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Vitamin D Supplementation in COVID-19 Patients: A Clinical Case Series

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Background: Coronavirus disease 2019 (COVID-19) has infected more than 4.4 million people and caused more than 300,000 deaths partly through acute respiratory distress syndrome with propensity to affect African American and Hispanic communities disproportionately. Patients with worse outcomes have exhibited higher blood plasma levels of proinflammatory cytokines. Activation of the vitamin D receptor expressed on immune cells has been shown to directly reduce the secretion of inflammatory cytokines, such as interleukin-6, and indirectly affect C-reactive protein.

Areas of Uncertainty: The significance of the vitamin D pathway in patients diagnosed with COVID-19.

Therapeutic Innovation: Vitamin D supplementation in patients after diagnosis of COVID-19.

Patients and Pharmacological Interventions: We report 4 vitamin D deficient patients diagnosed with COVID-19 in April 2020 who were provided with either cholecalciferol of 1000 IU daily (standard dose) or ergocalciferol 50,000 IU daily for 5 days (high dose) as part of supplementation.

Clinical Outcomes: Patients that received a high dose of vitamin D supplementation achieved normalization of vitamin D levels and improved clinical recovery evidenced by shorter lengths of stay, lower oxygen requirements, and a reduction in inflammatory marker status.

Conclusions: Vitamin D supplementation may serve as a viable alternative for curtailing acute respiratory distress syndrome in patients in underserved communities where resources to expensive and sought-after medications may be scarce. Randomized clinical trials will serve as an appropriate vessel to validate the efficacy of the therapeutic regimen and dissection of the pathway.

Keywords: vitamin D, COVID-19, IL-6, CRP, ARDS

BACKGROUND

Since May 14, 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected more than 4.4 million people and caused more than 300,000 deaths. The onset of symptoms, including fever, headache, dry cough, myalgia, and diarrhea, typically develops within 11.5 days.[1,2] Severe cases can progress to acute respiratory distress syndrome (ARDS), typically 8–9 days after the onset of symptoms.[3] ARDS has been shown to induce widespread cytokine release leading to cytokine storm and symptoms of sepsis with multiorgan failure that often involves the pulmonary system with mechanical ventilation required and eventually death.[3,4] These patients exhibit higher blood plasma levels of proinflammatory cytokines, notably interleukin-6 (IL-6).

IL-6 is a mediator of fever and the acute phase response. Part of its proinflammatory effect is through

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induction of C-reactive protein (CRP).[5] Higher levels of IL-6 predict poorer clinical outcomes in patients with ARDS and multiorgan failure.[6] Activation of the vitamin D receptor, expressed on monocytes, dendritic cells, and macrophages, has been shown to directly reduce the secretion of inflammatory cytokines (IL-6) and indirectly affect CRP, reducing damage to other organs.[7] Studies demonstrated that vitamin D administration significantly reduced levels of IL-6 and mortality in patients with ventilator-associated pneumonia.[8] We report 4 vitamin D deficient patients diagnosed with coronavirus disease 2019 (COVID-19) who received vitamin D supplementation and detail improved clinical recovery.

METHODS

This single-centered observational study was conducted at the Long Island Jewish Forest Hills Hospital (Queens, New York: 312 beds). The Northwell Health Institutional Review Board approved this case series as minimal-risk research using data collected for routine clinical practice and waived the requirement for informed consent.

We analyzed 4 patients with confirmed COVID-19 hospitalized from April 1 to April 30, 2020. Each case presents narration of patient endorsed symptoms, physical examination findings, laboratory values, and excludes personal identifiable information. SARS-CoV-2 was detected by nasopharyngeal swab polymerase chain reaction (PCR) assay. Patients were provided with either cholecalciferol of 1000 IU daily (standard dose) or ergocalciferol 50,000 IU daily for 5 days (high dose) as part of supplementation. Day 0 marks when the patient was diagnosed with COVID-19 and when vitamin D supplementation began.

RESULTS

Patient 1

A 41-year-old Hispanic man with no medical history was admitted to the Long Island Jewish Forest Hills Hospital, New York, (LIJ-FHH) with complaints of fevers, cough, dyspnea, body aches, and profuse diarrhea. His oxygen saturation was 70% on ambient air, and he was put on 15 L nonrebreather face mask (NRB) and brought to the LIJ-FHH emergency department (ED).

He was febrile to 103.1°F, blood pressure of 129/66 mm Hg, pulse 98 beats per minute, respiratory rate 30 breaths per minute, and saturating 95% on 15 L NRB. Crackles were noted bilaterally on lung examination, and chest x-ray demonstrated extensive bilateral multifocal pneumonia. The patient tested positive for COVID-19, and laboratory test results showed leukocytosis with lymphopenia. Vitamin D level was decreased at 18.1 ng/mL. CRP, erythrocyte sedimentation rate (ESR), ferritin, IL-6, lactate dehydrogenase (LDH), and procalcitonin levels were all elevated (Table 1).

He was given hydroxychloroquine and a high-dose vitamin D for 5 days. A chest x-ray on day 4 demonstrated unchanged bilateral opacities. On day 5, no fever was noted. On day 6, the patient was weaned to 6 L oxygen by nasal cannula (NC). Laboratory test results demonstrated a reduction of CRP, undetectable concentrations of IL-6, and doubling of levels of vitamin D (Table 1). On hospital day 9, he was saturating 94% on ambient air and then discharged the following day.

Patient 2

A 57-year-old Hispanic woman with no medical or surgical history presented to the LIJ-FHH ED with right-sided stabbing pains involving the shoulder, back, chest, and flank for 3 days. She denied fever, cough, dyspnea, dysuria, trauma, immobilization, or recent sick contacts. Patient was on no medications.

Vitals showed temperature of 98.1°F, blood pressure 133/88 mm Hg, pulse 100 beats per minute, and oxygen saturation of 99% on ambient air. Remainder of physical examination was unremarkable. As seen in Table 1, patient had leukocytosis with no lymphopenia and elevations in D-dimer, ESR, CRP, IL-6, along with vitamin D deficiency (Table 1).

Computed tomography angiography demonstrated segmental pulmonary emboli associated with atelectasis or pulmonary infarctions and patchy ground glass opacities in the upper lungs. The COVID-19 PCR assay was positive. The patient was started on hydroxychloroquine and full dose anticoagulation with low–molecular weight heparin (LMWH).

Antibiotics were initiated with ceftriaxone 1 g daily to cover superimposed bacterial pneumonia, along with a high-dose vitamin D for 5 days. On hospital day 3, the patient stated improvement in symptoms despite increases in ESR and CRP (data not shown). Cultures were negative and antibiotics were discontinued. On day 4, patient was transitioned onto warfarin.

The patient remained stable with no supplemental oxygen given during hospital stay. Repeat laboratory testing, as shown in Table 1, demonstrated improvements of the leukocytosis, inflammatory markers, more than doubling of vitamin D levels, and undetectable concentrations of IL-6. She was discharged after reaching a therapeutic International Normalised Ratio (2–3).

Patient 3

A 74-year-old Hispanic man presented to the LIJ-FHH ED with intermittent headache, weakness, and neck pain for 1 month. Temperature was 97.4°F, blood

Table 1. Demographics, laboratory findings, and treatments.

	Vitamin D - high dose				Vitamin D - standard dose			
	Patient 1		Patient 2		Patient 3		Patient 4	
Demographics								
Age (yr)	41		57		74		53	
Gender	Male		Female		Male		Male	
Body mass index	32.9		29.6		29.9		28.1	
Hypertension	No		No		Yes		Yes	
Diabetes mellitus	No		No		Yes		Yes	
Length of stay (d)	10		10		13		15	
Laboratory								
Day of COVID-19 diagnosis	0	6	0	6	0	6	0	6
Oxygen use (L)	15 L	0 L	0 L	0 L	2 L	2 L	3 L	6 L
White Blood Count (3.8–10.5 K/μL)	12.69	5.7	18.92	8.8	11.07	13.04	8.91	6.19
Hemoglobin (13–17 g/dL)	13.2	14.1	13.1	11.3	11.4	9.9	13.1	13.2
Platelets (150–400 K/μL)	178	588	370	314	172	120	202	403
Polymorphonuclear cells (1.8–7.4 K/μL)	11.17	4.28	15.32	5.43	9.52	10.2	8.29	4.88
Lymphocytes (1–3.3 K/μL)	1.27	0.91	1.52	2.28	0.67	1.36	0.18	0.59
Lymphocytes % (13%–44%)	10	16	8	25.9	6.1	10.4	2	9.5
Neutrophil / Lymphocyte Ratio Ratio	8.80	4.70	10.08	2.38	14.21	7.50	46.06	8.27
D-dimer (<229 ng/mL)	278	372	1964	1070	1139	814	226	696
ESR (0–10 mm/h)	78	46	96	100	75	119	79	89
CRP (0–0.4 mg/dL)	30.68	1.98	16.86	7.53	13.38	22.39	21.24	18.48
Ferritin (30–400 ng/mL)	1511	1636	315	445	120	241	1025	2043
Procalcitonin (0.02–0.10 ng/mL)	1.69	N/A	0.1	0.03	5.46	3.55	0.57	0.3
Creatinine (0.5–1.3 mg/dL)	1.11	0.83	1.16	0.96	2.06	1.88	1.01	0.82
Glomerular Filtration Rate (>60 mL/min/1.73 m^2)	82	109	52	66	31	35	85	101
Alkaliine Phosphatase (40–120 U/L)	40	49	88	73	74	89	63	107
Aspartate Aminotransferase (10–40 U/L)	29	99	16	54	16	75	60	155
Alanine Aminotransferase (10–60 U/L)	24	131	18	65	16	59	73	122
Lactate Dehydrogenase (120–225 U/L)	413	295	245	214	185	240	454	568
25-hydroxyvitamin D (30–80 ng/mL)	18.1	39.9	21.9	50.5	18	19.2	17.4	20.1
IL-6 (<5 pg/mL)	14	<5	10	<5	<5	<5	6	11
Treatment								
Interleukin inhibitor	No		No		No		No	
Antibiotics	Azithromycin & ceftriaxone 4 d		Ceftriaxone 3 d		Ceftriaxone 3 d		No	
Steroids	Methylprednisolone 120 mg 3 d		No		Prednisone 40 mg taper 6 d		No	
Anticoagulation	LMWH		LMWH		Unfractionated heparin		LMWH	
Admission to intensive care unit	No		No		No		No	

pressure 102/64 mm Hg, pulse 75 beats per minute, and oxygen saturation was 95% on ambient air. Laboratory test results demonstrated an elevated serum creatinine of 3.23 mg/dL (0.5–1.3 mg/dL) [baseline 1.2 mg/dL in 2018 (data not shown)].

On day 3 of admission, he developed rigors and a temperature of 101°F. Blood cultures were negative. Chest x-ray showed bilateral interstitial infiltrates. Patient tested positive for COVID-19. Urine culture revealed *Escherichia coli*, and he was started on ceftriaxone. He was

also found to have vitamin D deficiency, leukocytosis, and lymphopenia. CRP, ESR, ferritin, procalcitonin, and LDH levels were all elevated, although IL-6 concentrations were undetectable (Table 1).

He was started on hydroxychloroquine and a standard daily dose of vitamin D, but he continued to have daily fevers (temperature maximum of 102.3°F). On day 4, he began to desaturate to 91% and was placed on 2 L NC. On day 6, oxygen was removed. Last fever was noted on day 7. His vitamin D levels improved minimally; his CRP, ferritin, and ESR levels continued to rise, and IL-6 levels remained undetectable. Respiratory status improved. On day 13, clinical signs and symptoms of infection and acute kidney injury resolved. He maintained 94% oxygenation on ambient air and was discharged.

Patient 4

A 53-year-old African American man was admitted to the LIJ-FHH with flu-like symptoms, dyspnea, and diffuse myalgias for 5 days. Patient stated he was having subjective fevers not relieved by Tylenol. Chest x-ray demonstrated multifocal patchy opacifications, and PCR testing for COVID-19 was positive.

On admission, he was febrile to 102.8°F with blood pressure of 178/99 mm Hg, pulse 114 beats per minute, respiratory rate 18 breaths per minute, and required 3 L NC to maintain oxygen saturation above 95%. The patient was in mild respiratory distress with rales on auscultation bilaterally. Vitamin D levels were low with lymphopenia. CRP, ESR, ferritin, IL-6, procalcitonin, and LDH levels were all markedly elevated. Patient was also noted to have mild transaminitis (Table 1).

He was started on hydroxychloroquine for 5 days and a standard dose of daily vitamin D. He continued to have daily fevers, increased oxygen requirements, and developed hiccups. By day 5, the patient was on an NRB requiring 10 L of oxygen to maintain 95% oxygen saturation. Repeat chest x-ray demonstrated increasing infiltrates on the left side. On hospital day 6, his vitamin D levels increased minimally while CRP levels decreased slightly; however, ferritin increased significantly and IL-6 levels nearly doubled (Table 1).

On hospital day 8, the patient was tapered to 6 L NC and the back complaints and hiccups resolved. On day 14, he was weaned off supplemental oxygen, clinically improved, while breathing 94% on ambient air and discharged home.

DISCUSSION

Cases of COVID-19 continue to rise, and although our understandings of the pathophysiological changes of the infection are unclear and still being elucidated, ARDS is widely apparent and responsible for most of the fatalities. Lessening the severity of ARDS and preventing the pathologic state are essential factors in clinical management. We report a case series of patients with COVID-19, all of whom were vitamin D deficient and improved after administration with vitamin D supplementation in the early stage of clinical deterioration.

SARS-CoV-2 has been shown to involve a wide clinical spectrum of symptoms, and the patients above presented with vitamin D deficiency and symptoms days before their admission. Patients 1 and 2 received a high-dose vitamin D for 5 days as a means of achieving sufficient levels of vitamin D in the body during their course of infection while patients 3 and 4 received a standard dose. Although all patients received supplementation our data show that by day 6 the patients who received the higher dose of vitamin D were noted to have lower lengths of stay and oxygen requirements (Figure 1B, C). Evidence demonstrated consistent decreases in CRP (Figure 1H) and LDH (Figure 1G) with increasing blood concentrations of vitamin D. Levels of vitamin D increased in all patients after supplementation. Two of the 4 patients almost doubled their concentrations in the 5-day period to adequate levels, whereas the other 2 patients remained deficient (Figure 1D). The patients who received a high-dose vitamin D supplementation initially had markedly elevated levels of IL-6 on the day of diagnosis but then had undetectable levels after completing the 5-day course. One patient's IL-6 levels increased considerably, and another patient's IL-6 was undetectable at both time points (Figure 1I). These measurements were further illustrated in the vitamin D to CRP and IL-6 ratios, highlighting higher ratios with higher supplementation (Figure 1J, K) and ultimately accelerated discharge.

Vitamin D deficiency has been linked to an increased risk or severity of HIV. It also seems to be a risk factor for tuberculosis.[9,10] Historical analysis of the case fatality rate in 12 communities in the United States during the 1918 influenza pandemic demonstrated that climates in the sunnier southern and western part of the country had statistically significant lower case fatality rates compared with the northeast.[11] Current literature has reached no consensus regarding the proper concentrations needed for adequate protection and clinical responsiveness. However, some studies have showed that 30–50 ng/mL are associated with a lower disease burden compared with concentrations of 10–20 ng/mL.[12] Interestingly, our patients who had higher doses of vitamin D and ultimately shorter lengths of stay achieved this threshold level of vitamin D, whereas those who received

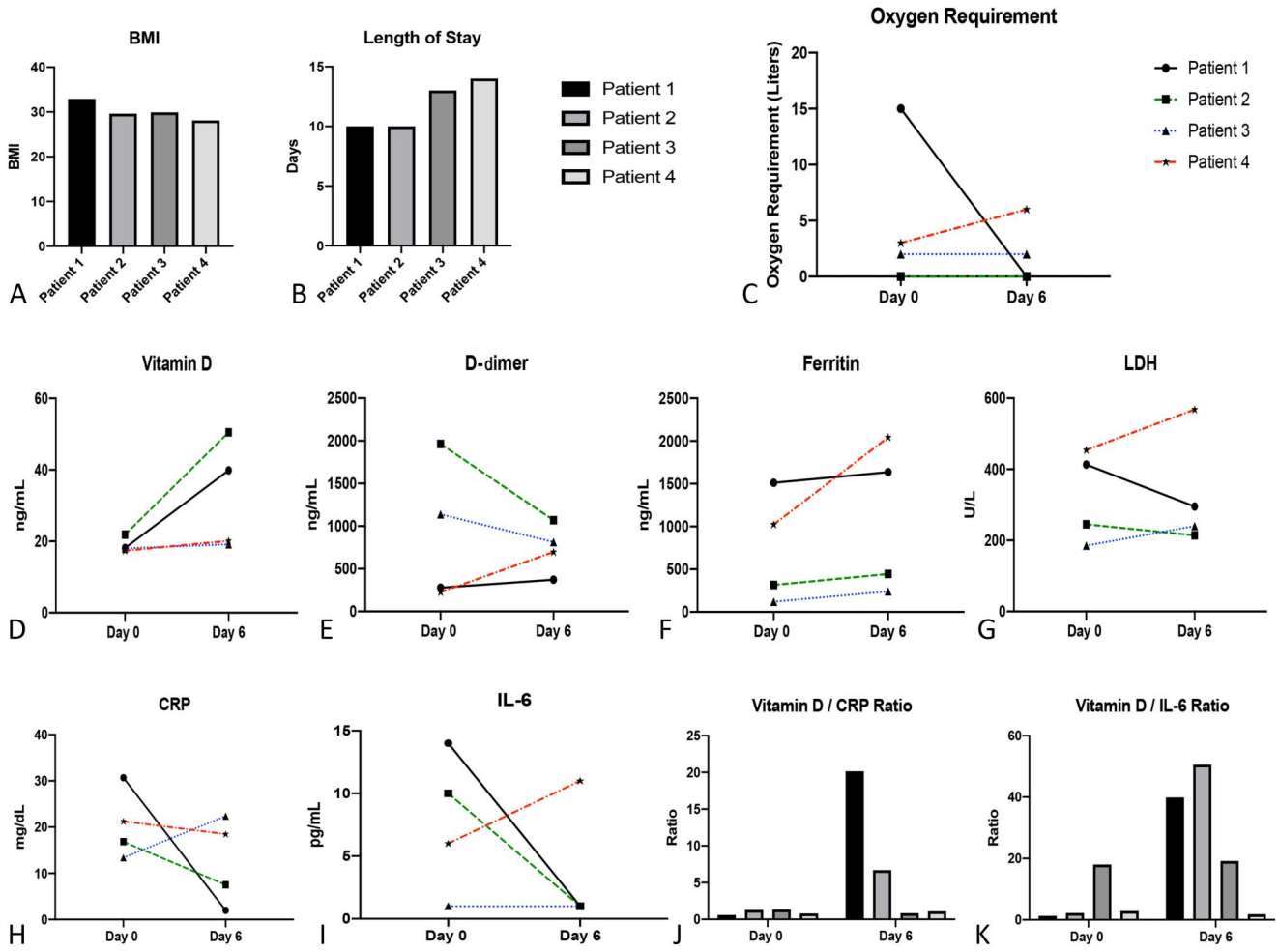

FIGURE 1. Demographics and clinical summary of patients on day 0 (Day of COVID-19 diagnosis) and day 6 after vitamin D supplementation. (A) BMI of patients. (B) Length of stay in hospital. (C) Oxygen requirement. (D) Vitamin D concentration in blood (ng/mL). (E) D-dimer levels (ng/mL). (F) Ferritin levels (ng/mL). (G) LDH levels (U/L). (H) Levels of CRP (mg/dL) and (I) IL-6 (pg/mL) in the blood. (J) Ratio of vitamin D to CRP levels in the blood. (K) Ratio of vitamin D to IL-6 levels in the blood. BMI, body mass index.

a standard dose did not. Therefore, achieving and maintaining these levels in patients diagnosed with COVID-19 may be an effective strategy to decrease a potential risk of secondary bacterial infections observed with interleukin inhibitors.[13]

Results from our report are compelling but limited by the small number of patients. The patients had similar body mass indices (Figure 1A) and self-identified as underrepresented minorities. This is important because current literature has demonstrated links between outcomes of COVID-19 and ethnicity. According to the Center of Disease Control's Morbidity and Mortality report in March 2020, among the 1482 laboratory-confirmed COVID-19–associated hospitalizations, 33% of the patients were non-Hispanic (African American) and 8.1% Hispanic suggesting minorities are disproportionately affected. Reasons may include population density, reduced access to health care, and higher rates of comorbidities.[14] Furthermore, these populations have been shown to have lower concentrations of vitamin D compared with non-Hispanic whites, a feature all of our patients possessed. Two out of the 4 patients highlighted in this case series had a clinical history of diabetes and hypertension. A recent meta-analysis concluded that the most prevalent comorbidities in those with COVID-19 were hypertension and diabetes, which were also associated with the severity of infection.[15] The 2 patients who received standard doses of vitamin D had a history of diabetes and hypertension while the other 2 did not.

Further evidence is needed to help confirm the observations we have detailed in this case series to elucidate the utility of vitamin D therapy in COVID-19. Vitamin D supplementation may serve as a treatment

to curtailing ARDS in patients in underserved communities where resources for expensive and sought-after medications may be scarce. Randomized clinical trials are recommended to validate the efficacy of vitamin D supplementation.

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