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Vitamin D Deficiency and Clinical Outcomes in Patients with COVID-19

Chalak M. Noori, Medical Lab Technology Department, Kalar Technical Institute, Sulaimani Polytechnic University, Kalar, 46021, Iraq
Email: chalak.noori@mhe-krg.org

Saman M. Amin Saeed , Ministry of Health, General Directorate of Garmian, Kalar, 46021, Iraq.

Rezan Huseen H. Salih, Department of Chemistry, College of Science, University of Garmian, Kalar, 46021, Iraq

Hersh Jalil, Ministry of Health, Hiwa Hospital, Sulaimania, 46001, Iraq

Nawzad O. Ahmad, MSc Molecular Biology Ministry of Health

Masoud Muhammed, MSc Physical chemistry University of Garmian College of science

Abstract:

Background:
COVID-19, also known as the new coronavirus, has been linked to a variety of clinical outcomes, including moderate respiratory symptoms, severe respiratory failure, multi-organ failure, and death. The disease's severity can vary depending on a number of factors, including age, pre-existing medical disorders, and immunological function.

Aim:
The aim of this study was to monitor the 25OH-Vitamin D serum level with clinical outcomes including CRP for patent's infected with SARS-CoV-2.

Method:
In this study a total of 59 patients and 25 normal cases (for control) were enrolled for investigation the role of Vitamin D in the disease severity in patients infected with SARS-Cov-2.

Results:
The result showed a significant decrease of vitamin D in abnormal group compared with normal group (15.74±5.63 vs 33.41±12.18 ng/dl, p = 0.0001). Additionally, the patients in infected group (6.7±12.64) had significantly ($p<0.0001$) lower CRP level in comparison with control group (1.77±3.12). There are no significant differences reported (0.612) in ages between the infected COVID-19 group 38.35±6.15 and control group (37.85 ± 7.28). Furthermore, The RT-

PCR had no significantly reported differences between COVID-19 cases and control group 29.98±5.25 *vs* 39.89 ± 5.01.

Conclusion:

we found that COVID-19 patients with vitamin D deficiency were more likely to increase the risk of severe COVID-19 infection and complications; it helps regulate the body's inflammatory response, which is important in fighting off infections.

Key words: COVID-19, severity, 25OH-Vitamin D, CR-Protein, inflammatory response

Introduction:

The SARS-CoV-2 virus causes the coronavirus (COVID-19) globally, highly contagious respiratory complications. The virus was found in Wuhan, China, in December 2019 and has since spread rapidly over the world, resulting in a global pandemic[1]. Importantly, lots of signs and symptoms are reported in patients with COVID-19 including; Fever, cough, sore throat, shortness of breath, exhaustion, muscle aches, and loss of taste and/or smell. Acute respiratory distress syndrome (ARDS), sepsis, and organ failure may occur in severe cases[2]. Some patients with severe COVID-19 may also develop complications such as blood clots, heart damage, and neurological symptoms[3]. In 2020, the first observed SARS-CoV-2 reinfection case were reported in Iraq, with 4.5 months between two episodes, with mild symptoms reported with that case[4,5]. The SARS-CoV-2 virus that causes COVID-19 has undergone numerous mutations since its emergence in late 2019, resulting in the emergence of different genetic lineages, or clades. These clades are defined based on specific sets of mutations in the virus's genome, and they can help researchers track the spread and evolution of the virus[6,7].

Additionally, some researchers outlined that many factors affecting the severity and progression of infection with COVID-19 rather than the mutations and the subsequent reinfection, systemic co-morbidity and mortality[8] may one of the factors increase the severity of COVID-19 cases. Moreover, lots of studies observed a number of factors influencing the severity; hence, smoking was one of the factors that reported. Smoking damages the respiratory system, making it more difficult for the body to fight respiratory infections. COVID-19 primarily affects the respiratory system, and smokers may be at a higher risk of developing severe symptoms, such as pneumonia, acute respiratory distress syndrome (ARDS), and even death, if they contract the virus[9], despite this, study they outlined that smoking is not significantly correlated with severe covid19[10].

Extensive clinical trials have proven that the mRNA vaccinations (single and/or booster doses) are both safe and efficient in building the strong immunity and preventing COVID-19. They can have adverse effects like any other vaccination, although the vast majority of them are moderate and transient, such as discomfort at the injection site, exhaustion, and fever, while in some cases the severity may progress depending on age and personal health[11,12].

Vitamin D is also thought to help regulate the body's response to viral infections by modulating the production of cytokines, which are proteins that help the immune system fight off infections. A number of studies have revealed that those with low vitamin D levels are more likely to suffer post-infection and respiratory problems, such as COVID-19 and may progress their signs and symptoms within COVID-19 infection. Additionally, they are outlined previously and they found that there have found a link between low vitamin-D ranges and increased COVID-19 severity and mortality[13]. However, it is important to note that observational studies cannot prove causality, and other factors may be at play such as comorbidity, age and psychological issues. While there is some preliminary evidence to suggest that vitamin D may be beneficial in reducing the severity of COVID-19, more research is needed to fully understand this relationship. It is important to speak with a healthcare provider before starting any vitamin D supplementation, as excessive intake can have harmful effects. Importantly, CRPs are mainly made in the liver in response to inflammation in order to reduce tissue damage brought on by autoimmune diseases, infections, and other conditions. Epidemiological studies also support a possible inverse relationship between CRP and vitamin D, which is suggested by the inflammatory cells' capacity to convert vitamin D metabolites into calcitriol (the active form of vitamin D) and to express the nuclear receptor for vitamin D. It is often used as a marker of inflammation and infection, as well as a predictor of the risk of developing cardiac disease and complications[14,15].

CRP levels can be measured through a blood test, and elevated levels of CRP may indicate the presence of an underlying inflammatory or infectious condition. Conditions that can lead to increased CRP levels include infections, autoimmune diseases, cancer, and chronic inflammatory conditions such as arthritis[16]. Other studies have demonstrated the role of vitamin D in building the immune system with supportive modulation. Vitamin D may reduce cytokine production by simultaneously strengthening the innate immune system and decreasing over activation of the adaptive immune system in response to viral load[14,17]. Several studies have suggested that vitamin-D supplementation may reduce CRP levels in individuals with COVID-19, although more research is needed to confirm these findings. Some studies have also suggested that patients with taking supplementation of vitamin D may improve outcomes in COVID-19 patients, although more research is needed to determine the optimal dosing and timing of vitamin D supplementation[17]. Hence, By considering the higher prevalence of COVID-19, the aim of this study was to correlate patients infected with SARS-CoV-2, serum 25OH-Vitamin D (25OHD) level with biological analysis especially CR-Protein level to monitor the level of infection and the role of Vid D.

Materials and Method

Study Design and patients

Total 59 newly diagnosed COVID-19 patients, who ranged in age from (38.35±6.15) years old and 25 controls group (37.85 ± 7.28), were recruited in the current study. Molecular investigation for SARS-Cov-2 confirmation is carried out for all cases by RT-PCR for the first time between January 2022 and June 2022. The patients' clinical data, including age, gender, were reported for all cases.

Sampling procedure

This procedure was done in biosafety laboratory level 2, for screening of SARS-CoV-2. The procedure was in a semi-automated manner based on magnetic bead extraction by using a Nucleic Acid Isolation System that can extract 96 samples at a time. Specific polymeric groups of adsorbed nucleic acids (DNA/RNA) are found on the surface of the magnetic beads included in the kit.

Molecular profile (RT-PCR):

Molecular analysis was carried out for the investigation and confirmation of COVID-19 cases. SARSCoV2 was identified using real-time RT-PCR on viral RNA isolated from nasopharyngeal swab samples. Using the Qiagen EZ1 Advanced XL technique, total RNA was extracted automatically 45 minutes after collection. (Qiagen). The presence of SARSCoV2 was then determined by amplification of portions of the SARSCoV2 open-reading frame 1ab (ORF1ab) and envelope-(E) genes using the Power-Chek RT-PCR kit for SARSCoV2 (Kogene-Biotech). The amplification parameters on a Rotor Gene Q thermocycler were 50°C for 30 minutes, 95°C for 10 minutes, 40 cycles of 95°C for 15 seconds, and lastly 60°C for 1 minute (Qiagen - Germany). When specific real-time RT-PCR revealed that the two target genes (ORF1ab and E) were positive, a cycle threshold value (PCR Ct value) of 36.5 was regarded positive, while a Ct value more than 36.5 was considered negative. In RT-PCR testing, the PCR Ct-value is a semi quantitative measurement used to quantify the materials of viral genetic concentration in patient nasopharyngeal samples..

Ethics Statement and Consent to Participate

The protocol was approved by the Ethics Licensing Committee of Sulaimani Polytechnic University, Kalar Technical College (No. KTC09 on February 5, 2023) and followed the Helsinki Declaration. All participants provided written informed consent and permission for publication, and the study adhered to the ARRIVE 2.0 principles. Permission to publish was obtained by signing the approved agreement of all study participants. All techniques were consistent with the Helsinki Declaration of 1964. Questionnaire for all participants were filled for those section that are required.

Biochemical Assay

The Cobas c111 analyzer was used for CRP investigation in this study. It uses a combination of photometric and electrochemical methods to measure a variety of analyses, such as glucose, cholesterol, electrolytes, liver and kidney function markers, and proteins. The analyzer is capable of processing up to 93 patient samples per hour and requires minimal operator intervention.

Additionally, Cobas e411 analyzer, recruited in the analysis of Vitamin D level for both COVID-19 cases and control group. Cobas e411 is a widely used immunoassay analyzer used to perform diagnostic tests on patient samples such as blood, serum, and urine. The analyzer is manufactured by Roche Diagnostics and is used in hospitals, clinical laboratories, and other healthcare settings around the world. The Cobas e411 analyzer uses an electrochemiluminescence (ECL) detection technology to measure a wide range of analytes, including hormones, tumor markers, infectious diseases, cardiac biomarkers, and allergy tests.

Results:

In this study, a total of 59 patients and 25 normal cases (for control) with no significant differences between these two groups in gender were enrolled for investigation the role of Vitamin D in the disease severity in patients infected with SARS-Cov-2. The result showed a significant decrease of vitamin D in abnormal group compared with normal group (15.74±5.63 vs 33.41±12.18 ng/dl, p = 0.0001), as in Table 1. Additionally, the patients in infected group (6.7±12.64) had significantly ($p<0.0001$) lower CRP level in comparison with control group (1.77±3.12). There are no significant differences reported (0.612) in ages between the infected COVID-19 group 38.35±6.15 and control group (37.85 ± 7.28). Furthermore, The RT-PCR had no significantly reported differences between COVID-19 cases and control group (29.98±5.25) *vs* (39.89 ± 5.01). Table 1

Table 1. The demographic and serum biochemical parameters between cases and controls

Parameters	Patients N=59	Control N=25	*P*-Value
Age	**38.35±6.15**	**37.85 ± 7.28**	**0.612**
PCR-Ctv	**29.98±5.25**	**30.89 ± 5.01**	**0.0432**
Vitamin D (Ng/Ml)	**15.74±10.41**	**33.41±10.18**	**<0.0001**
CR-Protein (Mg/Dl)	**6.17±12.64**	**1.77±3.12**	**<0.0001**

*Chi-square P ≤ 0.05, Data presented as number (n) and percentage (%).

As showed in Figure 1, Significant differences were reported between group1 COVID-19 cases (G1: 59 confirmed with SARS-Cov-2 via RT-PCR analysis) and control group (G2: 25 control negative cases with no ct values > 40) in both biochemical investigations; Vitamin D and CR-Protein level. Hence, in G1, Vitamin D levels are reported with low concentrations while CR-Protein ranges are showed high levels among patients infected with COVID-19. However, in G2 both levels of Vitamin D concentrations and CR-Protein ranges are reported normal with > 20 ng/ml and < 5.0 mg/dl respectively.

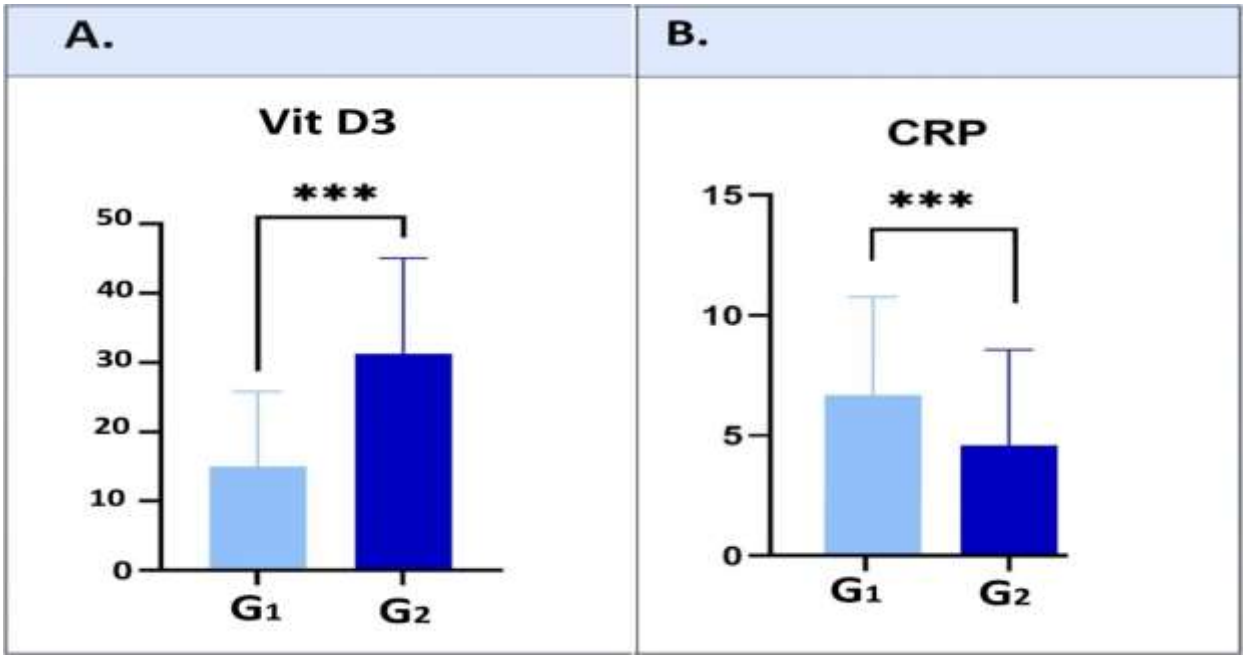

Fig. 1 Association between serum 25(OH)D and serum CR-Protein level in patients infected with COVID-19 and control group. A. Vitamin D level in G1: group 1, COVID-19 cases and G2: group 2, control group

Discussion

Despite worldwide and international efforts to give treatment and medicines using newly developed vaccines, the annual number of patients infected with novel variants has remained high, owing in part to the ongoing emergence of SARSCoV-2 variants[18]. Studies have shown that most people who have had COVID-19 develop an immune response that provides some level of protection against the virus for at least several months. However, this protection may not be strong enough to prevent reinfection in all cases. The risk of reinfection may also depend on factors such as the severity of the initial infection, the length of time since the initial infection, and the presence of new or more infectious variants of the virus[19]. According to the Endocrine Society's that dealing with endocrine system with the supportive agents in this area[20] suggested cut point of 30 ng/mL for 25(OH)D, The current study separated all patients into two

groups to examine the association between vitamin D sufficiency and illness severity and physiologic decompensation of a patient, particularly by monitoring CRP levels[21].

In fact, the anti-inflammatory properties of 1,25(OH)2D may explain vitamin D's protective effects against immunological hyper-reaction and cytokine storm in a subgroup of COVID-19 patients. This is also in line with a new in this aspect finding that the severity of COVID-19 was correlated with C-reactive protein (CRP), a proxy for vitamin D level. Hence, currently we found that COVID-19 patients with higher vitamin D levels had lower CRP levels and better clinical outcomes compared to those with lower vitamin D levels, this approach is in line with other studies reported regarding both clinical biomarkers[22]. However, it should be noted that these trials do not establish causation, and additional study is required to determine whether vitamin-D supplementation is beneficial can actually reduce serum CRP levels and improve outcomes in COVID-19 patients. Additionally, there are many other factors that can affect CRP levels, including age, obesity, and underlying health conditions, so it's important to consider these factors as well when interpreting the results of these studies[5].

CRP is an inflammatory marker in the body, and higher levels of CRP have been connected to poorer results in COVID-19 cases. Inadequate vitamin D levels have also been related to increased inflammation in the body. Several studies have discovered a link between vitamin D insufficiency and high CRP levels in COVID-19 patients. One study discovered that COVID-19 patients with low vitamin D levels had higher CRP levels and were more likely to require mechanical breathing than those with adequate vitamin D levels[23]. It is possible that the correlation between both laboratory analysis; vitamin D deficiency, CRP levels, and COVID-19 outcomes may be due to other factors that are associated with vitamin D deficiency, such as poor diet or underlying health conditions[5].

Importantly, Serum CRP levels in COVID-19 patients can rise quickly and stay high for several weeks. CRP elevation has been linked to more severe disease, such as the development of acute respiratory distress syndrome (ARDS) and the requirement for mechanical ventilation, and an increased risk of death. Monitoring CRP levels can be a useful tool in assessing the severity and progression of COVID-19, as well as in determining the effectiveness of treatment. CRP levels may also be used to help guide the use of anti-inflammatory treatments, such as steroids or monoclonal antibodies. They concluded that vitamin D insufficiency was associated with greater CRP levels and an increased probability of severe COVID-19 in that a bad immune system may affect the severity and increase the inflammatory parameters[22,24].

Their discovery is consistent with what we discovered. Our findings revealed that patients with greater serum 25(OH)-D levels had lower CRP levels than individuals with serum 25(OH)D values of 30 ng/mL (Table 1: Figure 1). Additionally, patients with adequate vitamin D levels had less severe COVID-19 infections than patients with lower amounts of 25(OH) D. The anti-inflammatory effects of vitamin D on decreasing inflammatory markers like CRP found in our study can help explain this finding[25]. The COVID-19 patients' cytokine storm may be prevented by vitamin D's anti-inflammatory properties, which could also account for the patients' lower fatality and severity rates. A recent research revealed that CRP levels were positively correlated with lung lesions in the early stages of COVID-19, which may have indicated the severity of the illness[26].

In conclusion,

the current study investigated the relationship between low vitamin-D levels in COVID-19 cases and blood CRP in general. Because CRP is a proxy for cytokine storm and is connected to vitamin D deficiency, we suggest that vitamin D may play a role in lowering difficulties associated with uncontrolled inflammation and cytokine storm based on retrospective data and indirect evidence. To control for other causes, an in-depth inquiry is required to directly evaluate vitamin D levels in COVID-19 patients. Overall, while there is some evidence to suggest a potential link between vitamin D levels and CRP levels in COVID-19, more research is needed to fully understand this relationship and to determine the most effective strategies for preventing and treating COVID-19. Hence, maintaining adequate vitamin D levels is critical for overall health and well-being. Individuals should eat a healthy diet to guarantee optimal vitamin D consumption. While sun exposure can provide vitamin D, many people do not get enough vitamin D from this source alone, especially during the winter months or in areas with minimal sunlight. As a result, it is recommended that people get enough vitamin D by eating a balanced diet rich in egg yolks, fatty fish, and fortified foods like milk and cereal.

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