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Original Paper

IMPACT OF VITAMIN D THERAPY ON C-REACTIVE PROTEIN, FERRITIN, AND IL-6 LEVELS IN HOSPITALISED COVID-19 PATIENTS

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Vitamin D insufficiency is associated with poor prognosis in COVID-19 patients. Vitamin D supplementation is related to improved clinical outcomes in terms of intensive care unit admission and death, particularly in individuals with moderate-to-severe forms of COVID-19. The placebo-controlled five-day study was performed on 99 hospitalised COVID-19 patients with vitamin D insufficiency randomised into two groups. Vitamin D in the form of a sublingual sprayable microemulsion was given three times daily (daily dose 12,000 IU) to 51 patients with blood 25(OH)D levels below 30 ng/ml. Forty-eight patients in the control group received a placebo spray in the same daily regimen. Intention-to-treat (ITT) analysis and pre-protocol analysis were used to verify the impact of 25(OH)D level elevation on inflammatory markers. There was a statistically significant increase by 8.7 ± 7.6 ng/ml in 25(OH)D level from the baseline level of 15.6 ± 6.5 ng/ml in the case group. Individuals with moderately severe disease showed negative correlation between changes in 25(OH)D and C-reactive protein (CRP) levels in both ITT and pre-protocol analysis ($p < 0.05$). Mild and severe cases showed no statistical significance in CRP levels. There were no statistically significant changes in ferritin and IL-6 levels in ITT and pre-protocol analysis. In conclusion, high-dose vitamin D therapy was accompanied by significant decrease in CRP levels in COVID-19 patients with a moderate to severe illness.

Keywords: *Vitamin D insufficiency, sublingual sprayable microemulsion, inflammatory markers.*

INTRODUCTION

Several studies suggest that low 25(OH)D levels may be a predictor of poor prognosis in COVID-19 patients (Bilezikian *et al*., 2023). Vitamin D supplementation, as demonstrated by Pal *et al.*, is related to improved clinical outcomes in terms of ICU admission and death, particularly in individuals with moderate-to-severe COVID-19 necessitating hospitalisation (Pal *et al*., 2022). In the study the term *vitamin D insufficiency* is used to describe the clinical manifestation of COVID-19 in the presence of a low blood vitamin D level. The observational study performed by Kaufman *et al*. showed that the rate of SARS-CoV-2 positivity is both directly and inversely linked with the amount of circulating 25(OH)D, a connection that holds across latitude, race/ethnicity, sex, and age (Kaufman *et al*., 2020). Severity of clinical disease and mortality in COVID-19 upturns in case of vitamin D insufficiency. Vitamin D insuffi-

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ciency patients have a more pronounced inflammatory response, which is accountable for the increase in morbidity and mortality (Demir and Durmaz, 2021).

Numerous clinical studies in individuals with a 25(OH)D level of less than 20 ng/ml demonstrated an increased risk of COVID-19 compared to individuals with a 25(OH)D level of 30–34 ng/ml (Kaufman *et al*., 2020; Ling *et al*., 2020; Radujkovic *et al*., 2020; Xu *et al*., 2020; Demir *et al*., 2021; Sulli *et al*., 2021). An extensive retrospective cohort study published by Oristrell *et al.* showed that those who received cholecalciferol or calcifediol supplementation and achieved serum 25(OH)D levels of 30 ng/ml had superior COVID-19 treatment results (Alcala-Diaz *et al*., 2021; Oristrell *et al*., 2021).

Numerous studies have been performed to determine the benefits of vitamin D on individuals with COVID-19 (Murai *et al*., 2021; Da Rocha *et al*., 2021). However, researchers produced contradictory findings (Bilezikian *et al*., 2023). After high-dose intramuscular D3 treatment in the early period of COVID-19, no difference in duration of hospital stays, endotracheal intubation, or death rates in critical patients in the ICU has been seen in the study of Güven and Gültekin (Güven and Gültekin, 2021). Another study had similar findings, showing no link between 25(OH)D levels and COVID-19 severity or death in 341,484 UK Biobank individuals (Hastie *et al*., 2020). The Mendelian randomisation study by Butler-Laporte *et al.* found no evidence to indicate a relationship between 25(OH)D levels and COVID-19 susceptibility, severity, or hospitalisation in a two-sample MR investigation (Butler-Laporte *et al*., 2021). The systematic review and meta-analysis done by Bassatne and colleagues, where they analysed 31 peer-reviewed observational studies, found that while the existing data to date, derived primarily from low-quality observational studies, may be interpreted as indicating a tendency toward a link between low blood 25(OH)D levels and COVID-19-related health outcomes, this link was not found to be statistically significant. A possible preventive effect of calcifediol supplementation on COVID-19-related ICU admissions could be found (Bassatne *et al*., 2021).

At the same time, it is worth mentioning contradictory findings as well in response to inflammatory markers. Higher levels of CRP during COVID-19 have been found to have greater complications and a more severe case of COVID-19 overall (Sadeghi-Haddad-Zavareh *et al*., 2021). Several studies that are in line with our study, have shown an inverse association between vitamin D and CRP (Tao *et al*., 2015; Kruit and Zanen, 2016). One study showed inverse correlation between vitamin D and CRP, but more importantly highlighted that inverse correlation is stronger in patients who have inflammatory diseases compared to patients who do not (Kruit and Zanen, 2016). Yet, another study shows that there is not a noticeable inverse relation between vitamin D supplementation and inflammatory biomarkers, specifically in asymptomatic adults (Amer and Qayyum, 2012). The study where vitamin D and inflammatory marker CRP were compared in people aged 60 years and older, showed that CRP levels were lower in patients with overall higher 25(OH)D levels. These findings with vitamin D intervention study could help answer the question if vitamin D decreases CRP levels or if CRP decreases 25(OH)D levels (Aspell *et al*., 2019).

A single-centre study for COVID-19 and inflammatory markers showed that in the first wave of COVID-19 inflammatory markers were higher than in the second wave, most likely due to changed guidelines on treating patients (Asghar *et al*., 2021).

Vitamin D may affect ferritin and IL-6 levels as it influences iron metabolism and erythropoiesis. Iron is one of the essentials for vitamin D synthesis (Azizi-Soleiman *et al*., 2016). There is a probability that vitamin D downregulates mRNA expression of hepcidin levels. It is believed that antimicrobial hepcidin peptides influence iron absorption and release through activating and suppressing ferroprotein, which is a cellular iron exporter (Zughaier *et al*., 2014). In a systematic review done by Arabi *et al.* that included a total of 14 reports and 1385 individuals with mean baseline of 25(OH)D levels ranging between 10 and 30 ng/ml, it was observed that vitamin D supplementation in 11 of the included studies did not improve ferritin concentrations overall. The study concluded that vitamin D supplements had no significant effect on ferritin levels, while having positive effects on transferrin saturation and iron status (Arabi *et al*., 2020). However, a prospective observational study by Singh *et al.* that included 343 COVID-19 positive asymptomatic and 59 ICU patients, argued that inflammatory markers such as serum ferritin and IL-6 were significantly elevated in critically ill patients and high levels of 25(OH)D were correlated with reduced levels of IL-6 (Singh *et al*., 2021). In another cross-sectional study by Teama *et al*. that included 124 patients diagnosed with COVID-19, a negative correlation was observed between vitamin D and ferritin. The study concluded that vitamin D deficiency significantly and negatively correlated with ferritin. This indicates that vitamin D might have a beneficial role on the systemic inflammatory state of COVID-19 (Teama *et al*., 2021).

The aim of this study was to investigate the impact of high dose vitamin D supplementation on laboratory markers of systemic inflammation such as CRP, ferritin, and IL-6 in hospitalised patients with COVID-19.

MATERIALS AND METHODS

The study was performed at Pauls Stradiņš Clinical University Hospital (PSCUH) during the COVID-19 pandemic from February till July 2021 (ClinicalTrials.gov Identifier: NCT05502068). The blood samples were analysed at the Joint Laboratory of the hospital. Patients with confirmed SARS-CoV2 infection (PCR) were randomly divided into two groups: the intervention group (group B) received vitamin D in the form of a sublingual sprayable microemulsion (food supplement LYL love your life® sunD3 LYLmicro™) of 4,000 IU three times daily after breakfast, lunch

and dinner; the control group (group A) received the same regiment of placebo spray.

Population. A total of 99 inpatients were selected for the study, 48 patients in the vitamin D group and 51 in the control group. All patients received standard care for COVID-19 and existing comorbidities (diabetes, arterial hypertension, etc.) according to hospital approved protocol. The primary outcome was defined as the change in the level of inflammatory markers CRP, ferritin, IL-6, and the severity of the disease. Only those patients whose 25(OH)D level was below 30 ng/ml were included in the study. Patients with mental health problems, eGFR ≤ 30 ml/min, 25(OH)D level ≥ 30 ng/ml, pregnant women and any other illness or condition that the researcher deemed may interfere with the results were excluded. All individual patient data obtained during the study were coded and were available only to the study participants. The duration of the pharmaceutical intervention was five days during admission in the COVID-19 ward.

Disease severity was defined by the blood oxygen saturation level. Mild clinical manifestation was characterised by SpO2 ≥ 94%, moderate 90% ≤ SpO2 < 94% and severe – SpO2 < 90%. Age, BMI, GFR, vitamin D and COVID-19 severity were considered as randomisation parameters. 25(OH)D, ferritin and IL-6 were analysed by chemiluminescence immunoassay (Atellica IM 1300 Analyzer, Siemens) while C-reactive protein (N: 0–5 mg/l) was processed by a turbidimetric method using Atellica CH 930 Analyzer, Siemens.

Statistical analysis. Patient data were analysed in two runs: including all patients (Intention-to-Treat (ITT) analysis) and stratifying patients according to the increase in 25(OH)D (pre-protocol analysis for 25(OH)D elevation effect: responders/non-responders). Each patient's sample was coded by signing the consent form. The specific code was used throughout the study, thus ensuring patient anonymity. Patient's personal information and the corresponding code were contained in a database, the access of which was coded with a password and available only to specific employees of the study. Thus, the preservation of patients' personal information was prevented. Only the patient code was used in the second database, where data on measurements, patient treatment steps, and other study-related data were entered. This data were used to obtain and analyse research results.

Shapiro–Wilk (n < 50 in the group) or Kolmogorov–Smirnov (n > 50 in the group) tests were used to evaluate whether the data followed the normal distribution with statistically significant PN. The difference between groups with a nominal distribution was determined by the chi-squared ($\chi 2$) criterion method. A statistically significant difference between groups was considered at $P\chi < 0.05$. Cramer's V was chosen to determine the relationship between nominal data: above 0.10 — weak relationship, above 0.30 — medium, and above 0.50 — strong relationship. The T-test (statistical confidence PT) was used to determine differences between group numerical values (mean or median) if data from both groups were normally distributed. The Mann–Whitney test (PMV) was applied if at least one group was not normally distributed. The ANOVA test (PF) or Kruskal–Wallis (PKV) test was used if more than two groups were compared.

The relationship between nominal and numerical indicators was determined using the eta (η) indicator: up to 0.2, the relationship was considered very weak; from 0.2 to 0.4 weak; from 0.4 to 0.7 moderately tight; from 0.7 to 0.9 tight; above 0.9 very tight, and 1.00 perfect. In all tests, a statistically significant difference between groups was considered when $p < 0.05$. All tests were performed using IBM SPSS Statistics version 25.0.

RESULTS

The mean age in the placebo group was 67.1 ± 13.5 years, with an interval of 34 to 88 years. The confidence interval (CI 95%) for the mean was 59.2 to 67.0 years. The mean age in the vitamin D group was 63.1 ± 13.9 years, with an interval of 34 to 90 years. Both groups had normal distribution according to the specific indicator.

In the case of group B only responders (true case group), and in group A only non-responders (true placebo group) were selected. Inclusion/exclusion was determined by statistically significant changes in 25(OH)D levels according to the coefficient of variation (CV) of the laboratory equipment (CL5I DocumentEPQ5-A3). Those participants whose 25(OH)D level on the sixth day was higher than on the first day were considered to be responders. The equation used for inclusion was: CvitD2 CvitD1+ CV (responders); CvitD2CvitD1+CV (non-responders); CvitD2 – level of 25(OH)D on the 6th day; CvitD1 – level of 25(OH)D on the 1st day; CV – coefficient of variation.

90.2% of all participants in group B fit the criteria of the true case group (Table 1), whereas 34 participants (70.7%) in the placebo group showed no increase in 25(OH)D levels in the blood.

The distribution of patients in both groups by severity of disease was statistically similar (Table 2). The difference between groups was not statistically significant ($p = 0.06$).

The level of 25(OH)D in group B increased on average by 8.69 ± 7.63 ng/ml, the median increased by 5.82 ng/ml with an IQR (interquartile range) of 8.37 ng/ml. The baseline of 25(OH)D levels in true case group was 15.58 ± 6.48 mg/l

Table 1. Number of responders (CvitD2 > CvitD1+CV) and non-responders (CvitD2 < CvitD1+CV) in intervention (B) and control (A) groups

Study group	Total number of patients	Response to vitamin D therapy			
		CvitD2 > CvitD1+CV		CvitD2 < CvitD1+CV	
		number	%	number	%
A	48	14	29.2	34	70.8
B	51	46	90.2	5	9.8

Table 2. Distribution of patients according to severity of disease COVID-19 in case (B+) and control (A-) group

Disease severity	Group				Statistical analysis	
	A- group		B+ group		P_χ	V
	number	%	number	%		
Mild	8	23.53	8	17.39	0.06	0.27
Medium	21	61.76	20	43.48		
Severe	5	14.71	18	39.13		
Total	34	100%	46	100%		

P_χ – statistical reliability of chi-squared ($\chi 2$) criterion method; V – Cramer's V index for relationship.

Table 3. Changes of 25(OH)D in the case (B+) and control (A-) group

Study group	Delta values				Statistical analysis	
	mean, ng/ml	SD, ng/ml	median, ng/ml	IQR	P_{MV}	η
A-	–1.87	1.97	–1.88	3.05	**2.72×10^{-14}**	0.44
B+	8.69	7.63	5.82	8.37		

SD – standard deviation; IQR – interquartile range; P_{MV} – statistical reliability of the difference in delta medians between the two groups (A- vs B+) using the Mann–Whitney U test; η – eta or relationship between the nominal and numerical indicators. Value in bold – statistically significant.

(median 13.35 mg/l, IQR 12.56 mg/l), while in true placebo group – 17.33 ± 6.71 mg/l (median 16.74 mg/l, IQR 12.15 mg/l). The change in 25(OH)D levels in group B over five days was considered statistically significant PV = 2.72×10^{-14} (Table 3, Fig. 1). However, it should be noted that the delta values of 25(OH)D level in five patients (9.8%) from group B did not rise above the coefficient of validation.

In the placebo group, the 25(OH)D level decreased on average by 1.87 ± 1.97 ng/ml. The resulting mean change was also statistically significant.

There were no statistical differences in delta values of 25(OH)D level comparing disease-severity groups (Table 4). However, the largest increase in 25(OH)D level was observed in patients with a severe form of COVID-19. The median value in the severe group was twice as high than in the mild group.

A decrease of C-reactive protein (CRP) was observed in both groups. The baseline of CPR levels in true case group was 98.11 ± 74.55 mg/l (median 76.47 mg/l, IQR 104.86 mg/l), while in true placebo group 63.40 ± 45.45 mg/l (median 52.57 mg/l, IQR 77.78 mg/l). However, the delta values did not have a normal distribution, and thus the medians were compared (Fig. 2). The mean delta value of CRP level before and after the treatment (Table 5) in the B vial group was significantly higher than in the A vial group: –52.98 ± 82.34 mg/l vs. –18.77 ± 54.17 mg/l. The differences between two groups were statistically significant ($p < 0.05$). No statistically significant differences were found between the groups when we analysed CRP changes or deltas by ITT analysis. No statistically significant differences in delta values of the CRP level in mild and severe groups were found

Table 4. Changes of 25(OH)D according to severity of the disease in the case (B+) and control (A-) group

Severity of COVID-19	Delta values (25(OH)D)				Statistical analysis	
	mean, ng/ml	SD, ng/ml	median, ng/ml	IQR	$P_{F\ or\ KV}$*	P_{KV} $P_{T\ or\ MV}$ ^
	A- group					
Mild	–1.58	2.15	–2.14	3.97	0,43	**1.44×10^{-11}**
Moderate	–1.72	1.83	–1.83	3.03		
Severe	–2.93	2.31	–4.08	4.35		
	B+ group					Mi: **$3{,}10 \times 10^{-4}$**
Mild	5.53	3.65	4.06	5.86	0.14	Mo: **4.31×10^{-8}**
Moderate	6.57	3.64	5.46	4.14		
Severe	12.44	10.43	7.92	14.51		S: **7.96×10^{-4}**

SD – standard deviation; IQR – interquartile range; * P_F – statistical reliability with ANOVA (underline value) of mean; P_{KV} – statistical reliability with Kruskal–Walli test of median; ^ P_T – statistical reliability of the difference in delta mean between the two groups (A- vs B+) using the T-test (underline value); P_{MV} – statistical reliability of the difference in delta medians between the two groups (A- vs B+) using the Mann–Whitney U test; Mi – Mild; Mo – Moderate; S – Severe. Values in bold – statistically significant.

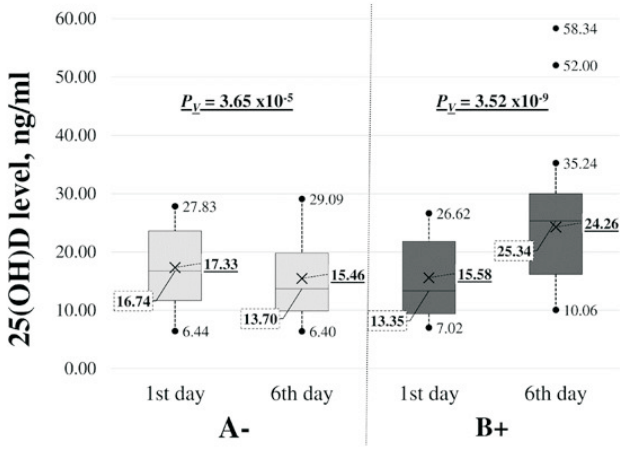

Fig. 1. Statistically significant increase of 25(OH)D level in the true case group (B +) in comparison with the control group (A-).

This box plot shows the median (value in a dashed square) with quartile distribution in patients. The end of the dashed line outside box has a maximum and minimum value; arithmetic mean (underlined); Pv – statistical reliability for paired data with Wilcoxon signed-rank test.

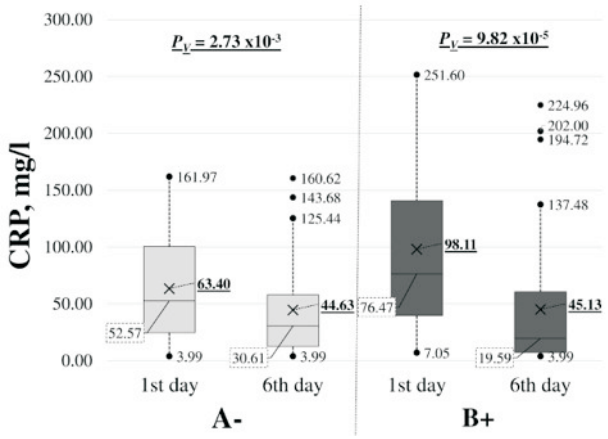

Fig. 2. Statistically significant decrease of CRP level in the true case group (B +) in comparison with the control group (A-).

Table 5. Changes of CRP in case (B+) and control (A-) group

Study group	Delta values				Statistical analysis	
	mean, ng/ml	SD, ng/ml	median, ng/ml	IQR	P_{MV}	η
A-	–18.77	54.17	–15.59	46.85	**$4{,}24 \times 10^{-2}$**	0.05
B+	–52.98	82.34	–37.74	87.57		

SD – standard deviation; IQR – interquartile range; P_{MV} – statistical reliability of the difference in delta medians between the two groups (A- vs B+) using the Mann–Whitney U test; η – relationship between the nominal and numerical indicators. Value in bold – statistically significant.

Table 6. Changes of CRP according to severity of the disease in the case (B+) and control (A-) group

Severity of COVID-19	Delta values (CRP)				Statistical analysis	
	mean, ng/ml	SD, ng/ml	median, ng/ml	IQR	P_F	P_F P_T ^
			A- group			
Mild	–23.69	36.09	–20.77	51.40	0.57	0.31
Moderate	–11.81	54.23	–11.02	44.97		
Severe	–40.15	79.70	–19.00	147.03		
			B+ group			Mi: 0.69 Mo: **4.06×10^{-2}** S: 0.82
Mild	–32.05	42.62	–20.73	73.75	0.50	
Moderate	–64.60	96.72	–64.40	145.62		
Severe	–49.38	79.79	–40.27	66.68		

SD – standard deviation; IQR – interquartile range; P_F – statistical reliability with ANOVA (underline value) of mean; ^ – P_T – statistical reliability of the difference in delta mean between the two groups (A- vs B+) using the T-test; Mi – Mild; Mo – Moderate; S – Severe. Value in bold – statistically significant.

(Table 6). However, the decrease in CRP level in the moderate severe group was statistically significant compared to the placebo group ($p < 0.05$) in ITT analysis and also in pre-protocol analysis (Table 6). In the ITT analysis, the difference between the groups was less significant or smaller than in the pre-protocol analysis.

Therefore, it can be concluded that vitamin D in the moderate-severe COVID-19 patient subgroup contributed to the reduction of CRP level.

The response of other inflammatory markers such as ferritin and IL-6 was also investigated. The ferritin level in the placebo group decreased on average, but in the B group, the indicator increased on average (Table 7). It should be noted that there was no normal distribution in group B and thus the median values were compared. Despite the rise in average ferritin value, the median delta value in group B indicated a decrease of ferritin level. The differences between true and placebo groups were not statistically significant, and obtained data also showed a very large distribution in blood levels of ferritin.

The ferritin delta values between the two groups were also not statistically significant applying a non-parametric data analysis method. In addition, there was a high dispersion in both groups.

Table 7. Changes in ferritin level in the case (B+) and control (A-) group

Study group	Delta values				Statistical analysis	
	mean, ng/ml	SD, ng/ml	median, ng/ml	IQR	P_{MV}	η
A-	–51.51	288.02	–82.80	402.73	0.28	0.03
B+	90.98	493.76	–26.40	469.93		

P_{MV} – statistical reliability of the difference in delta medians between the two groups (A- vs B+) using the Mann-Whitney U test; η – relationship between the nominal and numerical indicators.

Table 8. Changes in IL-6 level in the case (B+) and control (A-) group

Study group	Delta values				Statistical analysis	
	mean, pg/ml	SD, pg/ml	median, pg/ml	IQR	P_{MV}	η
A-	–10.99	54.93	–4.20	43.95	0.29	0.01
B+	–17.29	37.18	–20.90	41.60		

P_{MV} – statistical reliability of the difference in delta medians between the two groups (A- vs B+) using the Mann–Whitney U test; η – relationship between the nominal and numerical indicators.

A decrease of IL-6 was observed in both groups, but the delta value did not have a normal distribution, and thus non-parametric data methods were applied. There was no statistically significant difference in delta values between the groups ($p > 0.05$). The wide range of delta values in both groups, especially in group A (Table 8) may have contributed to such results.

A possible explanation of such distribution could be explained by the different baseline levels, which could again be tested by analysis in different groups of patients with disease severity. However, there was also no statistically significant difference between the severity groups of patients.

It should be noted that there was one patient in each group who showed significantly higher IL-6 levels compared to others. The IL-6 levels in the patients of A and B groups were 1552.10 pg/ml and 1766.50 pg/ml, respectively. Due to this, two patients were excluded from analysis.

DISCUSSION

Our data showed that large doses of vitamin D may effectively decrease the CRP level in vitamin D deficient COVID-19 patients during just five-day-intervention compared to those who had not received vitamin D. Literature analysis shows that vitamin D decreases synthesis of proinflammatory markers in macrophages by increasing synthesis of anti-inflammatory markers in T-cells (Th1). As a proinflammatory marker IL-6 impacts synthesis of CRP in liver and thus, as a result, vitamin D decreases CRP via decrease of IL-6 synthesis in macrophages (Calton *et al.*, 2015). In our study we did not observe a statistically significant decrease of IL-6. We did not also observe a significant decrease of IL-6 synthesis in both groups. The study results do not exclude the impact of rapid decrease of IL-6 values in group B at the first day of intervention, and thus a dynamic

evaluation is crucial. For these reasons additional studies are necessary to observe the dynamic changes in IL-6 in blood induced by vitamin D. The increase of vitamin D level by average 8 ng/ml in blood was accompanied by decrease of CRP level in patients with moderately severe clinical manifestation of the disease. Exogenous vitamin D toxicity (25(OH)D > 150 ng/ml) is a serious condition, but it is relatively rare. Cholecalciferol supplementation is less likely to produce excessively high values of 25(OH)D because it is the gold standard for the equivalence between international units and molecular mass. The conversion of vitamin D3 to calcifediol is related to many factors, including liver function and vitamin D storage in adipose tissue. Our intervention was significantly shorter compared to the study (Fassio *et al*., 2020) where the high-dose cholecalciferol intervention didn't highly accelerate the levels of 25(OH)D during the first week of interventions. Study results showed that a dose of 100,000 IU per two weeks increased the mean 25(OH)D levels by 10 ng/ml in the first week. We did not use calcifediol in this study due to a high risk of vitamin D excess, promoting undesired side effects (such as kidney failure). The halftime of vitamin D3 is 24 h, while for calcifediol it is 2–3 weeks. In the study we defined the true case group to investigate the effect of the 25(OH)D level increase on inflammatory markers compared to those, who did not receive the supplement. Group B patients whose 25(OH)D levels did not rise above the coefficient of variation were excluded. It was necessary to analyse the effect of the increase of 25(OH)D levels on inflammatory markers. The true placebo group was defined to exclude an uncontrolled increase of 25(OH)D levels from the food supplements or other exogenous sources of vitamin D in group A.

Based on the results, one might assume that only the moderate severity of COVID-19 has the most positive outcome. However, it is worth mentioning that in most cases mild clinical manifestation of the disease is self-limiting; thus, the intervention with vitamin D might not cause a statistically significant improvement. The severe form of COVID-19 is not significantly affected by vitamin D, thus showing that supplementation with vitamin D3 should be investigated according to other comorbidities and drug interactions.

For instance, a similar randomised placebo-controlled study (SHADE) where participants were randomised to receive 60,000 IU of cholecalciferol daily for seven days did not show any effect on IL-6, ferritin, and CRP levels (Rastogi *et al*., 2022). Comparing the two studies, we observed differences in dosing and patients' recruitment criteria. During the SHADE study, the level of vitamin D was increased by ~40 ng/ml on average, compared to the 8.6 ng/ml increase in our study. Such a change of 25(OH)D level was achieved by 60,000 IU/daily intervention, compared to our intervention (12,000 IU/daily). It is worth mentioning that the included population in the SHADE study didn't have a significantly high level of CRP to allow to study the impact of vitamin D. Secondly, the population was significantly lower compared to our study. Thirdly, there was no stratification of patients by disease severity compared to the study provided in our research site. Additional survival study, however, is necessary to verify the most appropriate therapy for severe COVID-19 form.

The total vitamin D dose in our study was at 60,000 IU, which was much lower compared to other high-dose interventions (Murai *et al*., 2021; Cannata-Andía *et al*., 2022; Annweiler *et al*., 2022; Rastogi *et al*., 2022).

The study with a single oral bolus dosage of 100,000 IU of cholecalciferol did not show any improvement in the outcomes of COVID-19. However, this study showed that a lower D vitamin level at admission time was associated with higher pulmonary involvement and a higher rate of ICU admission. According to this study, the level of 25(OH)D 25 ng/ml was associated with better outcome (Cannata-Andía *et al*., 2022). Thus, it may be helpful to provide screening blood tests of vitamin D to select patients with a higher risk and start immediate supplementary treatment with cholecalciferol.

Studies with a single high bolus dose of 200,000 IU of cholecalciferol did not show any effect on mortality, length of hospital stay, hospital discharge, ICU admission, and rates of mechanical ventilation, despite achieving sufficient 25(OH)D levels ≥ 30 ng/mL (Murai *et al*., 2021). However, studies with a larger single dose of 400,000 IU compared to the standard dose of 50,000 IU, in older adults within 72 hours after the diagnosis of COVID-19 suggested reduced overall mortality on day 14. The increase of 25(OH)D levels on day 7 was significantly higher in the high-dose group on average at 38 ng/ml compared to 8.4 ng/ml in the standard-dose group (Annweiler *et al*., 2022). There are some trials with smaller population groups receiving smaller doses of cholecalciferol for two weeks (Sabico *et al*., 2021; Sánchez-Zuno *et al*., 2021).

In another multicentre randomised controlled trial with patients who had mild to moderate COVID-19 symptoms and suboptimal vitamin D were receiving 5000 IU and 1000 IU of oral cholecalciferol daily for 2 weeks. This study reports that a 5000 IU daily oral vitamin D3 supplementation significantly shortened recovery time, but there were no significant differences in ICU, mortality events, and days to discharge. Within-group comparisons also showed a significant decrease in IL-6 levels over time in both groups but were not clinically significant in between-groups. However, the increase in vitamin D level was statistically significant on average at only 3.6 ng/ml. It is worth mentioning that 47% of patients also received vitamin C supplementation (Sabico *et al*., 2021).

In a small randomised clinical trial, 22 outpatients with a mild disease course received oral supplementation of 10,000 IU daily of vitamin D3 for 14 days. The administered supplementation was sufficient to increase total 25(OH)D serum levels significantly on day 14 (28.2 ng/ml, on average), and the intervention group had fewer symptoms on the 7^{th} and 14^{th} day of follow-up (Sánchez-Zuno *et*

al., 2021). According to research conducted in Brazil (200,000 IU/5000 g) (Murai *et al*., 2021) and in France (80,000 IU/2000 g) (Annweiler *et al*., 2020), using vitamin D3 during COVID-19 hospitalisation does not decrease the risk of death. Additional studies are necessary to analyse mortality in patient groups who have received vitamin D according to our protocol and to determine the optimal dosage.

We settled for this model of placebo-controlled prospective study in order to escape several limitations of other studies, e.g., in the case of observational studies the randomisation was limited due to clinical judgments of healthcare providers according to patients' clinical condition (Alcala-Diaz *et al*, 2021). In the case of prospective studies, there are only a limited number of placebo-controlled trials available. There are limitations in statistical analysis if only the intervention was taken into account, without consideration of the true changes in blood of 25(OH)D levels, which is an essential factor for the analysis of the variations in inflammatory markers (Murai *et al*., 2021; Da Rocha *et al*., 2021; Fernandes *et al*., 2022)

According to the result of this study vitamin D did not produce any significant changes in ferritin and IL-6 levels. Other studies support current findings. A retrospective study by Feld *et al.* showed that despite greater ferritin levels being related to all-cause mortality, ferritin could not predict numerous critical outcomes, including death, with any certainty (Feld *et al*., 2020). Some researchers suggested that ferritin levels could be used to predict the severity of COVID-19 (Kappert *et al*., 2020; Ruscitti *et al*., 2020; Taneri *et al*., 2020). On the other hand, a retrospective cohort study that included 158 confirmed COVID-19 patients showed that COVID-19 patients with low serum iron levels were prone to suffer from severe disease and multiple organ damage (Lv *et al*., 2021). In our case, IL-6 levels, similarly to ferritin levels, did not show any statistically significant changes. A supporting study by Fernandes *et al.* indicated that a single high dose of 200,000 IU vitamin D had no effect on cytokines, chemokines, and growth factors in patients with moderate to severe COVID-19 (Fernandes *et al*., 2022).

CONCLUSIONS

There was a rapid elevation of circulating 25-hydroxyvitamin D levels in hospitalised vitamin D deficient COVID-19 patients treated by high-dose sublingual sprayable vitamin D microemulsion for five days. Pre-protocol analysis revealed that high-dose vitamin D therapy was accompanied by significant decrease in CRP levels in patients with a moderate to severe illness. In contrast, ITT analysis was not able to detect statistically significant changes in all measured inflammatory marker (CRO, ferritin and IL-6) levels during the short term high-dose vitamin D spray therapy. Additional studies must be performed to verify the correlation between vitamin D intervention and mortality outcomes in COVID-19 patients.

ETHICS

The study was conducted in accordance with the declaration of Helsinki and approved by the Ethics Committee of Pauls Stradiņš Clinical University Hospital (code of approval: 170621-24L; date of approval: 25/03/2021). ClinicalTrials.gov Identifier: NCT05502068 (date of approval**:** 16/08/2022). Informed consent was obtained from all subjects involved in the study.

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D VITAMĪNA TERAPIJAS IETEKME UZ C REAKTĪVO OLBALTUMU, FERITĪNA UN IL-6 SERUMA KONCENTRĀCIJU HOSPITALIZĒTIEM PACIENTIEM AR COVID-19

D vitamīna nepietiekamība Covid-19 pacientiem ir saistīta ar sliktu prognozi. D vitamīna substitūcija pacientiem ar vidēji smagas un smagas norises Covid-19 samazina risku nomirt vai nokļūt intensīvās terapijas nodaļā. Mēs veicām nejaušinātu placebo kontrolētu piecu dienu pētījumu 99 hospitalizētiem Covid-19 pacientiem ar 25(OH)D līmeni asinīs zem 30 ng/ml. D vitamīns zem mēles izsmidzināmas mikroemulsijas veidā tika ievadīts trīs reizes dienā (dienas deva 12 000 SV) 51 pacientam, bet 48 pacienti kontroles grupā saņēma placebo aerosolu tādā pašā dienas shēmā. Lai pārbaudītu 25(OH)D līmeņa paaugstinājuma ietekmi uz iekaisuma marķieriem, izmantojām ITT (*intention-to-treat*) analīzi un pirmsprotokola analīzi. Aktīvās terapijas grupā novērojām statistiski nozīmīgu 25(OH)D pieaugumu no sākotnējā līmeņa 15,6 ± 6,5 ng/ml par 8,7 ± 7,6 ng/ml. Pacientu grupa ar 25(OH)D līmeņa paaugstināšanos tika definēta kā aktīvās ārstēšanas grupa. Indivīdiem ar vidēji smagu slimību konstatējām negatīvu korelāciju starp 25(OH)D un CRP līmeņa izmaiņām gan ITT, gan pirmsprotokola analīzē ($p < 0,05$), bet vieglas un smagas slimības norises gadījumā neatradām statistiski nozīmīgas CRP izmaiņas. Tāpat ITT un pirmsprotokola analīzē neatradām statistiski nozīmīgas feritīna un IL-6 līmeņa izmaiņas. Secinājums: piecu dienu ilga D vitamīna terapija saistīta ar būtisku CRP līmeņa pazemināšanos Covid-19 pacientiem ar vidēji smagu slimības gaitu.