VIA MEDICA

ORIGINAL ARTICLE

Disaster and Emergency Medicine Journal
2021, Vol. 6, No. 3, 144–153
DOI: 10.5603/DEMJ.a2021.0024

ISSN 2451–4691, e-ISSN 2543–5957

RELATIONSHIP BETWEEN SERUM 25-HYDROXYVITAMIN D CONCENTRATION AND ACUTE INFLAMMATORY MARKERS IN HOSPITALIZED PATIENTS WITH SARS-COV-2 INFECTION

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ABSTRACT

INTRODUCTION: There is experimental and clinical evidence that the serum concentration of 25-hydroxyvitamin D [25(OH)D)] may decrease in acute systemic inflammatory responses; in this context, low values may not necessarily indicate a pre-existing deficiency. This may also apply to low 25(OH)D levels found in the context of the systemic inflammatory response caused by SARS-CoV-2 infection.

To conduct a systematic review of the relationship between serum 25(OH)D and the concentrations of C-reactive protein (CRP), interleukin 6 (IL-6) and tumour necrosis factor α (TNF-α) in acutely hospitalized patients with SARS-CoV-2 infection.

MATERIAL AND METHODS: We searched PubMed, EMBASE, Google Scholar and the Cochrane Database of Systematic Reviews for studies published between January 2020 and February 2021. In each study, the authors compared levels of inflammatory markers between patients reported as having low levels of 25(OH)D and those above the study cut-off.

RESULTS: 18 studies were included (n = 3482, mean age 63.5 ± 9.3 years, 56.9% men). The cut-off for the definition of low 25(OH)D varied across studies. In all studies, mean values for inflammatory markers were higher in the low 25(OH)D groups. These differences were statistically significant ($p < 0.05$) in 6/15 studies with CRP, 4/8 with IL-6 and 0/1 with TNF-α.

CONCLUSIONS: Markers of acute systemic inflammatory response were elevated in patients with SARS-CoV-2 infection and low concentrations of 25(OH)D. Therefore, the vitamin D status in those patients should be interpreted with caution, and studies should be designed to assess whether hypovitaminosis D could be an epiphenomenon.

KEY WORDS: SARS-CoV-2, COVID-19, interleukin 6, C-reactive protein, vitamin D, 25-hydroxyvitamin D

Disaster Emerg Med J 2021; 6(3): 144–153

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INTRODUCTION

The COVID-19 pandemic has by March 2021 caused more than 2.7 million deaths worldwide [1] and forced medical science not only to create vaccines at a pace never seen before but also to study risk factors, especially modifiable ones, to reduce the risk of severe or fatal forms of SARS-CoV-2 infection. One of the studied modifiable risk factors has been vitamin D status.

To date, four systematic and meta-analytical studies have analysed the issue and have concluded that there is a probable cause-and-effect association between low concentrations of 25-hydroxyvitamin D [25(OH)D] and increased mortality and severity due to SARS-CoV-2 infection [2–5]. Scientific controversy has arisen for three reasons: first, because there is experimental and clinical evidence before the COVID-19 pandemic, that acute inflammation can cause a reduction in 25(OH)D concentrations, in patients who previously had normal concentrations, for which the evaluation of the status of this vitamin should be taken with caution in this scenario [6–8]. Second, because the studies on which the metanalytical studies were based did not determine baseline concentrations of 25(OH)D before infection or hospital admission for severe or fatal forms of SARS-CoV-2 infection. Szeto *et al.* (2020) recently published a study where they determined the serum concentration of 25(OH)D in patients with SARS-CoV-2 infection before being hospitalized and found no relationship between 25(OH)D concentration and discharge status, mortality, length of stay, intubation status, or renal replacement therapy [9]. Third, a meta-analytic study that analysed clinical trials in which vitamin D_3 was administered in patients with SARS-CoV-2 infection and hypovitaminosis D, did not reduce mortality [10].

To further evaluate the association between high acute illness severity and vitamin D status in SARS-CoV-2 patients, the authors conducted a systematic review of the relationship between serum 25(OH)D and the concentration of serum markers of acuity of illness such as C-reactive protein (CRP), tumour necrosis factor α (TNF-α) and interleukin 6 (IL-6) in patients acutely hospitalized with SARS-CoV-2 infection. Those three markers were selected because it has been experimentally reported in humans that their elevation may be associated with a decrease of the concentration of previously normal 25(OH)D [11].

MATERIAL AND METHODS

This study was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [12].

Search strategy

Two independent investigators performed a systematic search in PubMed, EMBASE, Google Scholar and the Cochrane Database of Systematic Reviews for studies published between January 2020 and February 2021. In addition, a secondary search based on the reference lists of retrieved articles was conducted. The following combined search terms were used in PubMed: ('Novel coronavirus' or 'Coronavirus disease 2019' or 'Corona-virus 2019' or 'nCoV-2019' or '2019-nCoV' or 'COVID-19' or 'SARS-CoV-2' or '25OHD' or 'acute-phase proteins' or 'C-reactive protein' or 'tumour necrosis factor (TNF) –α' or 'interleukin (IL) -6'.

Eligibility criteria

We searched for randomized controlled trials (RCTs) or observational studies reporting data on serum 25(OH)D concentration and SARS-CoV-2 infection severity or mortality. Studies in English or other languages meeting the following criteria were included: a) acutely hospitalized COVID-19 patients aged 18 or more years who were diagnosed according to the interim guidance of the World Health Organization [13]; b) inclusion of the median or mean and standard deviation for laboratory test values of 25(OH)D, and sample size with information on demographics, comorbidities and complications; c) the study presented data on serum CRP, TNF-α and/or IL-6. The following exclusion criteria were applied: reviews, abstracts, discussion summaries, and insufficient reported data.

Quality assessment

The quality of observational studies (cohort and case-control studies) and RCTs were assessed according to the Newcastle-Ottawa Quality Assessment Scale (NOS) [14] and the Cochrane Risk of Bias Assessment Tool [15], respectively. Two investigators evaluated the quality of the studies independently. Conflicting results were resolved by discussion and involvement of a third reviewer if necessary.

Data extraction

The following data were extracted from each study: authors, study location, year of publication,

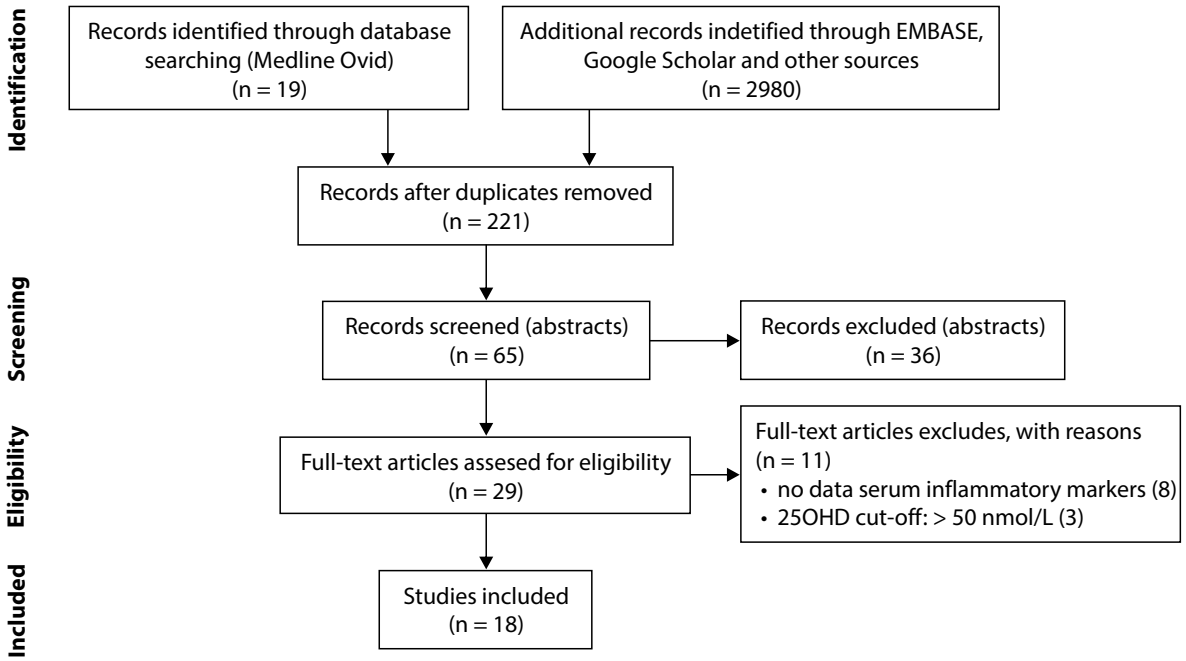

FIGURE 1. Flowchart of included studies

study design, number of participants, sex, age at baseline, serum 25(OH)D concentration, and concentration of CRP, TNF-α and IL-6. Even though some studies have considered other 25(OH)D cut-off values [16], where possible 25(OH)D deficiency was considered as $<$ 50 nmol/L ($<$ 20 ng/ml) [17]. In each study, concentrations of inflammatory markers between patients reported as having low concentrations of 25(OH)D and those above the study cut-off were compared. The p-value resulting from the comparison between groups of patients with and without low concentrations of 25(OH)D was calculated with the 2-sided Mann Whitney U test.

RESULTS

After screening 2999 citations, 18 observational eligible studies (cohort, 10; case-control, 10; cross-sectional, 4) were included (Fig. 1), combining to a total sample of 3482 participants. The characteristics of included studies are summarized in Table 1. The studies were from Austria [18], Germany [19], China [20], Greece [21], India [22, 23], Iran [24], Italy [25–27], Spain [28], Turkey [29–31], UK [32–34], and USA [35].

Overall, the mean age of the participants was 63.5 $\pm$ 9.3 years and 56.9% were men. The mean NOS score of included studies was 8 (range: 7–9). The outcomes reported in the included studies are presented in Table 1.

All measurements of inflammatory markers were performed during hospitalization, and none of the studies measured serum 25(OH)D concentrations before hospitalization. In all 18 studies, patients with low 25(OH)D had elevated concentrations of CRP, IL-6 and/or TNF-α. These differences were statistically significant ($p < 0.05$) in 6/15 studies with CRP, 4/8 with IL-6 and 0/1 with TNF-α (Tab. 2).

DISCUSSION

The present study on the relationship between 25(OH)D and markers of systemic inflammatory response in SARS-CoV-2 infection found elevated concentrations of CRP, IL-6 and/or TNF-α in patients with low concentrations of 25(OH)D. In the context of a patient with SARS-CoV-2 infection, the present finding can be interpreted in two ways; first, that there may be a relationship between the low concentrations of 25(OH)D and the acute inflammatory process (as evidenced by elevations of CRP, IL-6 and/or TNF-α), which could be confounded as the low concentrations of 25(OH)D being associated with greater SARS-CoV-2 severity or mortality. Second, that the acute inflammatory process may induce a reduction in the concentration of 25(OH)D in patients who prior to infection

Table 1. Characteristics of the 18 studies included

Author	Country	Study design	Sample size	Sex Male (%)	Mean age	Result of the study on the relationship between D[25(OH)D] < 50 nmol/L and outcomes	25(OH)D Measurement Method	Comorbidities	NOS
Carpagnano et al. 2020	Italy	CC	42	71	65	Higher mortality	Chemiluminescence immunoassay method	Hypertension (62%), Cardiovascular Disease (38%), Chronic kidney disease (38%), Diabetes type II (26%), Malignancy (12%), COPD (12%)	9
Panagiotou et al. 2020	UK	CS	134	29.7	68.5	Higher Severity (Admission to ICU)	NR	Hypertension (42%), Diabetes (28%), Malignancy (11%), Respiratory (31%), Cardiovascular Disease (15%), Kidney and Liver diseases (14%)	7
Radujkovic et al. 2020	Germany	CC	185	51	60	Higher severity/mortality	Immunoassay (ADVIA Centaur Vitamin D Total Assay)	Cardiovascular Disease (31%), Diabetes (10%), Chronic kidney disease (4%), Chronic lung disease (8%), Malignancy (9%)	9
Baktash et al. 2020	UK	C	70	60	81.3	Higher ICU admission/no increased mortality	NR	Hypertension (57%), Diabetes mellitus (43%), Ischaemic heart disease (25%), Chronic respiratory disease (22%), Heart failure (20%)	9
Hernández et al. 2020	Spain	CC	197	62.4	61	No increased severity/mortality	Automated electrochemiluminescence system	Hypertension (39%), Diabetes (17%), Cardiovascular Disease (11%), COPD (8%), Active cancer (4%), Immunosuppression (8%)	9
Luo et al. 2020	China	CS	335	44.2	56	Higher severity, no mortality	Chemiluminescence immunoassay (DiaSorin, Inc.)	NR	8
Cereda et al. 2020	Italy	C	129	54.3	77	No association with mortality/ severity (ICU admission)	Chemiluminescence immunoassay	COPD (13%), Diabetes (31%), Hypertension (70%), Ischaemic heart disease, (41%), Cancer (21%), Chronic kidney disease (19%)	9
Jain et al. 2020	India	CC	154	66.66	54.42	Higher mortality/severity (ICU admission)	Automated immunoassays Architecti1000sr Make 2015	NR	9
Vassiliou et al 2020	Greece	CC	30	80	65	Higher mortality, no severity (Mechanical ventilation)	Electrochemiluminescence immunoassay (ECLIA)	Hypertension (50%), Hyperlipidaemia (30%), Diabetes (17%), Coronary artery disease (13%), Chronic obstructive pulmonary disease (3%)	8
Jevalikar et al 2020	India	CS	410	69	54	No higher severity/mortality	NR	Diabetes (46%), Hypertension (40%), Hypothyroidism (15%), Coronary artery disease (9%), Lung or airway disease (6%), Cancer (3%)	7
Demir et al. 2020	Turkey	C	227	43.43	44.15	Higher severity (affected number of lung segments)	NR	NR	7

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Table 1. Characteristics of the 18 studies included (cont.)

Author	Country	Study design	Sample size	Sex Male (%)	Mean age	Result of the study on the relationship between D[25(OH)D] < 50 nmol/L and outcomes	25(OH)D Measurement Method	Comorbidities	NOS
Tehrani et al. 2021	Iran	CS	205	33.65	59.71	No higher severity/mortality	NR	Diabetes (35%), Hypertension (44%), Chronic kidney disease (23%), Hypothyroidism (4%), Ischaemic heart disease (25), COPD (6%, Cancer (5%)	7
Buchtele et al. 2021	Austria	C	178	66	61	Higher ICU admission/mortality	Chemiluminescent immunoassay	Cancer Hematologic (61%), Solid cancer (39%)	8
Mazziotti et al. 2020	USA	CC	348	63.56	69	Higher need ventilation	Chemiluminescent methods	Arterial hypertension (52%), Diabetes mellitus (34%), Coronary artery disease (22%), Cancer (15%), COPD (12%), CKD (12%)	8
Orchard et al 2021	UK	CC	41	58	57	No ICU admission	NR	Diabetes mellitus (27%, Hypertension (32%), Ischaemic heart disease (6%), Congestive cardiac failure (2%), Chronic kidney disease (4%)	8
Karahan et al. 2021	Turkey	CC	149	54.4	63.5	Higher mortality	NR	Hypertension (57%), Diabetes mellitus (41%), COPD (10%), Malignancy (15%), Chronic atrial fibrillation (10%), Congestive heart failure (12%)	7
Ricci et al. 2020	Italy	CC	52	48.08	77.5	Higher pulmonary involvement	NR	Hypertension (43%), Obesity (21%), Chronic Renal failure (4%), COPD (10%)	7
Tuncay et al. 2021	Turkey	CC	596	69.2	68.2	Higher mortality/severity	NR	Hypertension (35%), Diabetes (38%), COPD (19%), CKD (19%), Cancer (23%).	8

Table 2. Within-studies comparisons between serum 25-hydroxyvitamin groups (high vs. low) in relation to reported values of inflammatory markers

Study	25-hydroxyvitamin (nmol/L)	Size sample	CRP (mg/L) (mean/median)	Interleukin-6, pg/mL (mean/median)	Serum TNF α in pg/mL (mean/median)
Carpagnano et al. 2020	< 25	10	102 ± 79.98	244 ± 468.35	NR
	> 50	11	91 ± 41.74	83 ± 44.39	NR
Panagiotou et al. 2020	33.5 ± 16.8	42	143.4 ± 99.4	NR	NR
	48.1 ± 38.2	92	107.9 ± 92.0*	NR	
Radujkovic et al. 2020	≤ 30	29	NR	70.5 (32.0–326.3)	NR
	>30	64	NR	29.7 (14.3–59.9)*	NR
Baktash et al. 2020	≤ 30	39	191(108–274)	NR	NR
	> 30	31	155((96–252)	NR	NR
Hernández et al. 2020	< 50	162	61 (31–136)	58.9 (19.1–124.0)	NR
	> 50	35	32 (23–87)	45.6 (20.5–119.0)	NR
Luo et al. 2020	23.1 (18.1–28.3)	74	64.5 (12.3–422)	9.33 (2.4–28.0)	NR
	27.5 (21.8–34.5)	261	12 (5.5–30.0)**	2.1 (1.5–4.1) **	NR
Cereda et al. 2020	< 50	99	115 (55.6–171.4)	NR	NR
	≥ 50	30	68.1 (40–143.9)	NR	NR
Jain et al. 2020	< 50	90	NR	19.34 ± 6.17	13.26 ± 5.64
	> 50	64	NR	12.18 ± 4.29*	11.87 ± 3.15
Vassiliou et al 2020	< 38	15	190 (50–260)	NR	NR
	> 38	15	100 (40–170)	NR	NR
Jevalikar et al 2020	< 50	197	62.2 ± 343.7	46.3 ± 113.5	NR
	> 50	212	45.1 ± 56.0	45·9 ± 121	NR
Demir et al. 2020	< 25	99	22.49 ± 2.88	NR	NR
	> 50	42	10.99 ± 4.10**	NR	NR
Tehrani et al. 2021	< 25	25	4.34 ± 2.17	NR	
	> 50	88	3.55 ± 1.7*	NR	
Buchtele et al. 2021	< 30	96	233 (76–334)	NR	
	> 50	47	184 (62–408)	NR	
Mazziotti et al. 2020	< 30	161	105 (10–2270)	74.0 (4–1573)	NR
	> 50	36	60 (10–210)	22.0 (8–451)	NR
Orchard et al 2021	< 50	41	167(120-221)	NR	NR
	> 50	9	147 (116–242)	NR	NR
Karahan et al. 2021	26 ± 16.0	47	108.7 ± 78.3	NR	NR
	65.75 ± 21	102	44.2 ± 59.5**	NR	NR
Ricci et al. 2020	< 25	22	NR	85.2 ± 78.01	NR
	≥ 25	30	NR	39.6 ± 17.87**	NR
Tuncay et al. 2021	26.25 ± 3.44	26	14.1 ± 9	NR	NR
	52.93 ± 12.83	450	4.4 ± 1**	NR	NR

*$p < 0.05$; **$p < 0.001$; NR — not reported

may have had a normal 25(OH)D level. Therefore, low concentrations of 25(OH)D reported in the included studies may represent an epiphenomenon of the acute inflammatory process associated with SARS-CoV-2 infection, especially in its severe forms.

Before the pandemic, there was experimental evidence in animals [36] and humans that the acute in-

flammatory process can induce a reduction in serum 25(OH)D concentrations in a secondary way [11]. Smolders *et al.* investigated whether systemic inflammation lowers circulating 25(OH)D concentrations using the experimental human endotoxemia model (bolus of *E. Coli*-derived lipopolysaccharide, LPS), and they found a significant decrease in 25(OH)D concentrations 2–3 hours after infusion, compared to baseline concentrations [11]. On the other hand, the fall in the concentrations of 25(OH)D coincided with an increase in the concentrations of proinflammatory cytokines TNF-α, IL-6, and IL-8, and 25(OH)D concentrations recovered to baseline 6 hours following cessation of LPS infusion. In a systematic study, Silva *et al.* found that patients with normal total concentrations of 25(OH)D undergo a significant reduction in those levels when facing an acute injury [6].

Acute insults where this phenomenon of acute reduction in total 25(OH)D concentration occur are knee/hip arthroplasty [37–39], acute myocardial infarction [40], acute pancreatitis [41], first dose IV bisphosphonate [42], and cardiopulmonary bypass surgery [43]. In all the studies included in the systematic study, CRP was elevated. The recovery of the basal concentrations took 2 weeks, although in 2 studies it took up to 90 days [38, 40]. In two studies, the concentration of a total of 25(OH)D was not modified, but the baseline sample was taken on the second day of the event [6]. Hypothetically, in some cases of SARS-CoV-2 infection, patients with previously normal 25(OH)D concentrations, after several days of the onset of the disease, may go to hospitals where low concentrations of 25(OH)D are detected, but this may be induced by the acute inflammatory process. It should be noted that the magnitude of the decrease in concentrations of 25(OH)D could depend on other unknown factors, which should be investigated.

The mechanisms by which the acute inflammatory process may induce a decrease in 25(OH)D are unknown, but it has been hypothesized that the contributing factors are acute stress haemodilution, interstitial extravasation, decreased synthesis of binding proteins, and renal wasting of 25(OH)D [44]. The methods to discern if a reduction in 25(OH)D may be induced by an acute inflammatory state are — apart from the baseline measurement that is not feasible in COVID-19, the correction according to CRP concentrations and albumin [8, 38, 45] or the determination of 25(OH)D_3 in hair [46]. The correction for IL-6 concentrations has been reported for the correction of the measurement of concentrations of iron, zinc and selenium, which also decrease in an acute inflammatory process [47]. Studies before the pandemic have recommended taking the results of a patient's vitamin D status with caution if they have a CRP $>$ 10 mg/L and albumin concentrations $>$ 3.5 g/dL [8]. On the other hand, it should be taken into account that establishing a cause-effect relationship between severity/mortality of COVID-19 and vitamin D, solely from measurements of 25(OH)D is difficult because to know exactly the vitamin D status of a patient requires measurement of not only 25(OH)D (circulating reservoir), but also of 1,25-dihydroxy vitamin D and vitamin D binding protein (VDBP). Approximately 85% of VDBP binds total circulating vitamin D [48]. The non-VDBP fraction (bioavailable vitamin D) consists primarily of albumin-bound (14%), leaving the remainder in the free form (less than 1%) [49]. The design of new studies is necessary to know in detail the relationship between vitamin D status and the severity/mortality of COVID-19.

Butler-Laporte et al. recently published a study using Mendelian randomization with genetic variants strongly associated with 25(OH)D levels in a genome-wide association study (GWAS) of 443.734 participants of European ancestry, and they did not observe evidence to support an association between 25(OH)D levels and COVID-19 susceptibility, severity, or hospitalization [50]. It is interesting that the findings of the present systematic study and the results of the described 2-sample Mendelian randomization study carried out with different methods, contribute with the evidence according to which there would not be a causal relationship between decreased 25(OH)D levels and severity of COVID-19.

Limitations

The present study has the limitation of being based on observational studies and although 15 studies reported inflammation markers such as CRP concentrations, only 10 and one studies reported measurement of IL-6 and TNF-α, respectively, and some studies had different cut-off points for 25(OH)D levels. Another limitation is the lack of a comparison group (i.e. Vitamin D status in patients with mild illness or normal concentrations of proinflammatory cytokines). In addition, as stated above, none of the included studies had ascertained Vitamin D concentrations before hospital admission.

CONCLUSIONS

In conclusion, the present study found that markers of the acute systemic inflammatory response are elevated in patients with low concentrations of 25(OH)D and with SARS-CoV-2 infection. Therefore, the results of the vitamin D status in these patients should be taken with caution, and studies should be designed to assess whether hypovitaminosis D could be an epiphenomenon of the systemic inflammatory response.

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