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Association between vitamin D and C-reactive protein level in post-COVID recovery period

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ABSTRACT

Background: Severe acute respiratory distress syndrome coronavirus 2 pandemic shows a spectrum of symptoms and complications which are variably dependent on individual's immune status. Vitamin D deficiency, often preexisting, causes poor prognosis in the post-COVID recovery phase of the survivors characterized by increased C-reactive protein (CRP) and decreased D-dimer levels. **Aims and Objectives:** The aims of this study were to find any correlation exists between vitamin D level and inflammatory marker CRP and D-dimer in post-COVID period. **Materials and Methods:** Seventy post-COVID recovery patients from the follow-up medicine outpatient department of College of Medicine and Sagore Dutta Hospital were tested for vitamin D, D-dimer, and serum CRP levels. **Results:** CRP levels of patients with lower vitamin D level (<20 ng/ml) were significantly higher (P<0.001) than the patients with higher vitamin D level. The D-dimer levels of vitamin D deficient group found to be significantly higher than the other group. There is statistically significant negative correlation found between CRP and vitamin D level and significant positive correlation has been found between D-dimer and vitamin D (P<0.001). **Conclusion:** Vitamin D may have an important role in recovery stage of COVID patients.

Key words: Vitamin D; COVID; D-dimer; C-reactive protein

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INTRODUCTION

The challenge of COVID-19 pandemic is not over. It is one of the most extensive pandemic in world history caused by novel coronavirus, known as severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2).[1,2] Since February 2020, it is spreading all over India very rapidly as well as in other countries. Along with treating the disease, many vitamins such as vitamin D, vitamin C, and other supplements are under experiment tools to boost the immune system to fight against this viral pandemic.

Vitamin D deficiency effects almost 40–99% of Indian population of different age, sex, and socioeconomic conditions[3] which reflect the magnitude of the problem. This highly prevalent nutritional deficiency is having a wide range of consequence as vitamin D is having its effect from immune system to cardiovascular system and many more. Many authors suggest a role of vitamin D deficiency in SARS-CoV-2 infection severity.[4] Many studies show that vitamin D receptor (VDR) receptor is present in activated T- and B-cell, monocytes, macrophage, and natural killer cells, thus modulates the action of immune cells and having its role in phagocytosis also.[5-7]

There is a high prevalence and increased fatality in some conditions which are also more prone for vitamin D deficiency, for example, old age, diabetes, hypertension, cancer, and cardiovascular disease.[8-10]

It is evidenced now that SARS-CoV-2 induces a cytokine storm which causes the thrombotic complications by

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triggering the coagulation cascade and severity of these can be measured by D-dimer level.[11] The circulating D-dimer concentration is used to diagnose thrombotic state which is formed during fibrinolysis of blood clots.[12] Increased C-reactive protein (CRP) is found in 86% of severe COVID-19 patients.[13] CRP and D-dimer are, now, considered as diagnostic as well as prognostic marker for SARSCoV-2.

Along with the large number of new infections every day, a large number of patients are in post-COVID recovery stage and showing a spectrum of complications.

Aims and objectives

Hence,we design our study to find out if the vitamin D status in patients is having any significance in post-COVID recovery.

MATERIALS AND METHODS

It is a cross-sectional hospital-based and analytical study conducted at College of Medicine and Sagore Dutta Hospital (CMSDH) Kamarhati, Kolkata-58, West Bengal in the period between April 2021 and September 2021, involving Department of Medicine, Pathology, and Biochemistry.

Study was approved by the Institutional Ethics Committee on 03/4/2021 (memo no- CMSDH/IEC/235/03-2021).

Inclusion criteria

Seventy recovered (6 weeks after reverse transcription-polymerase chain reaction [RT-PCR] positive and without active symptoms) COVID-19 (diagnosed by RT-PCR) patients aged between 18 and 60 years, attending the medicine outpatient department for follow-up at CMSDH, considered as subject.

Exclusion criteria

We have excluded patients or controls with malabsorption disorders, malignancy, liver cirrhosis, serum creatinine levels >1.9 mg/dl, or previous treatment with anticonvulsants.

Sample collection and handling: After taking valid written consent, 5 ml overnight fasting blood sample was collected. Serum was separated and collected after centrifugation. Blood samples was analyzed for CRP, by following the manufacturer's instruction with ERBA EM360/640 Autoanalyzer and serum vitamin D by cobas e 411. D-dimer was analyzed by coagulometer STA Satellite Max 605.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences version 17.0 and GraphPad software. Continuous variables were expressed as mean (standard deviation) and the differences were accomplished by comparison through unpaired two-sided t-test or correlation coefficient as applicable.

RESULTS

Out of the 70 patients, depending on serum vitamin D concentration, the patients are grouped in two broad groups. Those who are having vitamin D value <20 ng/ml are grouped as A(Group A)d they are 34 in number and the other group B contains 36 patients having vitamin D level equal or more than 20 ng/ml (Group B)

The unpaired student's t-test shows a statistically significant variation exists in the CRP and D-dimer values in the above-mentioned groups (Table 1).

Table 2 shows a statistically significant negative linear correlation between vitamin D and CRP values in Group A, whereas though D-dimer is high in Group A, but it is not correlated with the vitamin D. Group B shows very week corelation in between vitamin D with CRP and D-dimer.

Figure 1 shows the scattered plot of Vitamin D and CRP in group 1.

DISCUSSION

Even after severe and active symptoms resolved, persistent high CRP and D-dimer levels are observed in many cases which may be an indication of future complications.

In our study, we found that a low vitamin D level is

Table 1: Demographic and biochemical characteristics of the study

Parameter	Group A (n=34) Mean±SD	Group B (n=36) Mean±SD	P-value (unpaired t-test)
Vitamin D	11.35±2.75	27.84±4.85	<0.0001
CRP	51.06±25.96	3.75±1.47	<0.0001
D-dimer	3.01±1.99	0.38±0.19	<0.0001

CRP: C-reactive protein

Table 2: Pearson's correlation coefficient

Parameter	r	P
Group A		
Vitamin D and CRP	−0.75	<0.05
Vitamin D and D-dimer	0.2472	<171574
Group B		
Vitamin D and CRP	0.2434	<0.1715
Vitamin D and D-dimer	0.3591	<0.03

CRP: C-reactive protein

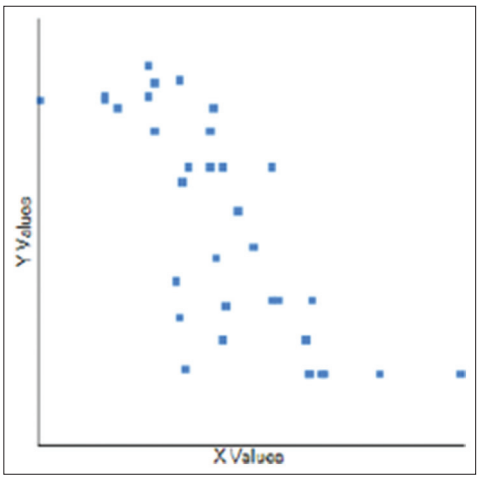

Figure 1: Scattered plot showing X-axis as vitamin D and Y-axis CRP in Group 1

associated with high CRP and high D-dimer values and CRP is negatively correlated with vitamin D level. Patients having normal vitamin D level are comparatively low CRP and D-dimer level than compared to above. The study done by Li et al., Saponaro et al., and Elibol et al., also shows similar finding.[15-17]

However, the study done by Grant et al., there is no significant change of vitamin D has been found in COVID infection.[17]

Most of the immune cells such as T- and B-cells, dendritic cells, and macrophages express the intracellular receptor for 1,25 (OH)2D. Cathelicidin (LL37) is induced by 1,25 (OH)2D through VDR receptor. These LL37 are having a protective role against enveloped bacteria like SARS-CoV-2 infection.[5] Vitamin D being a steroid hormone is involved in the modulation of the innate and acquired immune system and also takes part in the production of antimicrobial peptides. It also regulates the expression of genes involved in the intracellular destruction of pathogens. The lower level of serum 1,25 (OH)2D levels is frequently found to have poor prognostic factors for COVID-19 which can be expressed by increased CRP and D-dimer level.[18]

The CRP being a non-specific marker of any systemic infection and consistent with the severity or grade of the infection. Chen et al., shows that 86% of positive COVID patients show increased level of CRP and the level of it positively associated with the severity[14] which is similar to our finding.

The study done by Liu et al.,[12] shows increased level of D-dimer in COVID infection which is again proportional to the severity of infection. We also have the similar kind of finding. The study done by Barut et al., on Turkish population shows that higher levels of D-dimer and uric acid have been seen in vitamin D deficiency which shows poor prognosis in COVID-affected adolescent population.[14] The study of Malik MH, Michelino Di Rosa also finds similar findings.[20] Increased level of D-dimer can be explained by the SARS-COV-2-induced cytokine storm that triggers thrombotic complication which causes coagulation.[13]

Limitations of the study

Small study group and unknown base level of vitamin D before COVID infection and loss of long-term follow-up of cases are the limitations of the study.

CONCLUSION

Low vitamin D level may be associated with increased severity of COVID infection. Hence, early diagnosis of vitamin D status and supplementation with the same may improve the prognosis.

REFERENCES

1. Pinzon RT, Angela A and Pradana AW. Vitamin D deficiency among patients with COVID-19: Case series and recent literature review. Trop Med Health. 2020;48(1):102.
   https://doi.org/10.1186/s41182-020-00277-w
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-733.
   https://doi.org/10.1056/NEJMoa2001017
3. Sofi NY, Jain M, Kapil U, Seenu V, Ramakrishnan L, Yadav CP, et al. Status of serum Vitamin D and calcium levels in women of reproductive age in national capital territory of India. Indian J Endocrinol Metab. 2017;21(5):731-733.
   https://doi.org/10.4103/ijem.IJEM_134_17
4. Khafaie MA and Rahim F. Cross-country comparison of case fatality rates of COVID-19/SARS-COV-2. Osong Public Health Res Perspect. 2020;11(2):74-80.
   https://doi.org/10.24171/j.phrp.2020.11.2.03
5. Barlow PG, Svoboda P, Mackellar A, Nash AA, York IA, Pohl J, et al. Antiviral activity and increased host defense against influenza infection elicited by the human cathelicidin LL-37. PLoS One. 2011;6(10):e25333.
   https://doi.org/10.1371/journal.pone.0025333
6. Sigmundsdottir H, Pan J, Debes GF, Alt C, Habtezion A, Soler D, et al. DCs metabolize sunlight-induced Vitamin D3 to "program" T cell attraction to the epidermal chemokine CCL27. Nat Immunol. 2007;8(3):285-293.
   https://doi.org/10.1038/ni1433
7. Van Etten E and Mathieu C. Immunoregulation by 1,25-Dihydroxyvitamin D3: Basic concepts. J Steroid Biochem Mol Biol. 2005;97(1-2):93-101.
   https://doi.org/10.1016/j.jsbmb.2005.06.002
8. Joukar F, Naghipour M, Hassanipour S, Salari A, Alizadeh A, Saeidi-Saedi H, et al. Association of serum levels of Vitamin D with blood pressure status in Northern Iranian population: The PERSIAN Guilan cohort study (PGCS). Int J Gen Med. 2020;13:99-104.

https://doi.org.10.2147/IJGM.S244472

9. Mosekilde L. Vitamin D and the elderly. Clin Endocrinol (Oxf). 2005;62(3):265-281.
   https://doi.org/10.1111/j.1365-2265.2005.02226.x
10. Zhou F, Yu T, Du R, Fan G, Liu Y and Liu Z. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020;395(10229):1054-1062.
    https://doi.org/10.1016/S0140-6736(20)30566-3
11. Dariya B and Nagaraju GP. Understanding novel COVID-19: Its impact on organ failure and risk assessment for diabetic and cancer patients. Cytokine Growth Factor Rev. 2020;53:43-52.
    https://doi.org/10.1016/j.cytogfr.2020.05.001
12. Liu B, Li M, Zhou Z, Guan X and Xiang YJ. Can we use interleukin6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J Autoimmun. 2020;111:102452.
    https://doi.org/10.1016/j.jaut.2020.102452
13. Olson JD. D-dimer: An overview of hemostasis and fibrinolysis, assays, clinical applications. Adv Clin Chem. 2015;69:1-46.
    https://doi.org/10.1016/bs.acc.2014.12.001
14. Barut K,Sahin S,Adrovic A,Sinoplu AB,Uucel G,Pamuk Get al. Familial Mediterranean fever in childhood: a single-center experience.Rheumatol Int 2018;38(1):67-74.
15. Li Q, Dai Z, Cao Y and Wang L. Association of C-reactive protein and Vitamin D deficiency with cardiovascular disease: A nationwide cross-sectional study from national health and nutrition examination survey 2007 to 2008. Clin Cardiol. 2019;42(7):663-669.
    https://doi.org/10.1002/clc.23189
16. Saponaro F, Franzini M, Okoye C, Antognoli R, Campi B, Scalese M, et al. Is there a crucial link between Vitamin D status and inflammatory response in patients with COVID-19? Front Immunol. 2021;12:745713.
    https://doi.org/10.3389/fimmu.2021.745713
17. Elibol E and Baran H. The relation between serum D-dimer, ferritin and Vitamin D levels, and dysgeusia symptoms, in patients with coronavirus disease 2019. J Laryngol Otol. 2021;135(1):45-49.
    https://doi.org/10.1017/S0022215120002765
18. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, et al. Evidence that Vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients. 2020;12(4):988.
    https://doi.org/10.3390/nu12040988
19. Di Rosa M, Malaguarnera M, Nicoletti F and Malaguarnera L. Vitamin D3: A helpful immuno-modulator: Immunology. 2011;134(2):123-139.
    https://doi.org/10.1111/j.1365-2567.2011.03482.x
20. Atesa B, Sazaka S, Turkmenoglua Y, Irdemb A and Dursunc H. Relationship of serum Vitamin D, D-dimer and uric acid levels with attacks in children with familial Mediterranean fever. Egypt Rheumatol. 2022;44(4):301-305.
    https://doi.org/10.1016/j.ejr.2022.03.004

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SC- Concept, Selection of patients, Result interpretation**; SS-** Coordination,statistical analysis, intellectual resource collection; **SGS-** Coordination and preparation of primary manuscript; **SS-** Concept, coordination, preparation and revision of manuscript, statistical analysis and interpretation**; IC-** Concept and design of study.

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