RESEARCH ARTICLE

Does vitamin D level have an effect on COVID-19 positivity and COVID-19 related mortality? A retrospective study

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Abstract

Objective: To explore the possible relationship between vitamin D and coronavirus disease-2019 in an urban population known to have relatively low vitamin D levels.

Method: The retrospective study was conducted in Bursa, Turkey, and comprised data of 30 family health centers from March 1 to December 15, 2020, related to diagnosed inpatients of coronovairus disease-2019. The diagnosis was based on polymerase chain reaction test for severe acute respiratory syndrome coronavirus-2 infection. Vitamin D levels of these patients were obtained from previous records and compared with those without polymerase chain reaction positivity. Vitamin D levels of positive patients who survived were compared with those who died of coronavirus disease-2019. Data was analysed using SPSS 21.

Result: Of the 2,105 patients whose data was retrieved, 212(10%) were positive for coronavirus disease-2019, while 1,893(90%) were negative. Among the positive patients, 89(42%) were men and 123(58%) were women. The overall median age was 45 years (Q1-Q3(Q1: first quartile, Q3: third quartile): 35-56 years). Vitamin D level was not significantly different between the positive and negative patients ($p>0.05$). Among the positive patients, 2(0.9%) patients did not have new admissions to the designated centers and their data was excluded, 206(97.2%) survived and 4(1.9%) died. There was no significant difference in vitamin D levels between those who survived and those who died ($p>0.05$).

Conclusion: There was no significant relationship found between vitamin D levels and coronavirus disease-2019 infection and related deaths.

Keywords: COVID-19, PCR positivity, SARS-CoV-2 infection, Vitamin D. (JPMA 72: 1779; 2022)

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Introduction

Coronavirus disease-2019 (COVID-19) develops due to infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which uses angiotensin-converting enzyme 2 (ACE2) as a primary receptor for entry into human cells. ACE2 receptors are found in different organs and tissues, particularly the lungs.[1,2] Vitamin D is an important hormone that is synthesised in the body. It is essential for immune function and modulates host inflammatory responses to infection.[3,4] In some studies, vitamin D has been reported to have a possible positive effect in reducing the risk of respiratory tract infections (RTIs). Vitamin D may decrease the viral replication rate and proinflammatory cytokine concentrations by inducing cathelicidins and defensins. This decrease in levels of proinflammatory cytokines reduces inflammation, lung damage and pneumonia.[2-7]

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In a study investigating vitamin D levels in patients with COVID-19, levels of 25-hydroxy vitamin D (25[OH]D) were significantly lower in patients with SARS-CoV-2 infection than those without, and this difference was more pronounced in individuals aged >70 years. Moreover, advanced age and low 25(OH)D levels increase COVID-19-related mortality rates.[8]

In another study investigating calcium levels in patients with COVID-19, the levels of ionized calcium were lower in >80% of the hospitalised cases compared to those not hospitalised. Hypocalcaemia was associated with admission to the intensive care unit (ICU) and death. Additionally, it hinted that vitamin D deficiency may be related to the occurrence of hypocalcaemia.[9]

Vitamin D deficiency is common in countries worldwide.[10] Exposure to the sun has decreased because of the need to spend more time at home during the pandemic. This situation may worsen the issue of deficiency of vitamin D in the long term. Therefore, vitamin D supplementation may effectively prevent acute RTIs in patients with vitamin D deficiency and serum 25(OH)D level <20ng/mL.[11-13]

Although there is no definite and precise data about the effects of vitamin D levels and administration of vitamin D supplements on COVID-19,[2] vitamin D may play a

protective role in preventing and treating the disease.

As such, the current study was planned to explore the possible relationship between vitamin D and COVID-19 in an urban population known to have relatively low vitamin D levels.

Materials and Methods

The retrospective study was conducted in Bursa, Turkey, and comprised data of 30 family health centers from March 1 to December 15, 2020, related to diagnosed inpatients of COVID-19. After approval from the ethics review committee of Bursa Uludağ University, Bursa, the sample size was determined on the basis of our previous study[10] that had examined vitamin D levels in 17,812 cases. These examined cases were taken as a population, and the sample was raised by randomly including individuals in the light of the official COVID-19 incidence rate noted by the Ministry of Health with margin of error d=0.009 at alpha=0.05. The COVID-19 diagnosis was based on polymerase chain reaction (PCR) test for SARS-CoV-2 infection. The data was accessed after permission from the Turkish Ministry of Health.

Demographic information, vitamin D levels, and patients' comorbidities were noted. The vitamin D levels of these patients had been measured at the designated family health centers and recorded in their individual their files within the preceding two years. Vitamin D level of the positive patients were compared with those who were negatve. Also, vitamin D levels of positive patients who survived were compared with those who died of COVID-19. Data of PCR-positive patients who had not been inpateints at the study centers within the study period was excluded.

Data was analysed using SPSS 21. Normality of continuous variables was tested using the Shapiro-Wilk test. Vitamin D levels were found to be non-normally distributed. Descriptive statistics were presented as median Q1-Q3 (Q1: first quartile, Q3: third quartile) for continuous variables, and frequencies and percentages for categorical variables. Mann-Whitney U test was used for comparison between the groups. The level of statistical significance was set at $p<0.05$.

Results

Of the 2,105 patients whose data was retrieved, 212(10%) were positive for COVID-19, while 1,893(90%) were negative. Among the positive patients, 89(42%) were men and 123(58%) were women. The overall median age was 45 years (Q1-Q3: 35-56 years). Among the negative patients, 726(38.4%) were men and 1,167(61.6%) were women. The overall median age of 42 (Q1-Q3: 30-56 years). Covid-19-positive women were aged significantly higher than those who were negative ($p=0.007$). All other age comparisons were not significant ($p>0.05$). Among the negative patients, 174(9.19 %), and among the positive patients, 20(9.43%) were on vitamin D supplementation.

Table: Comparison of vitamin D levels in PCR-positive and PCR-negative SARS-CoV-2 cases.

			Yes (+)	No (-)	*p*-value
General	COVID-19	n	212	1893	0.380
		Median (Q1-Q3)	16.77 (11.42-24.60)	16.27 (10.02-23.96)	
Female	COVID-19	n	123	1167	0.102
		Median (Q1-Q3)	15.28 (10-23.57)	13.39 (8.83-22)	
Male	COVID-19	n	89	726	0.313
		Median (Q1-Q3)	18.13 (12-25.09)	19.56 (13.65-25.91)	

Data are given as median (Q1-Q3)(Q1: first quartile, Q3: third quartile); COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2.

Vitamin D level was not significantly different between the positive and negative patients ($p>0.05$) (Table).

Among the positive patients, 2(0.9%) did not have new admissions to the designated centers and their data was excluded, 206(97.2%) survived and 4(1.9%) died. There was no significant difference in vitamin D levels between those who survived and those who died ($p>0.05$).

Discussion

The study fund no significant difference between the vitamin D levels of patients who tested PCR-positive and negative for SARS-CoV-2 infection, as well as between those who survived COVID-19 and those died because of COVID-19. A statistically significant association between age and COVID-19 positivity was observed in females, but not in the male gender.

Clinical observations indicated that advanced age and male gender increased the risk of COVID-19.[4,14] Different from these observations, most patients in the current study were females, and, similar to these observations, COVID-19-positive females were older. The discrepancies in the current results might be due to the study's small smaple size.

Different studies indicated that vitamin D could positively affect acute RTIs by increasing the production of antimicrobial peptides in the respiratory epithelium and reducing inflammation related to the disease. Vitamin D may also have immune-supporting properties through modulation of the immune system, which could affect the severity of the response to COVID-19, and, therefore, vitamin D deficiency may be associated with COVID-19-related mortality. Vitamin D levels differ across the world, but even the more sunny countries in southern Europe

experienced seriously high incidence of COVID-19 and related mortalities.[15-17]

Vitamin D levels were found to be low in different studies conducted in Turkey, which is also located in the southern part of the northern hemisphere.[10] Therefore, it is crucial to investigate the relationship between COVID-19 and vitamin D levels.

There are conflicting results in literature about the vitamin D level status of COVID-19 patients, with some indicating lower vitamin D levels in patients with COVID-19, while other reporting otherwise.[18-22] The present study could not find a relationship between vitamin D levels and COVID-19.

The effectiveness of supplemental vitamin D in preventing RTIs has been reported in different studies.[6,12] Additionally, deficiency of vitamin D and the presence of some metabolic diseases can adversely affect the prognosis of COVID-19. It is evident that more comprehensive studies are needed to assess their effects on the impaired immunological system and prognosis in COVID-19.[23] A study suggested vitamin D as an immunomodulatory agent that confers protection against the severity of COVID-19 and that serum levels of 25(OH)D should be maintained within the range of 40-60ng/mL to minimise the risk and severity of COVID-19.[20] A study conducted in patients with COVID-19 reported a more frequent occurrence of pneumonia in patients without vitamin D supplementation 6 months before diagnosing COVID-19.[24] The present study could not find a relationship between vitamin D supplementation and the disease.

In the present study, the mean vitamin D levels were low in both PCR-positive and PCR-negative cases, and no significant difference was found between the groups. The current study has an important limitation as the vitamin D level had been tested much earlier than the diagnosis of COVID 19.

Considering the varying results reported by literature, large-scale, community-based studies are needed to investigate the impact of vitamin D on COVID-19 prevention, prognosis, and survival.

Conclusion

No significant relationship was found between low vitamin D levels and COVID-19 and related deaths.

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References

1. Astuti I, Ysrafil. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. Diabetes Metab Syndr 2020;14:407-12. doi: 10.1016/j.dsx.2020.04.020.
2. Ersoy CO. Covid-19 and Endocrine System Diseases. In: Heper C, eds. Multidisciplinary COVID-19: Bursa Medical Chamber Continuous Medical Education Pandemic Book. Bursa, Turkey: Bursa Medical Chamber Publications, 2020; pp 407-28.
3. Ma W, Nguyen LH, Yue Y, Ding M, Drew DA, Wang K, et al. Associations between predicted vitamin D status, vitamin D intake, and risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease 2019 (COVID-19) severity. Am J Clin Nutr 2022;115:1123-33. doi: 10.1093/ajcn/nqab389.
4. Manson JE, Bassuk SS. Commentary. Eliminating vitamin D deficiency during the COVID-19 pandemic: A call to action. Metabolism 2020;112:154322. doi: 10.1016/j.metabol.2020.154322.
5. Bilezikian JP, Bikle D, Hewison M, Lazaretti-Castro M, Formenti AM, Gupta A, et al. Mechanisms in endocrinology: Vitamin D and COVID-19. Eur J Endocrinol 2020;183:R133-47. doi: 10.1530/EJE-20-0665.
6. Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. J Infect Public Health 2020;13:1373-80. doi: 10.1016/j.jiph.2020.06.021.
7. Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord 2017;18:153-65. doi: 10.1007/s11154-017-9424-1.
8. D'Avolio A, Avataneo V, Manca A, Cusato J, De Nicolò A, Lucchini R, et al. 25-Hydroxyvitamin D Concentrations Are Lower in Patients with Positive PCR for SARS-CoV-2. Nutrients 2020;12:1359. doi: 10.3390/nu12051359.
9. Di Filippo L, Formenti AM, Rovere-Querini P, Carlucci M, Conte C, Ciceri F, et al. Hypocalcemia is highly prevalent and predicts hospitalization in patients with COVID-19. Endocrine 2020;68:475-8. doi: 10.1007/s12020-020-02383-5.
10. Göktaş O, Ersoy C, Ercan I, Can FE. Vitamin D status in the adult population of Bursa-Turkey. Eur J Gen Pract 2020;26:156-62. doi: 10.1080/13814788.2020.1846712.
11. McCartney DM, Byrne DG. Optimisation of Vitamin D Status for Enhanced Immuno-protection Against Covid-19. Ir Med J 2020;113:58.
12. 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;12:988. doi: 10.3390/nu12040988.
13. Carter SJ, Baranauskas MN, Fly AD. Considerations for Obesity, Vitamin D, and Physical Activity Amid the COVID-19 Pandemic. Obesity (Silver Spring) 2020;28:1176-7. doi: 10.1002/oby.22838.
14. Zhang Y, Wang M, Zhang X, Liu T, Libby P, Shi GP. COVID-19, the Pandemic of the Century and Its Impact on Cardiovascular Diseases.

Cardiol Discov 2021;1:233-58. doi: 10.1097/CD9.0000000000000038.

15. Laird E, Rhodes J, Kenny RA. Vitamin D and Inflammation: Potential Implications for Severity of Covid-19. Ir Med J 2020;113:81.
16. Mitchell F. Vitamin-D and COVID-19: do deficient risk a poorer outcome? Lancet Diabetes Endocrinol 2020;8:570. doi: 10.1016/S2213-8587(20)30183-2.
17. Greiller CL, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. Nutrients 2015;7:4240-70. doi: 10.3390/nu7064240.
18. Demir M, Demir F, Aygun H. Vitamin D deficiency is associated with COVID-19 positivity and severity of the disease. J Med Virol 2021;93:2992-9. doi: 10.1002/jmv.26832.
19. Orchard L, Baldry M, Nasim-Mohi M, Monck C, Saeed K, Grocott MPW, et al. Vitamin-D levels and intensive care unit outcomes of a cohort of critically ill COVID-19 patients. Clin Chem Lab Med 2021;59:1155-63. doi: 10.1515/cclm-2020-1567.
20. Charoenngam N, Shirvani A, Holick MF. Vitamin D and Its Potential Benefit for the COVID-19 Pandemic. Endocr Pract 2021;27:484-93. doi: 10.1016/j.eprac.2021.03.006.
21. Pinzon RT, Angela, Pradana AW. Vitamin D deficiency among patients with COVID-19: case series and recent literature review. Trop Med Health 2020;48:102. doi: 10.1186/s41182-020-00277-w.
22. Hastie CE, Mackay DF, Ho F, Celis-Morales CA, Katikireddi SV, Niedzwiedz CL, et al. Vitamin D concentrations and COVID-19 infection in UK Biobank. Diabetes Metab Syndr 2020;14:561-5. doi: 10.1016/j.dsx.2020.04.050.
23. Marazuela M, Giustina A, Puig-Domingo M. Endocrine and metabolic aspects of the COVID-19 pandemic. Rev Endocr Metab Disord 2020;21:495-507. doi: 10.1007/s11154-020-09569-2.
24. Ünsal YA, Gül ÖÖ, Cander S, Ersoy C, Aydemir E, Ateş C, et al. Retrospective analysis of vitamin D status on ınflammatory markers and course of the disease in patients with COVID-19 infection. J Endocrinol Invest 2021;44:2601-7. doi: 10.1007/s40618-021-01566-9.