	2641	322
Finland	67.7	449	7	1080	49
Denmark	65	933	38	1815	92
UK	47.4	895	105	3286	472
Ireland	56.4	1230	48	4685	297
Netherlands	59.5	1199	131	2497	318
Belgium	49.3	2019	193	4612	751
Germany	50.1	1309	25	2060	91
France	60	1671	167	2718	408
Switzerland	46	2686	103	3506	213
Italy	50	2306	292	3636	508
Spain	42.5	3137	314	5735	572
Estonia	51	893	18	1312	46
Czechia	62.5	488	9	763	26
Slovakia	81.5	125	0.4	267	5
Hungary	60.6	93	6	340	44
Turkey	51.8	453	10	1657	46
Portugal	39	1289	37	2715	112
Average	56.8	1393.4	80.4	2605.1	222.1
STDEV	10.6	1130.0	94.6	1601.1	221.4

In the table, cases/deaths per million population and vitamin D levels are rounded off to single decimal place

Table 2 Result of statistical analysis: correlation (linear regression) between average vitamin D levels and COVID-19 cases and deaths in European countries at different stages of current pandemic

	8 April 2020 (Most countries before peak)	12 May 2020 (All countries post peak)
Average cases per million population ± STDEV	1393.4 ± 1130.0	2605.2 ± 1601.0
Correlation: cases per million population vs vitamin D levels	$r(20)$: −0.4435; $R^2 = 0.1967$ p value: 0.0501	$r(20)$: −0.5504; $R^2 = 0.3029$ p value: 0.0119
Average deaths per million population ± STDEV	80.4 ± 94.6	222.1 ± 221.4
Correlation: deaths per million population vs vitamin D levels	$r(20)$:−0.4378; $R^2 = 0.1917$ p value: 0.0535	$r(20)$: −0.3935; $R^2 = 0.1549$ p value: 0.0860
Vitamin D levels ± STDEV	56.8 ± 10.6 nmol/L	

In the table, average cases/deaths per million population and vitamin D levels are rounded off to single decimal place while correlation and p values are rounded off to four decimal places

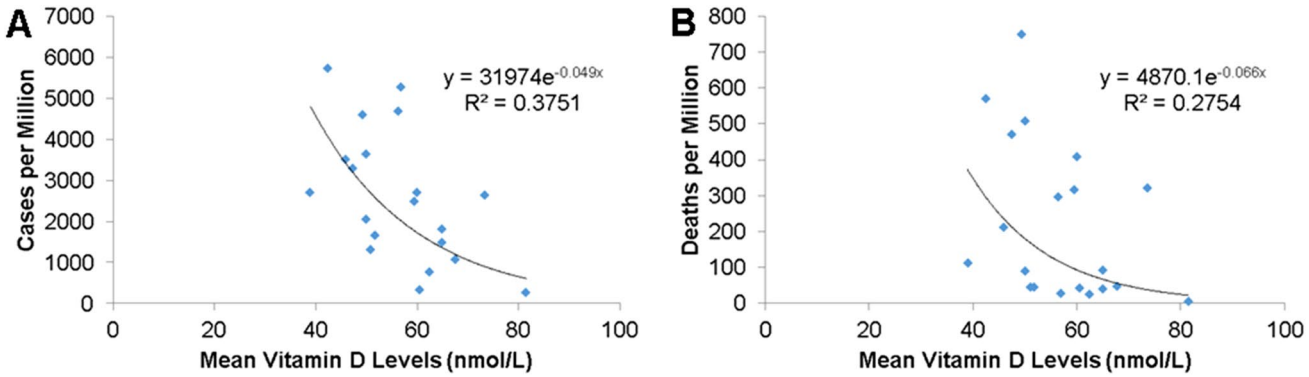

Fig 1. Vitamin D serum levels negatively correlated with COVID-19 cases per milloin population (**A**) and deaths per million population (**B**). The correlation between vitamin D levels and cases per million population had improved by 12 May 2020 when all countries had passed the peak of current wave of COVID-19 infections as compared to that on 8th April 2020 (See Table 2 for comparison of the linear regression analysis results) when in most countries it had not peaked (as per https://www.worldometers.info/coronovirus/)

for correlation was borderline (p value 0.0501 and 0.0534) as could be expected from countries included in the study being at different stages of the COVID-19 pandemic. For making the covariation analysis more robust, the data about cases and deaths per million population was also gathered from a later date, *i.e.*, 12 May 2020, when the COVID-19 situation had stabilized and countries had passed the peak of the infection. It was found that the cases per million had registred about 1.2 fold (e.g., Iceland, Norway) to fourfold increase (Ireland, Hungary, Turkey) while the death rates registered about 1.6 fold (e.g., Iceland) to 12.5 fold (*e.g.*, Slovakia) increase (Table 1). The standard deviation of the data mean had also reduced (Table 1). The strength and significance of correlation changed both between vitamin D levels and cases per million ($r(20)$: −0.4435; $R^2 = 0.1967$; p value: 0.0501 vs $r(20)$: −0.5504; $R^2 = 0.3029$; p value: 0.0119) as well as between vitamin D and deaths per million ($r(20)$: −0.4378; $R^2 = 0.1917$; p value: 0.0535 vs $r(20)$: −0.3935; $R^2 = 0.1549$; p value: 0.0860). The exponential curve fitting of the data displayed still better correlation with cases per million ($R^2 = 0.3751$) and deaths per million ($R^2 = 0.2754$), as expected for a biological system with bottlenecks and required thresholds for seeing an effect (Fig. 1). There is a possibility that there exists a cause and effect relationship.

The underlying differences in the population composition, age distribution, differential comorbidities distribution, medication practices, etc. maybe some other confounding variables lowering the estimate of correlation. So, it may be surmised that higher vitamin D levels may be positively correlating with a reduced infection rate while its covariation with the adverse outcome may not be significantly correlated. It should be noted here that comprehensive vitamin D data is not available for the populations under study and within the countries different subgroups had been shown to have quite different levels of vitamin D ranging from deficiency to insufficiency [8]. Particularly, children, women, aged, people of color are more prone to have vitamin D levels lower than the means of the populations. Complete dependence on mean values could be problematic in driving reliable inferences for protection from COVID-19. Studies involving target groups with known vitamin D levels would

be able to shed light on the reliability of the the observed protective correlation and establishing a cause and effect relationship.

A study to evaluate the effect of vitamin D levels or supplementation may be planned for SARS-CoV-2 infection using carefully matched (*i.e.,* age, basal vitamin D level, comorbidities, sex, genetic background, disease severity, etc.) control and test groups. Alternatively, relatively reliable estimates can be also made by collation of the required information from health systems, if needed, employing a surveillance questionnaire. The outcome of the suggested retrospective or exploratory studies would possibly provide a handle to limit the impact of COVID-19 in future waves of infection as well as limit its impact on the countries which are still in the early or middle phase of infections, e.g., Asian countries.

The current study indicated a stronger negative correlation between mean vitamin D levels of the European populations with COVID-19 cases per million in the populations than the association shown at an earlier stage of COVID-19 pandemic ($R^2 = 0.3751$ vs $R^2 = 0.1967$) [2]. However, the vitamin D levels correlation with deaths per million population among the studied countries seemed insignificant. As vitamin D is already known to boost the immune system and play an important role in reducing respiratory disease severity [4–6], it would be safe to assume its positive interaction with COVID-19 [3]. The biological role of vitamin D levels in avoiding infection and unfavorable outcomes of the COVID-19 must be thoroughly investigated through available medical records or survey-based epidemiological studies, with the follow-up scrutiny through controlled clinical trials for the protective effect. If found correlated, the vitamin D supplementation could allow a significant reduction in the COVID-19 impact on populations.

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Compliance with ethical standards

Conflict of interest There is no conflict of interest to disclose.

Ethical statement The study complied with the existing ethical standards.

Human and animal rights Considering the design of the study no human or animal rights were infringed upon.

Informed consent Considering the design of the study no informed consent was necessary.

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