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Vitamin D, Calcium and Phosphorus Status Involvement during COVID-19 Infection

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: COVID-19 is associated with a weak immune system in the human body. Vitamin D plays a role in the body's immune system and is known to enhance the function of immune cells. In this case, vitamin D inhibits some of the inflammation that can make COVID-19 more severe. The is study aims to determine the serum levels of vitamin D, calcium, and phosphorus in COVID-19 patients.
Methods: This was a cross sectional study conducted during the period from January 2021 to July

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2021. 50 COVID-19 patients as a case study and 50 healthy individuals as a control group were included in this study. Blood samples were collected from the study group and measured for vitamin D using Enzyme-linked immunosorbent assay (ELISA) technique. Calcium and phosphate were measured by the Cobas 6000 fully automated analyzer (Roche, Germany).

Results: The study result showed that in COVID-19 patients, vitamin D (27 ± 5 ng/mL), p-value = 0.000, and calcium (10.2 ± 4 mg/dL), p-value = 0.000, in comparison with control. There was a correlation between vitamin D (r = -.771; p =.000) and calcium (r = -.752; p =.000) and the severity of disease.

Conclusions: According to our research, vitamin D deficiency may increase the risk of developing COVID-19 and the risk of developing severe illnesses.

Keywords: COVID -19; vitamin D; calcium; phosphate.

1. INTRODUCTION

"Although most people with coronavirus disease 2019 (COVID-19) are asymptomatic or only experience minor symptoms, some patients may experience life-threatening clinical syndromes such as pneumonia, acute respiratory distress syndrome (ARDS), myocarditis, microvascular thrombosis, and cytokine storm" [1]. "To reduce the risk of developing a serious illness and, as a result, the death rate, it is necessary to protect people from COVID-19, which has become grown more contagious as a result of its mutation. A glimmer of hope has emerged in the global fight against COVID-19 with the approval of COVID-19 vaccinations for emergency use. There have been some severe cases of COVID-19, and the benefits of vaccinations for the immune systems have not yet been demonstrated conclusively. Vitamin D is a group of fat-soluble secosteroids responsible for increasing intestinal absorption of calcium, magnesium, and phosphate, and many other biological effects" [2,3]. "In humans, the most important compounds in this group are vitamin D3 (also known as cholecalciferol) and vitamin D2 (ergocalciferol) [2,3,4], vitamin D plays an important role in calcium homeostasis and metabolism". "Despite the rarity of reports of hypocalcemia during COVID-19 infection, we should therefore pay more attention to changes in calcium/phosphorus metabolism in patients with COVID-19 and closely monitor calcium levels, especially in those with a history of hypocalcemia" [5]. "The impact of vitamin D on the management and side effects of COVID-19, as well as its potential role in lowering the incidence of COVID-19, has been the subject of a great deal of investigation. By promoting the release of cathelicidin and defensin proteins in monocytes and macrophages, vitamin D has antiviral effects and prevents viral replication" [6,7]. "Due to its effects, such as promoting T lymphocyte chemotaxis and removing respiratory pathogens by triggering apoptosis and autophagy in the infected epithelium, vitamin D is crucial in avoiding infections of the respiratory system" [8]. "Some patients with COVID-19 with severe symptoms had low T lymphocyte counts, according to reports" [9]. "This finding supports the idea that vitamin D could be a potential anti-inflammatory agent because vitamin D administration increase the number of T lymphocytes" [10]. "There is evidence that vitamin D may prevent or improve outcomes in many infectious and inflammatory conditions , including acute and chronic respiratory infections. There is also a growing understanding of its immunomodulatory and anti-inflammatory functions. A recent meta-analysis found a 70% reduction in viral respiratory tract infections among people with vitamin D deficiency randomized to vitamin D treatment" [1]. "The potential importance of vitamin D in the spread of COVID in the USA is supported by the fact that nearly half of the population is vitamin D deficient, with higher rates among people with darker skin and/or lower sun exposure, including those living in higher latitudes in winter, nursing home residents and health care workers, who also have a greater risk of COVID-19". Adrian [11,12] "the previous study provided some of the first evidence to support the hypothesis that vitamin D deficiency can affect the risk COVID-19, finding that patients with vitamin D deficiency that was not adequately treated were 77% more likely to test positive for COVID-19 than patients who were not likely vitamin D deficient" [13]. "One of the most significant issues with the pandemic is the severe progression of COVID-19 in some patients. Studies have shown that patients with severe COVID-19 had a higher rate of thrombotic events and cytokine storms. These occurrences are to blame for tragic results" [14,15,16]. "Having enough vitamin D reduce the probability of a cytokine storm and controls

thrombotic pathways, as is well known" [17,18]. "Vitamin D deficiency (VDD) has been associated with increase COVID-19 severity and death, and vitamin D sufficiency has been suggested to decrease the increased levels of inflammatory markers and cytokine storm during COVID-19 disease" [18,19]. "As a result, there is a great deal of interest in the question of how VDD affects COVID-19 infection and outcomes. Some studies have shown that people who are in hospitals with severe COVID -19 also have low levels of vitamin D (vitamin D deficiency). However, the risk factors for developing severe COVID -19 are the same as those for developing vitamin D deficiency, so it is difficult to tell if vitamin D deficiency itself is a risk factor for severe COVID -19. Clinical studies showed that the most vulnerable populations to COVID -19 are the elderly populations and those with vitamin D deficiency" [20]. "older patients with comorbidities and below normal vitamin D have a higher rate of mortality" [21]. "Vitamin D deficiency has also been reported to be associated with an increased risk of severity in COVID -19" [22]. "It seems highly probable that adequacy of vitamin D supplementation for populations with a high prevalence of vitamin D deficiency may decrease the risk of severe consequences of COVID -19" [22].

2. METHODS AND MATERIALS

2.1 Study Design

A cross-sectional study was conducted during the period from December 2021 to April 2022 in Khartoum State. Sudanese patients with COVID-19 and patients who were diagnosed with COVID-19 during the study period were enrolled to participate in this study. The confirmation of COVID-19 will be based on a CT scan and/or RT-PCR. The total study group was 100, 50 patients with COVID-19 as a case study present during the period of study, and 50 healthy individuals were enrolled as a control group.

2.2 Inclusion and Exclusion Criteria

Covid -19 patients are included in the study group. Any diseases that may affect serum vitamin D levels, serum calcium levels, or serum phosphate, will be excluded.

2.3 Data Collection

Primary data collection were collected from the analytical results of the patients who had made tests. Secondary data collection were collected from medical journals, medical textbooks, and internet web sites.

2.4 Sample Collection

The venous blood sample will be collected using sterile, dry, plastic syringes and a tourniquet to make the veins more prominent. The puncture sites were cleared with 70% ethanol, and the amount of blood sample required is 5 ml, which will be collected in lithium heparin containers from each volunteer. The lithium heparin blood sample were centrifuged at 4000 rpm to obtain the plasma vitamin D tests. All samples were stored at (4 c) until the analysis.

2.5 Measurement of Biochemical Parameters

Method for measured vitamin D Enzyme-linked immunosorbent assay (ELISA) competitive binding method: This ELISA test kit is designed for the in vitro determination of 25 - OH vitamin D in human serum samples. Amount of 25 - OH vitamin D in the patient sample and a known amount of biotin-labeled 25 - OH vitamin D compete for the antibody binding sites in the microplate wells plate. Unbound 25 - OH vitamin D is removed by washing. For the detection of bound biotin-labeled 25 - OH vitamin D, a second incubation is performed using peroxidase-labeled streptavidin. In a third incubation using the peroxidase substrate tetramethylbenzidine (TMB) the bound peroxidase promotes a color reaction. The color intensity is inversely proportional to the 25 - OH vitamin D concentration in the sample. Calcium, and phosphate blood levels were measured by the Cobas 6000 fully automated analyzer (Roche-Germany).

2.6 Data Analysis

Data were analyzed by using the SPSS computer program, SPSS version 18. Statistical analysis was done using ANOVA for continuous variables, and Chi square test was used for proportion. Correlation between quantitative variables was assessed by Pearson's correlation coefficient. P. value <0.05 was considered to be statistically significant.

3. RESULTS

This study described 50 adult patients aged between 23 and 75 years who were hospitalized

with Covid -19 in an isolation center in Sudan. The serum level of vitamin D, calcium and phosphate in patients covid and compare the results with the control group. In Fig. 1 the patients with Covid -19 are classified into mild (n = 20), moderate (n = 12) and severe (n = 18) according to severity of disease. In Fig. 2 the majority of covid -19 are men (58%) who showed that the incidence of covid -19 is higher in men than women. Abnormal laboratory parameters were observed more frequently in confirmed patients with COVID19, particularly in mild, moderate, severe or critical patients, as shown in Fig. 2. In Table 1. This study showed that there was a significant decrease in the mean level of vitamin D and calcium in the mean level in patients with COVID-19 when compared to the control group (p-value = 0.000), there was no significant differences in the phosphorus levels when compared to the control group. There were no significant differences in the laboratory parameters levels according to sex in the case study in Table 2.

Pearson correlation investigates the relationship between COVID-19 disease stages and biochemical changes in plasma parameters in Table 3 and Figs. 3, 4, Negative correlation between vitamin D levels and disease severity stages, R= -0.7, P. value =.000 and negative correlation between serum calcium levels and disease stages, R = -0.74 , P =0.000.

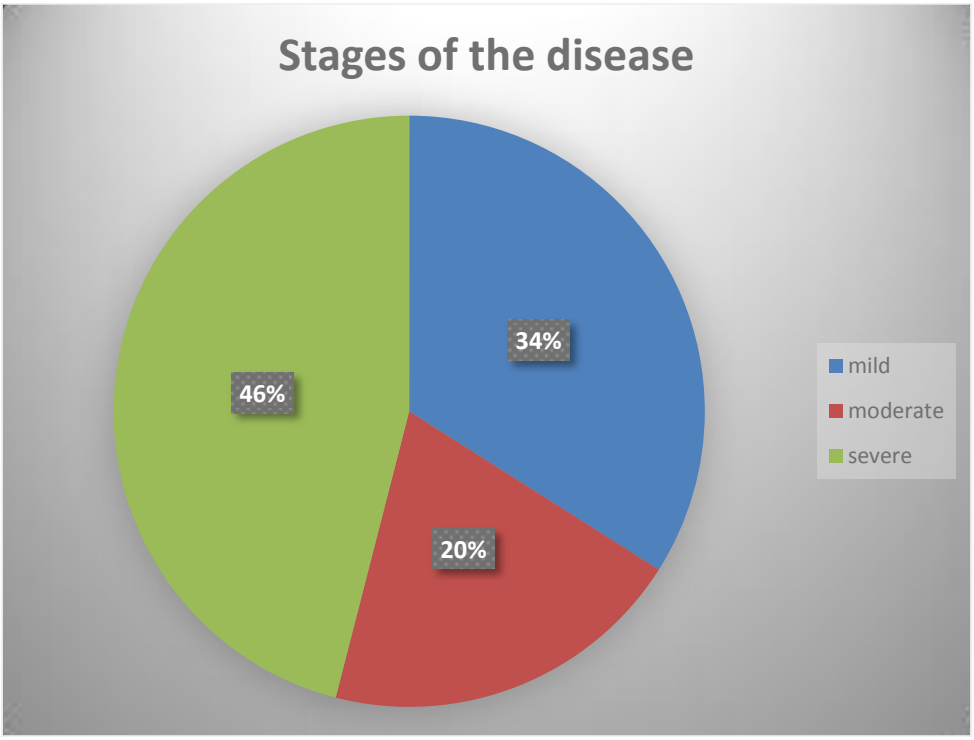

Fig. 1. Distribution of stages of the disease in the case study

Table 1. Comparison of biochemical parameters means and Sd. among of the study groups

Test	Study group	Control group	P. value
Vitamin D (ng/mL)	27±5	43±6	0.000
Calcium (mg/dL)	10.2±4	10.5±4.2	0.000
Phosphate (mg\dL)	4.5±2.2	3. 9±.024	0.15

Table 2. Comparison of biochemical parameters means and Sd. among of the study groups according to gender

Test	male	female	P. value
Vitamin D (ng/mL)	27±5	24±6	0.4
Calcium (mg/dL)	9.2±4	10.2±4	0.6

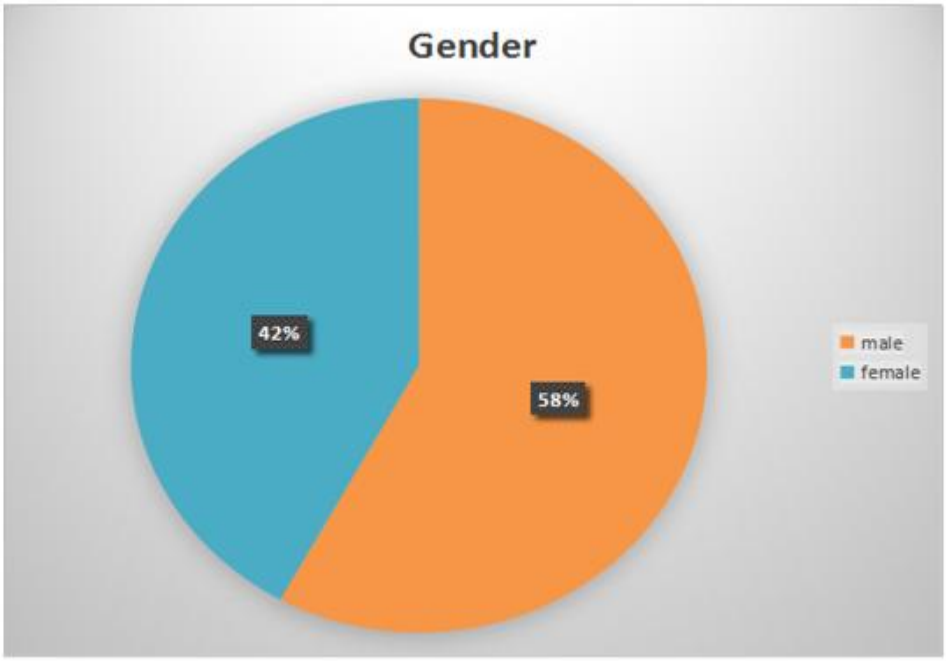

Fig. 2. Distribution of the case study patients according to gender

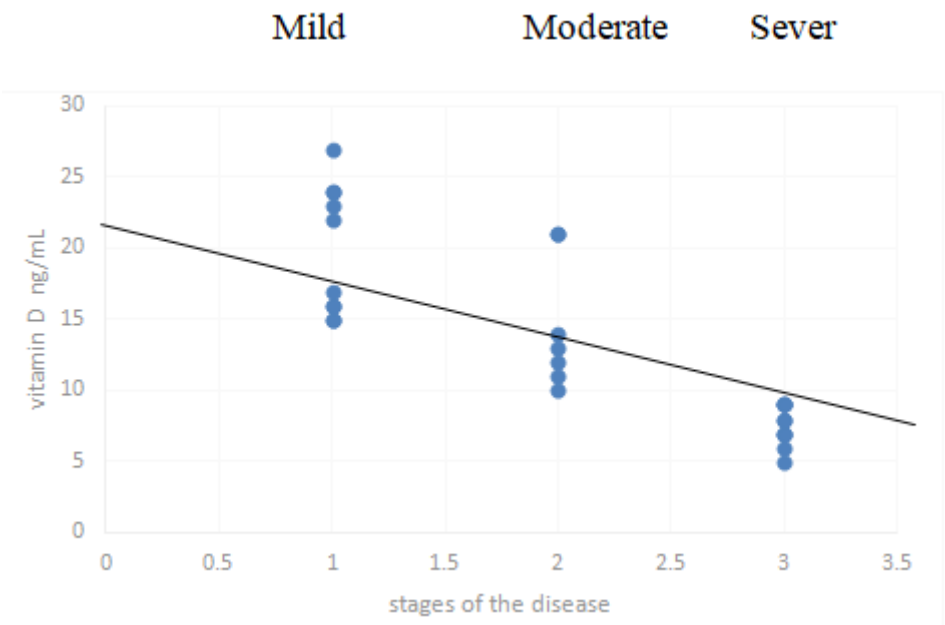

Fig. 3. Correlation between Plasma vitamin D level and stages of COVID-19 disease, R= -0.7, P. value =.000

Table 3. Correlation between the stages of the disease and biochemical changes in the plasma parameters

Test	Correlation - R. value	P. value
Vitamin D (ng/mL)	-.771	.000
Calcium (mg/dL)	-.752	.000

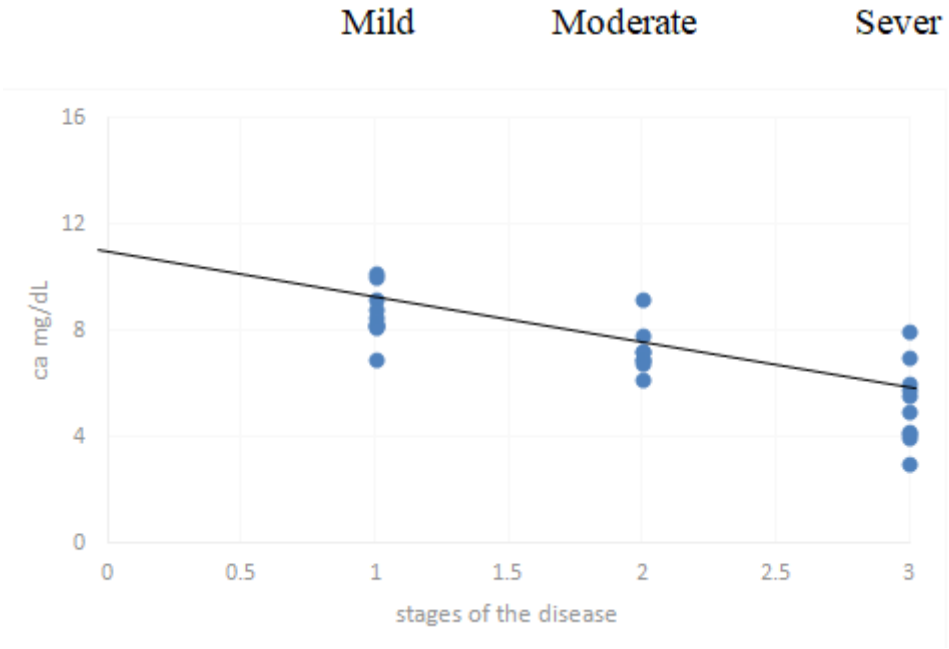

Fig. 4. Correlation between Plasma level calcium and stages of COVID-19 disease, R= -0.74 , P. value =0.000

4. DISCUSSION

The outbreak of COVID -19 in the Chinese city of Wuhan in early December 2019 caused havoc with an overall case-mortality rate of 2.3% (4,512 deaths among 68,151 confirmed cases) [23], it was found to spread from person to person like droplet infection [24] and was found to be highly contagious, which led to the city being closed to prevent spread of the disease [25]. It started spreading to all countries in the world and reached Sudan in March 2020 [26]. COVID -19 affects different people in different ways. Most people who get it have mild to moderate symptoms and recover without hospitalization. The most common symptoms of the disease include fever, dry cough and fatigue, while less common symptoms include aches and pains, sore throat, diarrhea, conjunctivitis, headache and loss of taste or smell, a rash, while serious symptoms of covid -19 disease include difficulty or shortness of breath, pain or pressure in the chest, loss of the ability to speak or move. This study described 50 adult patients between 23 and 75 years of age and determined the serum level of vitamin D, calcium, and phosphate in patients with COVID-19 and compared the results with the control group. COVID-19 patients are classified as mild, moderate, and severe according to stages of disease. In this study, the most of those infected with COVID-19 are male. which agrees with the study of Team TNCPERE [27] who demonstrated that the incidence of COVID-19 is higher in men than women. Recent studies suggest that this may be due to dissimilar innate immunity, steroid hormones, and factors related to sex chromosomes.

This study showed that there was a significant decrease in the levels of vitamin D and calcium in COVID-19 patients compared to the control group. These results showed an agreement with the finding of Abdolahi Shahvali Elham et al. [28], who found a deficiency in the levels of vitamin D and calcium in a group of COVID-19 patients compared to the control group. While the results of this study on calcium levels showed agreement with the previous study reporting a high prevalence of hypocalcemia in patients with the coronavirus [29].

Vitamin D plays a key role in regulating the balance of calcium. Additionally, it directly induces antimicrobial peptides at mucosal surfaces and regulates T cell activity, which has important impacts on the immune system. Low vitamin D levels are linked to an increased risk of respiratory tract infections, according to pre-pandemic observational data [30,31]. The results of Randomized trials were mixed, but two important meta-analyses showed some evidence that vitamin D supplementation may help prevent respiratory tract infections, especially in vitamin D deficient individuals [32-34].

Could vitamin D help with COVID-19 defense? Mechanistically, vitamin D increases the body's ability to fight against respiratory infections like the influenza A virus and the rhinovirus [35,36].

The statistical quality analysis revealed a difference in the amount of vitamin D between the case and control groups ($p = 0.000$), but not in the level of calcium ($p = 0.00$). This confirms with studies by Abdolahi Shahvali Elham [28], among others, who discovered a correlation between vitamin D levels and the severity of the disease. and the William et al. study, which shown that vitamin D has a positive impact on COVID-19 patients [37].

This contradicts the findings of studies by Abdolahi Shahvalili Elham and Hosseininezhad et al. [38] who found that there was no significant difference in the prevalence of vitamin D deficiency between males and females. The study found that the level of vitamin D in the serum of both sexes (males and females) had a significant difference between the case and the control group.

Observational data from past studies suggest that low levels of 25(OH)D may be a risk factor for severe COVID-19. [39] However, confounding or random influences may be responsible for this connection [40,41]. For instance, COVID-19 and vitamin D deficiency are both independently associated with obesity, old age (>65 years), and male sex. Two related, new randomized studies give this critical question the much-needed support it needs. The initial investigation was carried out in the United Kingdom between May and October 2021 [42]. Jolliffe and colleagues randomly assigned 3100 participants to receive either 3200 IU/day or 800 IU/day of vitamin D3 for a period of six months if their blood levels of 25-hydroxyvitamin D were below 75 nmol/L. 3,100 extra controls weren't examined or supplemented. The scientists concluded that neither of the vitamin D doses was impacted by the prevalence of COVID-19.

However, there are not enough cohort studies and clinical studies to identify how vitamin D affects the severity and/or prevention of COVID-19 infections. Initial research by Alipio [43] revealed a strong correlation between vitamin D3 level and infection severity; patients with sufficient vitamin D3 status (> 30 ng/mL) showed mild COVID-19 symptoms, while 72.8% of patients with vitamin D3 deficiency (20 ng/mL) showed severe symptoms.

This study found that the mean calcium level was substantially lower in COVID-19 patients than in the control group. Yang's [44] result that COVID-19 was independently related to hypocalcemia more so than the control group confirmed these similar findings. In a previous study, it was observed that the most common adverse effect of hypocalcemia was increased neuromuscular irritability, which is characterized by muscle spasms, tingling in the limbs, and perioral numbness.

A rare complication of hypocalcemia is reversible cardiomyopathy [45]. The findings of the current study are similar to those of Ramesh [46] who found that COVID-19 was significantly associated with hypocalcemia more so than among controls.

When compared to the control group in this investigation, COVID-19 patients had normal levels of phosphate see Table 1. Disagree with previous studies' findings that hypophosphatemia was more significantly linked with COVID-19 than the control group [44,46]. Other earlier research found that the risk variables for hypophosphatemia—excessive energy expenditure and catabolism, as well as insufficient dietary intake—were likely mediating the association between hypophosphatemia and poor outcomes. Malnutrition was a common problem for those with COVID-19, and it has been associated with poor outcomes for these patients [47-52].

The influence of vitamin D on COVID-19 has been examined in a number of recent research. In one study of 489 individuals, it was discovered that those with a vitamin D shortage had a higher likelihood of testing positive for the virus that causes COVID-19 than those with adequate vitamin D levels. According to other studies, patients with COVID-19 who develop acute respiratory failure had high rates of vitamin D deficiency. These patients had a significantly increased probability of dying [53]. Additionally, vitamin D deficiency is common in Sudan. The COVID-19 has disproportionately impacted these communities. In addition, those who are elderly, obese, or have a body mass index of 30 or more are more likely to suffer from a vitamin D deficiency (hypertension). These factors also raise the possibility of developing severe COVID-19 symptoms. According to the National Institutes of Health and the World Health Organization [53], there isn't enough data to recommend the use of vitamin D to prevent

infection with the virus that causes COVID-19 or to treat COVID-19. Further study is needed to determine whether vitamin D and vitamin D deficiency can help prevent and treat COVID-19.

5. CONCLUSION

This study concludes that there was a significant decrease in the level of vitamin D and calcium in COVID-19 patients when compared to the control group. There was a significantly strong correlation between the study parameters and COVID-19 disease severity.

CONSENT

Informed consent was obtained from each participant in the study after explaining the objectives of the study. An interview and a questionnaire were used to collect data.

ETHICAL APPROVAL

This study was approved by the Ethical Committee of the Faculty of Medical Laboratory Sciences - Alzaiem Alazhari University.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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