Effect of Vitamin D Concentration on Course of COVID-19

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Background: The course of COVID-19 disease is associated with immune deregulation and excessive release of pro-inflammatory cytokines. Vitamin D has an immunomodulatory effect. We aimed to assess the possible correlation between the incidence and severity of SARS-CoV-2 infection and serum vitamin D concentration.

Material/Methods: A total of 505 successive patients admitted to a COVID-19-dedicated hospital were included in the retrospective analysis. Serum 25-hydroxyvitamin D (25-OHD) levels and SARS-CoV-2 RT-PCR throat swab test results were determined for each patient. The course of COVID-19 was assessed on the basis of the serum Vitamin Modified Early Warning Score (MEWS), which includes respiratory rate, systolic blood pressure, heart rate, temperature, and state of consciousness), as well as number of days spent in the intensive care unit (ICU) and need for oxygen therapy.

Results: There was no difference in 25-OHD concentration between COVID-19-confirmed and negative results of the PCR tests. No correlation was found between serum 25-OHD in the COVID(+) group and the need for and time spend in the ICU, as well as the MEWS score. Multivariate analyses showed a positive correlation between need for oxygen therapy and lower 25-OHD concentration, as well as older age ($P<0.001$) and similar positive correlation between need for ventilation therapy with lower 25-OHD concentration, as well as older age ($P=0.005$).

Conclusions: Our findings do not support a potential link between vitamin D concentrations and the incidence of COVID-19, but low vitamin D serum level in COVID-19 patients might worsen the course of the disease and increase the need for oxygen supplementation or ventilation therapy.

Keywords: 1,25-dihydroxy-16,23-diene vitamin D3 • COVID-19 • SARS-CoV-2 • Calcitriol

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CLINICAL RESEARCH

Background

The active form of vitamin D is 1,25-dihydroxyvitamin D3 (1,25(OH)2D), which is also referred to as calcitriol. It is structurally related to steroid hormones and is actively hormone-like. It acts on target cells through the nuclear receptor VDR (vitamin D receptor). The breakthrough was the discovery that this receptor was not only present in bone cells, renal tubules, and intestinal epithelium, like previously was thought, but also in most cells in the human body; for example, in heart, blood vessel walls, brain, intestines, lymphocytes, macrophages cancerous, and many others [1]. It determines the presence of the VDR on many types of cells with pleiotropic effects of vitamin D. Particular importance is attached to the anti-inflammatory and immunomodulatory effects of vitamin D. 1,25(OH)2D stimulates the innate response, enhancing functions of macrophages, including chemotactic and phagocytotic properties, as well as the production of antibacterial peptides such as cathelicidines [2]. It also affects the specificity of the body's immune response, such as differentiation and function of T lymphocytes. It inhibits the maturation and differentiation of dendritic cells and indirectly causes the polarization of Th1 and Th17 lymphocytes toward cells with the Th2 phenotype [2]. 1,25(OH)2D directly affects the response of T lymphocytes by reducing the secretion of pro-inflammatory cytokines by Th1 and Th17 cells, as well as increasing the secretion of cytokines produced by Th2 [1-3]. At the same time, it promotes the development of regulatory T cell lines, both directly and indirectly, by dendritic cells (DC) operation. It also reduces the production of IgG and IgM by plasma cells. Cells of the immune system also express CYP27B1, the enzyme that converts 25 (OH)D to its active form, 1,25 (OH) 2D [1,2]. It is believed that a severe course of COVID-19 is associated with immune deregulation and excessive release of pro-inflammatory cytokines [3].

The best way to investigate whether the level of vitamin D is deficient, sufficient, or toxic is to measure 25-OHD levels in serum. Its half-life lasts 2-3 weeks and it reflects the concentration of vitamin D produced by the organism itself during sun exposure, as well as vitamin D that was taken as a supplement by the patient. Moreover, the level of 1,25(OH)2D can be influenced by hypocalcemia when increased secretion of parathyroid hormone can cause calcium mobilization from the skeleton and increase the renal production of 1,25(OH)2D while the patient is in fact vitamin D-insufficient or -deficient. The half-life of 1,25(OH)2D is only 4-6 [4] h, which is why in our study we decided to measure 25-OHD serum level.

Researchers in many countries have attempted to establish a correlation between the severity of the course of infection with the new coronavirus and the concentration of vitamin D in the serum and other factors [1,5-10].

The aim of our study was to determine whether vitamin D concentration influences the incidence and course of COVID-19 disease.

Material and Methods

This retrospective cohort study included 505 patients of the Central Clinical Hospital of the Ministry of the Interior and Administration (CSK MSWiA) in Warsaw discharged from the hospital between 21 April 2020 and 7 July 2020 (the observation period was 77 days). The study was conducted during the first wave of the COVID-19 pandemic in Poland, which was exceptionally mild for Poles. In each case, the end of the observation was the patient's discharge from the hospital or death. Patient age was 1-97 years. The patients stayed in surgical wards, non-invasive treatment wards, the Intensive Care Unit (ICU), and the Hospital Emergency Ward. During the observation, serum 25-OHD level (later called vitamin D as an abbreviation; 25-OHD level best reflects real vitamin D level in serum [4]) was determined with the chemiluminescence method using the DiaSorin Liaison apparatus. A level <20 ng/ml was considered deficient, a level ≥20 and ≤30 ng/ml was considered a suboptimal level, and >30 ng/ml was considered an optimal level. The confirmation of the SARS-CoV-2 virus infection was the result of a RT-PCR throat swab test performed on an ELITe InGenius® instrument with a Gene FinderTM COVID-19 Plus RealAmp Kit produced by ELITechGroup. Patients were divided into 2 groups according to the presence or the lack of COVID-19 infection and according to comorbidities recorded in the patient's medical history (or without comorbidities).

We analyzed the following associations: the prediction of COVID-19 incidence depending on the vitamin D level (comparative analysis of the COVID (+) and COVID (-) sub-cohorts), and the dependence of the course of the disease caused by SARS-CoV-2 on the vitamin D level (only in the group of COVID (+) patients) taking into account selected groups of comorbidities: respiratory tract diseases, cardiovascular disease, diabetes and others indicated by the patient. To assess the severity of COVID-19, the following criteria were used: use of oxygen therapy, use of ventilation therapy, patient's death (or discharge from the hospital), stay in the ICU, and the MEWS score [11] calculated on the 1st, 2nd, 4th, 6th, and 8th days of hospitalization. The information was obtained using electronic medical records stored in the IT systems, kept by medical staff in individual departments.

The study protocol was approved by the Bioethics Commission of the CSK MSWiA in Warsaw (no. 57/2020). The collected data were compiled performing a statistical analysis using a chi-squared test, Mann-Whitney U Test, and MANOVA for independent groups. A *P* value <0.05 was considered as statistical

Table 1. Vitamin D level in the study population.

Vitamin D level	COVID-19 (+)			COVID-19 (-)		
	Male	Female	Total	Male	Female	Total
Optimal (>30 ng/ml)	11	25	36 (19.4%)	26	39	65 (20.4%)
Suboptimal (20-30 ng/ml)	6	26	32 (17.2%)	39	32	71 (22.3%)
Deficiency (<20 ng/ml)	76	42	118 (63.4%)	98	85	183 (57.4%)
Total	**93**	**93**	**186 (100.0%)**	**163**	**156**	**319 (100.0%)**

Table 2. Occurrence of comorbidities in study population.

Comorbidities	COVID-19 (+)			COVID-19 (-)		
	Male	Female	Total	Male	Female	Total
Without any comorbidities	14	18	32 (17.2%)	20	32	52 (16.3%)
Diabetes	0	0	0	2	1	3 (0.9%)
Diabetes + respiratory tract diseases	0	0	0	0	1	1 (0.3%)
Diabetes + cardiovascular disease	1	0	1 (0.5%)	0	4	4 (1.3%)
Diabetes + other coexisting diseases	3	2	5 (2.7%)	2	1	3 (0.9%)
Diabetes + respiratory tract diseases + other coexisting diseases	0	1	1 (0.5%)	0	0	0
Diabetes + cardiovascular disease + other coexisting diseases	11	10	21 (11.3%)	18	13	31 (9.7%)
Diabetes + respiratory tract diseases + cardiovascular disease + other coexisting diseases	7	4	11 (5.9%)	10	10	20 (6.3%)
Cardiovascular disease	7	2	9 (4.8%)	14	3	17 (5.3%)
Cardiovascular disease + respiratory tract diseases	0	1	1 (0.5%)	1	4	5 (1.6%)
Cardiovascular disease + other coexisting diseases	20	25	45 (24.2%)	34	38	72 (22.6%)
Cardiovascular disease + Respiratory Tract Disease + other coexisting diseases	11	6	17 (9.1%)	21	16	37 (11.6%)
Respiratory tract diseases	1	0	1 (0.5%)	2	0	2 (0.6%)
Respiratory tract diseases + other coexisting diseases	4	4	8 (4.3%)	5	5	10 (3.1%)
Other coexisting diseases	14	20	34 (18.3%)	34	28	62 (19.4%)
Total	**93**	**93**	**186 (100.0%)**	**163**	**156**	**319 (100.0%)**

significance in accordance with the commonly accepted practice. For calculations we used PQ Stat version 1.8.2.160 and MS EXCEL 360.

Results

The study included 256 males (M=50.69%) and 249 females (F=49.31%). There were 186 COVID (+) patients (M=93, F=93) and 219 COVID (-) patients (M=163, F=156). There were 5 patients <18 years old and they constituted 1% of the study population.

Table 3. Correlation between vitamin D level in serum and oxygen therapy (Mann-Whitney U test).

Mann-Whitney Mann-Whitney U test	
Analyzed variables	Vitamin D (ng/ml); Oxygen therapy
Numerosity/not interpreted	0
Numerosity/lack of data	0
Significance level	0.05
Adjustment for continuity	Yes
Grouping variable	Oxygen therapy
Mann-Whitney	
U statistic	24 092.5
U' statistic	37 771.5
Two-sided P value (asymptotic)	0.0001
Z statistic (with correction for tied ranks)	4.2345
Two-sided (asymptotic) P value	0.000023

Summary		
Group	0*	1**
Abundance	296	209
Median	18.15	12.6
Lower quartile	11.75	7.2
Upper quartile	28.6	24

* Patients without oxygen therapy;
** patients who need oxygen therapy.

The median age was 65 years, the mean age was 61.23 years, and the standard deviation was 20.84. The comparison of vitamin D level in the COVID-19 infected group vs the uninfected group showed a 6.7% higher proportion of patients with vitamin D deficiency in the infected group (**Table 1**).

Patients suffering from selected groups of comorbidities were distinguished in the study population. Cardiovascular disease dominated in both studied groups – COVID (+) and COVID (-) – with a total share of about 40%. The proportion of patients with diabetes was about 20%, and a similar percentage of patients had respiratory tract diseases. In both groups, 16-17% of patients, had no comorbidities in their medical history. There were no significant differences in frequencies of comorbidities in the 2 study groups (**Table 2**).

The need for oxygen therapy increased with the decrease in vitamin D level in patients with COVID-19, especially in the case of comorbidities of respiratory tract diseases ($P<0.032$, chi-square) or other comorbidities ($P<0.042$, chi-square). There was a general association between the vitamin D level (classified into 3 groups: deficient, suboptimal and optimal level) and the need for oxygen therapy ($P=0.0147$, chi-square, $P=0.000023$, Mann-Whitney U test) (**Table 3**).

Multivariate analysis (MANOVA for independent groups) confirmed an association between lower vitamin D status and older age with the need for oxygen therapy in COVID (+) patients (**Table 4**).

The necessity for COVID (+) patients to stay in the ICU was significantly dependent on the presence of comorbidities ($P=0.009$, chi-square test, and $P=0.000236$, Mann-Whitney U Test) (**Table 5**). There was only 1 person (0.54%) in the ICU without comorbidities, and the remaining 36 patients referred to the ICU had comorbidities (19.35%). Comorbidities were present in 63.4% of patients without COVID hospitalized in the ICU.

The association between patient death and vitamin D level was at the borderline of statistical significance ($P<0.076$, chisquare), and 76.9% of those who died had low vitamin D levels (below 20 ng/ml). Among people with COVID-19 who had diabetes and in the group of patients with COVID-19 with comorbidities, a borderline association between death and vitamin D level was found ($P=0.057$; $P=0.098$, respectively, chi-square).

No association was found between vitamin D concentration in COVID (+) patients and need for ventilation therapy ($P=0.124$, chi-square), time spent in the ICU ($P=0.325$, chi-square), the need for hospitalization in the ICU ($P=0.1$, chi-square), and MEWS score on the 1st, 2nd, 4th, 6th, and 8th day of hospitalization ($P=0.279$; $P=0.326$; $P=0.218$; $P=0.401$; $P=0.919$, chi-square, respectively). These results are shown in **Table 1** (RAW data files).

However, multivariate analyses (MANOVA for independent groups) showed a positive correlation between the need to use ventilation therapy with lower 25-OHD concentration and older age ($P=0.005$) (**Table 3**).

Table 4. Correlation between age, vitamin D serum level, and oxygen therapy (MANOVA test).

One-way MANOVA		
	Age	**VIT D 3 (ng/ml)**
SS [BG]	45 041,87756	1592.355784
SS [WG]	173 811.4769	103 307.1697
df [BG]	1	1
df [WG]	503	503
F-statistic	130.348495	7.75314
P value	<0.000001	0.005564
Equality of variance – Brown-Forsythe		
F-statistic	39.76341	0.152249
P value	<0.000001	0.69656
Equality of variance – Levene		
F-statistic	38.732907	0.847033
P value	<0.000001	0.357834
F correction [Brown-Forsythe]		
F-statistic	145.381197	7.789529
Degrees of freedom	1/502,76916	1/451.665496
P value	<0.000001	0.005478
F correction [Welch]		
F-statistic	145.381197	7,789529
Degrees of freedom	1/502.76916	1/451.665496
P value	<0.000001	0.005478

MANOVA for independent groups	
Univariate MANOVA for independent groups	
Variables analyzed	Age; vitamin D3 (ng/ml); Oxygen therapy
Numerosity/uninterpreted	0
Numerosity/lack of data	0
Significance level	0.05
Grouping variable	Oxygen therapy
Numerosity	505
Number of groups	2
Number of variables in the model	2
Wilk's lambda	0.777974
Eta-square	0.222026
df1	2
df2	502
F-statistic	71.632777
P value	<0.000001

Table 4 continued. Correlation between age, vitamin D serum level, and oxygen therapy (MANOVA test).

MANOVA for independent groups	
Univariate MANOVA for independent groups	
Hotelling-Lawley Trace	0.28539
Eta-square	0.222026
df1	2
df2	502
F-statistic	71.632777
P value	<0.000001
Pillai-Bartlett Trace	0.222026
Eta-square	0.222026
df1	2
df2	502
F-statistic	71.632777
P value	<0.000001
BOX	
Degrees of freedom 1	3
Degrees of freedom 2	15 466 391.6
BOX M statistic	29.556415
F-statistic	9.807953
P value	0.000002

Descriptive statistics				
	0*		1**	
	Mean	Standard deviation	Mean	Standard deviation
Age	53.293919	20.764003	72.469	14.971776
Vitamin D3 (ng/ml)	21.318311	14.411123	17.713	14.216971

* Patients without oxygen therapy; **patients who need oxygen therapy.

Discussion

Our results show that low vitamin D level was associated with an increased frequency of using oxygen therapy and ventilation therapy in patients infected with SARS-CoV-2, and thus with a more severe course of disease.

Vitamin D reduces the risk of viral infections (eg, seasonal influenza) [1,2], and its deficiency is a risk factor for complicated course of some bacterial infections [12]. It is reasonable to check whether it has an impact on the incidence and course of COVID-19. In a systematic review of studies on the correlation between vitamin D level and respiratory tract infections in general and those caused by SARS-CoV-2, it was shown that serum 25-OHD deficiency increases the risk of severe acute respiratory infection (ARI), regardless of the etiological factor, and acute respiratory distress syndrome (ARDS), and worsens its course in children and adults [13]. It was found that higher 25-OHD level in the range of optimal level reduced the risk of respiratory tract infections in each age group [14]. In the study by Faul et al, a statistically significant association was found between low vitamin D level and the severity of COVID-19 and the development of ARDS [15]. There have also been several other key systematic review and meta-analysis

Table 5. Correlation between ICU hospitalization and comorbidities (Mann-Whitney U test).

Mann-Whitney U test	
Variables analyzed	ICU; comorbidities
Numerosity/not interpreted	0
Numerosity/lack of data	0
Significance level	0.05
Adjustment for continuity	Yes
Grouping variable	Comorbidities
Mann-Whitney	
U statistic	14 994.5
U' statistic	2 0369.5
Two-sided (exact) P value	0.000217
Z statistic (with correction for tied ranks)	3.676534
Two-sided P value (asymptotic)	0.000236

Summary		
Group	0*	1**
Abundance	84	421
Median	0	0
Lower quartile	0	0
Upper quartile	0	0

* Patients with no comorbidities;
** patients with comorbidities

studies that have the same conclusions, which are that reduced vitamin D levels are associated with an increased risk of infection from SARS-CoV-2 and increased duration and severity of COVID-19 [8-10].

We found no differences between the vitamin D level among those infected with SARS-CoV-2 and those uninfected, which indicates that the vitamin D level had no effect on the incidence of COVID-19 among the studied patients (*P*=0.4034, chi-square). These results do not coincide with the conclusions of the study on the US population in which an increased percentage of SARS-CoV-2-infected patients with low serum vitamin D levels were observed compared to patients with higher vitamin D level [16]. Researchers in Israel found a significant association between low vitamin D levels and a greater likelihood of developing COVID-19, as well as the risk of hospitalization for this reason [17]. Similarly, a UK study analyzed data of about 350 000 people and no significant association was found between vitamin D level and SARS-CoV-2 infection [18]. It should be considered that these studies were conducted in different populations. In the UK study, vitamin D levels were not measured during the pandemic, but in the past (in the years 2006-2010). When comparing the data resulting from both scientific works, factors that may have affected the obtained results, such as the average age of patients or the presence of comorbidities, should be examined.

It should be considered that the vitamin D level decreases significantly with age, and the older the age, the worse the course of infection [19]. As a result, the likelihood of a more severe course of COVID-19 may be due to the patient's age itself, not just vitamin D level. In the study from the United Kingdom,

it was found that low vitamin D level affects the severity of COVID-19, but does not translate into an increase in mortality [20]. Multivariate analysis in our study proved dependence between lower vitamin D status and older age with the need for oxygen therapy as well as ventilation therapy in COVID (+) patients. We showed an association at the border of statistical significance between low vitamin D level and death. This association is the most noticeable in patients who also have diabetes. However, in the whole study, the absolute number of patients whose disease was fatal was small (40 out of 186 COVID (+) persons). It can be assumed that if the group of people under study was larger, the association would be significant. This may be supported by the fact that 76.9% of patients who died were deficient in vitamin D. In another study, low calcium and vitamin D levels were associated with an increased risk of organ damage, sepsis, and death in patients with COVID-19 [21].

Based on the data of Italian researchers [22], it can be stated that there is no correlation between the level of sunlight in a given country and the observed percentage of COVID-19 patients.

However, based on data from Italy, no such association was found [22]. It follows that vitamin D alone cannot be the only determinant in assessing the risk of the incidence of COVID-19 and mortality due to COVID-19.

The limitation of the study is that we did not assess patients in terms of meeting the criteria of ARI and ARDS; therefore, the results obtained cannot be compared with other studies in this respect.

There is also a certain limitation associated with the retrospective character of our study, which made it difficult in certain cases to obtain specific information needed to make comparisons (eg, lack of assessing MEWS in certain patients).

Conclusions

The findings from this retrospective study from a single center in Poland supported the findings from other studies that low serum levels of vitamin D prolonged the course of COVID-19 disease and increased the need for oxygen therapy and respiratory support.

Another interesting conclusion is the patients with COVID-19 required hospitalization in the ICU more often if they had a comorbidity (without assessing the effect of vitamin D level). In our study, we showed that there is no effect of low vitamin D level in the serum on the incidence of COVID-19. Vitamin D level did not affect the transfer of the patient to the ICU, the length of the stay in the ICU (excluding patients who died), or the patient's condition according to MEWS on the 1st, 2nd, 4th, 6th, and 8th days of hospitalization. From the point of view of public health, it is very important to supplement and maintain vitamin D levels at the right level. This allows for milder symptoms of infection, no need for advanced medical procedures like mechanical ventilation, or hospitalization in the ICU, which translates into lower costs for the healthcare system. Supplementation is cheap, generally available, and easy to administer. Considering the other activities of vitamin D, its role in maintaining public health is large and continues to grow.

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