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Impact of Rapid Correction of Vitamin D Deficiency on Patients with COVID-19 Disease: A Randomized-Controlled Trial

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ABSTRACT

Background: Although antiviral properties of vitamin D are recognized, the influence of parental Vit D supplementation on COVID-19 disease has not been determined.

Objective: The aim of study was to evaluate impact of prompt treatment of Vit D deficiency on COVID-19 patients.

Patients and Methods: A randomized controlled experiment was carried out on 250 COVID-19 patients. Patients were categorized into two cohorts: one cohort received daily intramuscular injection of 200,000 IU cholecalciferol for four consecutive days, while other cohort received daily oral dose of 10,000 IU cholecalciferol. The latter group functioned as control group. Before and after therapy, serum 25(OH)D level, inflammatory markers and electrolytes were measured, besides, clinical follow-up.

Results: In Vit D group, the 25(OH)D levels considerably increased after 7 days compared to initial levels (32.48 ±9.64 Vs 13.77 ±6.51 ng/mL, respectively). All Vit D deficient patients have transitioned to sufficient status. Levels of markers (ESR 50.99±17.56 mm/hr, CRP 30.75 ±24 mg/L, and ferritin 392.05 ±139.17 ng/mL) decreased after seven days (29.74±8.97 mm/hr, 10.52 ±13 mg/L, and 94.59 ±27.14 ng/mL, respectively). A substantial clinical improvement occurred in Vit D group compared to their initial condition. Also Vit D deficiency was found to significantly increase risk of COVID-19 mortality by factor of 15.375 [AOR = 15.375, 95% CI: 1.898-124.52, p=0.01].

Conclusion: A daily intramuscular injection of 200,000 IU cholecalciferol for four consecutive days has been proven to significantly enhance clinico-labarotaory parameters in COVID-19 patients. Considering higher Vit D supplementation as a potential treatment for COVID-19 is a viable option.

Keywords: COVID-19, Vitamin D, Inflammatory markers, Cholecalciferol.

INTRODUCTION

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, is a major worldwide health crisis. The World Health Organization has observed a growing number of COVID-19 cases occurring more frequently and becoming more widespread globally. Due to the unprecedented nature of COVID-19 and no specific treatments that have been conclusively demonstrated to be both safe and efficacious, the Surviving Sepsis Campaign COVID-19 panel issued variable recommendations in an advanced manner of guidelines to support caring for COVID-19 cases [1].

Vitamin D (Vit D), a lipid-soluble vitamin and steroid prohormone, provides advantages that extend beyond its involvement in the metabolism of calcium and phosphorus and the maintenance of bone health. Studies have demonstrated a correlation between insufficient levels of Vit D and a range of health issues, including asthma, respiratory infections, malignancies, and cardiovascular disorders [2,3]. Epidemiological studies indicate a high occurrence of Vit D insufficiency among individuals of all age groups [4]. A 2020 study revealed a notable decrease in levels of 25-hydroxyvitamin D in persons who tested positive for COVID-19, in contrast to those who tested negative [5]. This inadequacy is a worldwide problem, impacting not just countries in the north but also becoming more frequently documented in southern areas [6]. Although Egypt receives ample sunlight and has high levels of UV exposure throughout the year, there is still a significant occurrence of Vit D insufficiency. This deficit affects 34.3% of women and 10.9% of men, and is mostly caused by urbanization and numerous societal factors [7].

There is strong evidence that shows a connection between low levels of Vit D and viral infections like respiratory syncytial virus. These infections are linked to a much higher risk of being admitted to the intensive care unit and requiring invasive mechanical ventilation. Supplementing with Vit D has demonstrated advantages for those receiving antiviral therapy [8]. Recent research indicates that a lack of Vit D could hinder the immune system's ability to protect the respiratory system, hence raising the likelihood of serious sickness and death caused by COVID-19 [9-11].

Vit D has a crucial role in fighting RNA viruses by perhaps improving the recovery of CD4+ T cells [12]. Cathelicidin, a peptide synthesized by the activation of Vit D, demonstrates antibacterial properties against enclosed viruses, such as coronaviruses [13]. In addition, Vit D inhibits the synthesis of pro-inflammatory cytokines while stimulating the production of anti-inflammatory cytokines [14,15]. The onset of COVID-19 symptoms is linked to immune system malfunction and the occurrence of cytokine storms [16]. Vit D has been

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found to control the functioning of immune cells [17] and impact the production and release of cytokines including interleukin (IL-6) and tumor necrosis factor (TNF) [18]. Given the immunological impacts, the administration of Vit D supplements could potentially serve as a preventive and therapeutic measure against COVID-19.

Vit D supplementation is generally regarded as highly safe, with instances of toxicity being few. Research indicates that toxicity issues emerge when blood levels exceed 150 ng/mL. Therefore, by setting a maximum threshold of 100 ng/mL, we may ensure a safety buffer to reduce the likelihood of hypercalcemia [4]. Vit D toxicity, which is marked by a variety of harmful symptoms, occurs in persons with blood 25-hydroxyvitamin D levels ranging from 213 to over 640 ng/mL [19].

The precise function of administering Vit D by injection in the management of COVID-19 has not been completely clarified. Hence, the objective of this study was to evaluate the effects of promptly treating Vit D insufficiency in COVID-19 patients by assessing enhancements in their laboratory and clinical parameters, along with overall illness outcomes.

Study Participants and Procedures

Design and population

This study was a hospital-based, prospective, open-label randomized controlled trial that enrolled COVID-19 patients admitted to the isolation unit of the Internal Medicine Department at Zagazig University Hospitals. The laboratory experiments were carried out in the Clinical Pathology Department of the same institution. The research was carried out between September 2020 and March 2021.

The trial consisted of two groups according to vit D deficiency and type of vit D administration. The first group included 170 patients who received a daily injection of 200,000 IU cholecalciferol/vitamin D3 (Devarol-S ampoule®, Memphis for pharmaceuticals and chemical industries, Egypt) into their muscles for four consecutive days (referred to as the Vit D group). The second group included 80 patients who received the standard daily oral dose of 10,000 IU cholecalciferol (referred to as the Control group). Both groups used the COVID-19 management protocol version 1.4/November 2020, which was issued by the Egyptian Ministry of Health and Population throughout the study period.

The process of choosing patients and gathering data.

The inclusion criteria encompassed patients who were admitted to the internal medicine isolation unit, aged 16 or above, and exhibited symptoms of COVID-19 that were confirmed by a positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) test for SARS-CoV-2 RNA from nasopharyngeal samples. The exclusion criteria included persons with end-organ failure (such as decompensated liver disease, heart failure, and renal failure), those using calcium or Vit D supplements, pregnant women, and patients who had received Vit D treatment within the last two months. Figure 1 depicts a graphical representation of the study in the form of a flowchart.

The categorization of COVID-19 patients in this study was based on the severity of the disease. The severity level was determined using indicators such as pulse, systolic blood pressure, respiratory rate, oxygen saturation, and oxygen flow rate as mild, moderate, severe and critical cases in both included groups [20].

The primary metric used to assess the results was the proportion of patients who had a negative result for SARS-CoV-2 RNA PCR test within the first 21 days of hospitalization.

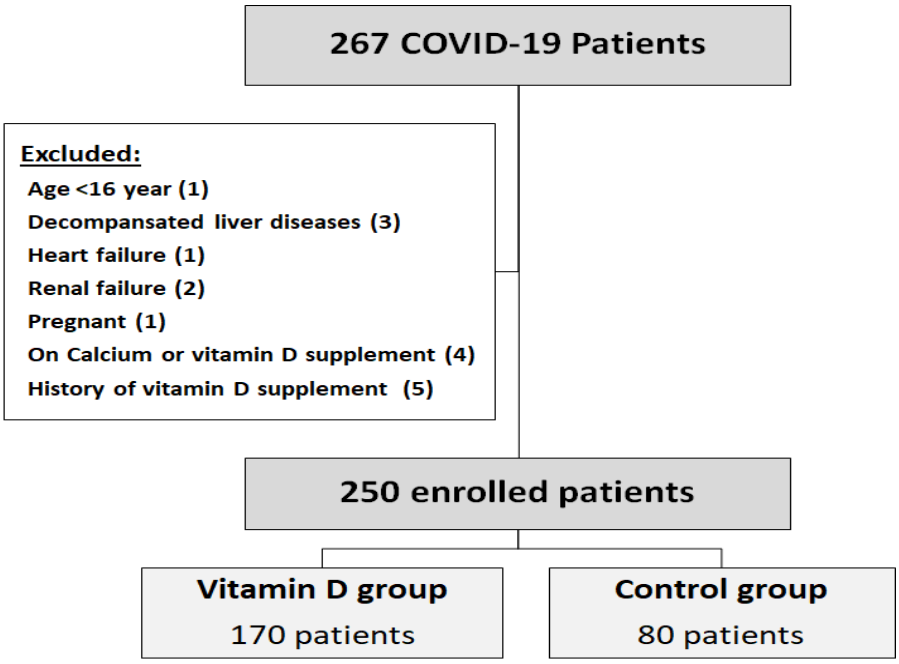

Figure 1: Study flowchart.

Clinical and laboratory assessments

Baseline data, such as age, gender, body mass index (BMI), residency, smoking status, body temperature, respiration rate, heart rate, blood pressure, and oxygen saturation, were collected for every patient participating in this investigation. The initial laboratory tests administered comprised of fasting blood glucose, HbA1C, renal and liver function tests, and coagulation profiles. In addition, blood 25(OH)D levels, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum ferritin, D-dimer, serum calcium, serum parathyroid hormone (PTH) and serum phosphorus were measured for both groups at the beginning of the trial and again seven days later. The categorization of Vit D levels was as follows: Vit D deficiency is characterized by a 25(OH)D level below 20 ng/mL, Vit D insufficiency is characterized by a 25(OH)D level between 20-30 ng/mL, and Vit D sufficiency is characterized by a 25(OH)D level between 30-100 ng/mL [21].

Samples:

Blood samples were obtained with the BD Vacutainer (Becton, Dickinson and Company, Franklin Lakes, NJ). At the beginning, a total of six tubes were collected from each patient, including one tube containing citrate, one tube for ESR testing, two plain tubes, and two tubes with EDTA. One EDTA tube was utilized for conducting a comprehensive analysis of blood components, whereas the second EDTA tube was employed specifically for quantifying the level of HbA1C. The unaltered vacutainer was kept undisturbed for a duration of 30 minutes to facilitate the process of coagulation, after which it was subjected to centrifugation with a force of 1200 times the acceleration due to gravity for a period of 10 minutes in order to separate the serum. The citrate sample was promptly subjected to centrifugation at 2000 x g for a duration of 15 minutes in order to conduct coagulation tests. After a period of seven days, we took more samples from each patient using citrate, ESR, and plain tubes.

Procedures:

The XS500i Hematology Analyzer (Sysmex, Kobe, Japan) was used to conduct the full blood count. Cell counts were obtained by analyzing blood films. The Westergren method was utilized to measure the erythrocyte sedimentation rate (ESR) [22]. The coagulation tests were performed using the Sysmex CS2100i apparatus manufactured by Siemens in Munich, Germany. Biochemical tests were conducted using the Cobas 8000 Modular Analyzer (Roche Diagnostics, Mannheim, Germany), with the exception of HbA1C, D-dimer, and PTH, which were evaluated using the Cobas 6000 Modular Analyzer (Roche Diagnostics, Mannheim, Germany).

Ethical considerations:

The study was done after being accepted by the Research Ethics Committee, Zagazig University. All patients provided written informed consents prior to their enrolment (ZU-IRB#6696-16-8-2020). The consent form explicitly outlined their agreement to participate in the study and for the publication of data, ensuring protection of their confidentiality and privacy. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical methods

The quantitative qualities were represented by the mean and standard deviation (SD), while the categorical elements were displayed as absolute values and percentages. The independent Student's t-test was employed to compare independent quantitative variables, whereas the paired t-test was used to examine related quantitative variables. The chi-squared test was used to compare categorical variables. A logistic regression analysis was performed to compute the adjusted odds ratio (AOR) and its related 95% confidence interval (CI). The statistical analysis was conducted using SPSS software, specifically version 25.0, designed for Windows operating system (SPSS; Chicago, IL, USA). A p-value below 0.05 was deemed to be statistically significant.

RESULTS

Two groups were formed by randomly assigning 250 patients diagnosed with COVID-19. A total of 170 individuals were administered an injection of Vit D, while 80 patients were given the typical daily oral dose of 10,000 IU cholecalciferol, which served as the control group. Table 1 presents the demographic and baseline characteristics of the subjects in both groups. The demographics, baseline characteristics, and test results were similar between the two groups. Figure 2 depicts the Vit D levels at the beginning and after seven days for both the Vit D group and the control group.

Table 1: Demographic and baseline characteristics of the study groups.

Parameters		**Vitamin D Group (N=170)**	**Control Group (N=80)**	**P-value**
Age (year)		52.81 ± 12.29	50.5 ±10	0.146
BMI (kg/m^2)		28.16 ± 5.08	29 ±6.3	0.261
Gender (Male/Female)		97/73 (57.1/42.9)	54/26 (67.5/32.5)	0.115
Residence (Rural/Urban)		97/73 (57.1/42.9)	46/34 (57.5/42.5)	0.948
Smoking: (Non/Smoker)		81/89 (47.6/52.4)	36/44 (45/55)	0.696
Comorbidity:	No	86 (50.6)	40 (50)	0.753
	Diabetes	45 (26.5)	18 (22.5)	
	Diabetes and IHD	3 (1.8)	3 (3.75)	
	Diabetes and Hypertension	12 (7.1)	5 (6.25)	
	Hypertension	18 (10.6)	10 (12.5)	
	Gout	3 (1.8)	2 (2.5)	
	Hypothyroidism	2 (1.2)	2 (2.5)	
Viral hepatitis:	No	160 (94.1)	76 (95)	0.942
	HCV	8 (4.7)	3 (3.75)	
	HBV	2 (1.2)	1 (1.25)	
Clinical manifestations:	Respiratory	132 (77.6)	66 (81.25)	0.871
	Respiratory/GI	36 (21.2)	12 (15)	
	Respiratory/GI/others	2 (1.2)	3 (3.75)	
Fasting Glucose (mg/dL)		117.19 ± 6.14	110.2 ±3.9	0.225
HbA1c (%)		7.87 ± 0.53	7.76 ±0.85	0.213
White Blood Cells (10^9/L)		6.54 ± 1.94	6.8 ±1.8	0.311
Lymphocyte (10^9/L)		1.47 ± 0.13	1.38 ± 0.17	0.263
Hemoglobin (g/dL)		12.3 ± 1.46	12.3 ±1.4	1
Platelet count (10^9/L)		247.24 ± 61.61	246 ±51	0.876
Total bilirubin (mg/dL)		0.77 ± 0.17	0.75 ±0.10	0.441
Direct bilirubin: (mg/dL)		0.22 ± 0.07	0.20 ±0.04	0.441
AST (U/L)		43 ±8	42 ±3	0.658
ALT (U/L)		36 ±28	37 ±21	0.778
Albumin (g/dL)		4.1 ±0.3	4.1 ±0.4	1
Total protein (g/dL)		7.37 ±0.37	7.36 ±0.38	0.844
ALP (U/L)		82.51 ± 20.95	86 ±20	0.214
INR		1.01 ± 0.12	0.99 ±0.19	0.304
Creatinine (mg/dL)		0.78 ±0.16	0.82 ±0.20	0.204
BUN (mg/dL)		14.1 ±2.3	13.7 ±2	0.195

Data are expressed as mean ± SD or number (%); ALP: Alkaline Phosphatase, ALT: Alanine Transferase, AST: Aspartate Transferase, BMI: Body Mass Index, BUN: Blood Urea Nitrogen, HbA1C: Hemoglobin A1C, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus, IHD: Ischemic Heart Disease, INR: International Normalized Ratio.

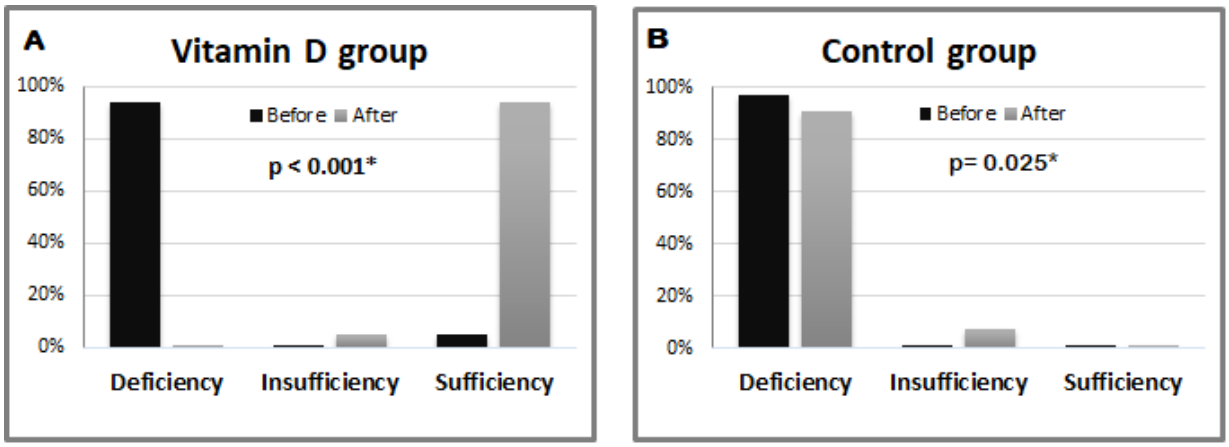

Figure 2: Comparison of patient percentages based on Vit D status at baseline and after 7 days in (A) the Vit D group and (B) the control group.

Vit D deficiency: serum 25(OH)D < 20 ng/mL, Vit D insufficiency: serum 25(OH)D = 20-30 ng/mL, Vit D sufficiency: serum 25(OH)D = 30-100 ng/mL. *: Significant.

An analysis was conducted to examine the correlation between Vit D levels and the severity of COVID-19.

Table 2 demonstrates that the only notable difference in Vit D levels among COVID-19 patients with varying severities was observed in mild instances. In this group, the control group had greater levels of Vit D compared to the Vit D group. The patients who died in both groups exhibited significant Vit D deficiency at the beginning of the trial (with serum 25(OH)D levels of 8.27 ± 5.34 ng/mL and 9.35 ± 4.46 ng/mL, respectively).

Table 2: Comparison of the Vit D status and COVID-19 severity in both groups at baseline of study.

COVID-19 severity	**Vitamin D group (N=170)**		**Control group (N=80)**		***P***
	No (%)	**Serum 25(OH)D**	**No** (%)	**Serum 25(OH)D**	
All cases	170 (100)	13.77 ± 3.51	80 (100)	14.35 ±3.58	0.283
Mild	80 (47)	17.13 ±2.81	35 (43.75)	18.41 ±1.07	0.01*
Moderate	50 (29.4)	12.23 ±2.31	25 (31.25)	13.92 ±2.26	0.07
Severe	22 (13)	13.36 ±2.86	12 (15)	12.37 ±2.64	0.595
Critical	18 (10.6)	8.27 ±1.34	8 (10)	9.35 ±.46	0.623

Data are expressed as mean ± SD or number (%), **p** of comparison between the two groups regarding to mean serum 25(OH)D, *: Significant.

Comparison of the clinical and biochemical parameters

The clinical and biochemical parameters at the baseline and after seven days from the start of study were presented in **Table 3**. Following a period of 7 days, the group receiving parenteral Vit D showed a notable enhancement in the levels of serum 25(OH)D and oxygen saturation. Additionally, there was a notable decrease in the respiratory rate and inflammatory markers. During the trial, there was no significant difference in the clinical and inflammatory markers between the control group and other groups, except for CRP, after seven days.

Table 3: Comparison of the clinical and biochemical parameters between the baseline and after 7 days in the two study groups.

Parameters	**Vitamin D Group** (N=170)			**Control Group** (N=80)			p#
	Baseline	**After 7 days**	**p**	**Baseline**	**After 7 days**	**p**	
O_2 Saturation (%)	84 ±8	93 ±4	**<0.001***	85 ±6	88 ±4	0.217	**<0.001***
Temperature (ºC)	37.4 ±2.2	36.1 ±4.14	0.405	37.2 ±3.1	36.4 ±5.3	0.246	0.257
Respiratory Rate (breaths/ min)	18 ±8	13 ±6	**<0.001***	16 ±10	15 ±14	0.603	0.115
Heart Rate (Pulse/min)	90 ±25	87 ±18	0.398	89 ±30	90 ±23	0.813	0.455
SBP (mm Hg)	120 ±25	118 ±27	0.708	117 ±28	119 ±18	0.537	0.346
ESR (mm/hr)	50.99±7.56	29.74 ± 8.97	**<0.001***	54.7 ±2.2	48.6 ±5	0.19	**<0.001***
CRP (mg/L)	30.75 ±4	10.52 ±1	**<0.001***	37.86 ±8	28.67 ±1	**0.002***	**<0.001***
Ferritin (ng/mL)	392 ±39.17	94.59±21.14	**<0.001***	368 ±58.4	297 ±68.2	0.065	**<0.001***
D-Dimer (ng/mL)	465 ±84.2	178.5±15.7	**<0.001***	398 ±34.9	289 ±19.7	0.165	**<0.001***
Calcium (mg /dL)	8.52 ± 0.56	8.6 ±0.39	0.127	8.49 ± 0.67	8.5 ± 0.47	0.913	0.078
Phosphorus (mg/dL)	4.1±1.2	4.0 ±1.8	0.547	3.9 ±0.8	4.1 ±1.3	0.422	0.657
PTH (pg/mL)	31.6 ± 5.66	30. 62 ±6.93	0.217	32.2 ±4.81	31.82 ±5.54	0.676	0.195
Vitamin D (ng/mL)	13.77 ± 3.51	32.48 ±5.64	**<0.001***	14.35 ±3.58	15.76 ±3.33	0.283	**<0.001***

Data are expressed as mean ± SD, ESR: Erythrocyte sedimentation rate, CRP: C-Reactive Protein, PTH: Parathyroid Hormone, SBP: Systolic Blood Pressure, Vit D: Serum 25(OH)D level, p value of comparison between before and after treatment. p# value of comparison between the two groups after the treatment. **:* Significant.

Comparison of outcome parameters

Table 4 displays the result parameters for both study groups. Within the Vit D cohort, the majority of cases exhibited amelioration and were released from the intensive care unit. Specifically, 12 patients were successfully transitioned from non-invasive ventilation, while 5 patients were successfully transitioned from invasive mechanical ventilation. Conversely, the control group had a greater length of time for improvement and discharge from the ICU. The duration of hospitalization from the beginning of the study was shorter in the Vit D group compared to the control group. The proportion of patients who received a negative result for SARS-CoV-2 RNA PCR test before day 21 was considerably greater in the Vit D group compared to the control group. The mortality rate from COVID-19 within the initial seven days of the research was considerably lower in the Vit D group compared to the control group.

A multivariate logistic regression analysis found that Vit D deficiency was associated with a significant 15.375-fold increase in the risk of mortality among COVID-19 patients [Adjusted Odds Ratio (AOR) = 15.375, 95% Confidence Interval (CI): 1.898-124.52, p = 0.01]. In contrast, Vit D insufficiency showed a non-significant 4.741-fold increase in that risk [AOR = 4.741, 95% CI: 0.613-36.695, p = 0.136].

Table 4: Comparison of outcome parameters between the two studied groups.

Parameters	Vitamin D group (N=170)	Control group (N=80)	P
COVID-19 mortality within 7 days from the start of study	8 (4.7)	22 (27)	**<0.001***
Duration of hospital stay from the start of study: (days)	8.81 ± 2.98	16 ± 5.42	**<0.001***
SARSCoV-2 RNA PCR negativity before day-21	135 (79.41)	16 (20)	**<0.001***

Data are expressed as mean ± SD or number (%), **:* Significant

DISCUSSION

Insufficient levels of Vit D are correlated with an increased risk of contracting COVID-19 and experiencing more severe outcomes, including fatality [10,23]. Previous research has shown that Vit D has immunomodulatory properties and provides protection against several viral infections [24]. However, there is a lack of data about the therapeutic effectiveness of Vit D in treating SARS-CoV-2 infection in COVID-19 patients.

Vit D can stimulate the production of the antimicrobial peptide cathelicidin in neutrophils, monocytes, and natural killer cells, leading to a reduction in the levels of the herpes simplex virus [25]. Moreover, it influences the expression of numerous genes associated with the body's immune defense mechanisms and inflammatory response, hence modifying the likelihood and severity of bacterial and viral infections [26].

SARS-CoV-2 enters cells by attaching to ACE-2 receptors, which are abundant on specific cell surfaces. Vit D has the capacity to reduce the formation of ACE-2 receptors, so inhibiting the virus from binding to and infiltrating the cell [27].

Research suggests that maintaining serum 25(OH)D levels over 30 ng/mL is associated with a significant reduction in the severity and mortality rate of SARS-CoV-2 infection [28]. Therefore, we undertook a study to investigate the impact of providing a high dose of Vit D on improving clinical and laboratory markers in persons with SARS-CoV-2 infection.

Our study findings indicate that administering a daily injection of 200,000 IU cholecalciferol to COVID-19 patients for four consecutive days can lead to improved clinical outcomes. This enhancement is evidenced by a significant reduction in inflammatory markers and a negative result in SARS-CoV-2 RNA PCR test after consuming the supplement. The results are consistent with a study conducted by **Rastogi *et al.*** [29], which found that 62.5% of patients infected with SARS-CoV-2 and deficient in Vit D showed a reversal of SARS-CoV-2 RNA positivity after receiving a daily oral dose of 60,000 IU Vit D 3 for seven days. Furthermore, these patients had a significant reduction in fibrinogen levels.

During the trial, individuals with Vit D deficiency received a solitary bolus dose of 540,000 IU of cholecalciferol. Consequently, the mean blood 25(OH)D concentrations rose over 20 ng/mL on the initial day and reached a maximum of 38.2 ± 16.5 ng/mL after one week [30]. Subsequent research revealed that the administration of a single dose of 600,000 IU of Vit D 3 successfully increased blood 25(OH)D levels to above 30 ng/mL in older individuals. This altitude was maintained for a duration of at least four weeks without any adverse consequences [31]. However, a thorough investigation of Vit D supplementation using a single oral dose of 100,000 IU demonstrated that it is not helpful in increasing 25(OH)D levels above 30 ng/mL [32]. Throughout our study, we administered a daily intramuscular injection of 200,000 IU of cholecalciferol, often known as Vit D 3, for four consecutive days, exceeding the necessary dosage. Nevertheless, we have confirmed that this treatment approach is indeed secure. After a duration of seven days, the mean serum 25(OH)D concentration increased to 32.48 ± 9.64 ng/mL from an initial level of 13.77 ± 6.51 ng/mL. Importantly, there were no occurrences of hypercalcemia or reductions in blood PTH levels, indicating the safety of delivering high doses of Vit D for a short period of time.

Frequent monitoring of inflammatory markers is beneficial for assessing and tracking the severity of COVID-19. Severe instances of COVID-19 display elevated levels of serological markers, including IL-6, CRP, ferritin, and ESR, in comparison to mild individuals [33]. Our findings align with this observation, since we observed a significant decrease in the levels of inflammatory markers in both groups after seven days, following the initial surge at the start of the trial. Furthermore, the group that was administered Vit D exhibited notable clinical improvements, such as elevated levels of oxygen saturation, when compared to the control group. This suggests a potential immunomodulatory effect of Vit D. However, our research findings on inflammatory markers differ from those of **Rastogi *et al.*** They found no significant differences in levels of inflammatory markers between groups, except for a decrease in fibrinogen levels among patients with Vit D levels above 50 ng/mL compared to those with a Vit D deficiency [29].

The multivariate logistic regression analysis demonstrated a statistically significant correlation between Vit D inadequacy and a heightened susceptibility to mortality caused by COVID-19. The results align with the findings of **Merzon *et al.*,** who discovered a link between decreased plasma 25(OH) Vit D levels and a greater incidence and increased severity of COVID-19 in a similar multivariate logistic analysis [5]. A recent meta-analysis of clinical research found that the use of Vit D reduced the incidence of acute respiratory tract infections. The incidence rate ratio was calculated to be 0.96, with a confidence interval of 0.92–0.997 and a p-value of 0.04 [26]. In the context of SARS-CoV-2 infection, a deficiency of Vit D may lead to the production of pro-inflammatory cytokines, which can contribute to a more severe presentation of COVID-19 [11,32].

The primary benefit of our research resides in the use of a prospective randomized controlled methodology and the regular administration of high-dose Vit D through intramuscular injections. The aim of this procedure is to promptly rectify Vit D insufficiency by elevating serum 25(OH)D levels above 30 ng/mL. This product precisely addresses the difficulties associated with low compliance

and limited absorption that are frequently encountered when taking oral Vit D supplements, particularly in instances of malabsorption. However, the study's open-label methodology, absence of data for inflammatory cytokines such as IL-6, TNF, and IL-1b, and inability to evaluate the impact of Vit D supplementation on cytokine levels are limitations. Further research is recommended to verify the validity of our findings.

CONCLUSION

Our study indicates a strong correlation between Vit D deficiency and increased mortality rates in COVID-19 patients. Additionally, administering a single intramuscular dose of 200,000 IU cholecalciferol for four consecutive days effectively improved both the laboratory and clinical outcomes for COVID-19 patients. This treatment also reduced the mortality rate and enhanced the clearance of the SARS-CoV-2 virus. Higher levels of parenteral Vit D supplementation could be considered a potential therapeutic approach for COVID-19 infection.

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