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THE ROLE OF VITAMIN D SUPPLEMENTATION IN REDUCING COVID-19 SEVERITY IN CHILDREN: A NARRATIVE REVIEW

Summary

Introduction. Vitamin D3 supplementation has been shown to play an important role in the immune response and protection against COVID-19 infection in all populations [1] but the effects of Vitamin D3 supplementation in pediatric patients infected with COVID-19 is yet to be explored. In this narrative review we studied the effects of 25-hydroxycholecalciferol (25-OHD) in children infected with COVID-19.

Purpose of the study. This secondary research aims to execute a search in the literature to identify the data regarding vitamin D3 supplementation and the severity of COVID-19 infection in children aged 1-18. This will allow us to determine if there is any correlation with vitamin D3 supplementation at higher doses with a reduction in COVID-19 mortality, duration of infection, etc.

Materials and methods. A comprehensive review of the literature located within electronic databases was conducted to identify relevant studies. Databases used include PubMed and Google Scholar. Studies were selected which met the inclusion criteria. Data extraction and quality assessment was performed using standardized methods. The studies required subjects aged 1-18 infected with COVID-19 and serum vitamin D3 levels. Some studies compiled into our review also included the severity of symptoms. Only studies published in the English language were included.

The results. The literature revealed correlations between vitamin D3 levels in children aged 1-18 years infected with COVID-19 and the severity of infection. There was a linear relationship between lower vitamin D3 levels and the increased severity of COVID-19 infection in pediatric patients. These results suggest that vitamin D3 should be supplemented to potentially be able to decrease the severity of COVID-19 infection in a pediatric patient population or as a prophylaxis to COVID-19 infection. However, serum levels are to be detected in what is used for the amount of vitamin D3 to show how much is needed to reduce the severity of COVID-19.

Keywords: *vitamin D3, 25-hydroxycholecalciferol, COVID-19 infection, pediatric patients.*

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РОЛЬ ДОБАВОК ВІТАМІНУ D У ЗНИЖЕННІ ТЯЖКОСТІ COVID-19 У ДІТЕЙ: НАРАТИВНИЙ ОГЛЯД

Аннотація

Вступ. Було показано, що добавки вітаміну D3 відіграють важливу роль в імунній відповіді та захисті від інфекції COVID-19 у всіх групах населення, але вплив добавок вітаміну D3 на педіатричних пацієнтів, інфікованих COVID-19, ще належить вивчити. У цьому нарративному огляді ми вивчали вплив 25-гідроксихолекальциферолу (25-OHD) на дітей, інфікованих COVID-19.

Мета. Це вторинне дослідження має на меті здійснити пошук у літературі для виявлення даних щодо прийому вітаміну D3 та тяжкості інфекції COVID-19 у дітей віком від 1 до 18 років. Це дозволить нам визначити, чи є якась кореляція з добавками вітаміну D3 у більш високих дозах зі зниженням смертності від COVID-19, тривалості інфекції тощо.

Матеріали та методи. Було проведено комплексний огляд літератури, розміщеної в електронних базах даних, щоб визначити відповідні дослідження. Використовувані бази даних включають PubMed і Google Scholar. Були відібрані дослідження, які відповідали критеріям включення. Вилучення даних та оцінка якості проводилися за допомогою стандартизованих методів. Для проведення досліджень були потрібні пацієнти віком від 1 до 18 років, інфіковані COVID-19 та їх рівні вітаміну D3 в сироватці крові. Деякі дослідження, зібрані в нашому огляді, також включали тяжкість симптомів. Були включені лише дослідження, опубліковані англійською мовою.

Отримані результати. У літературі виявлено кореляції між рівнем вітаміну D3 у дітей віком 1–18 років, інфікованих COVID-19 та тяжкістю інфекції. Існувала лінійна залежність між нижчим рівнем вітаміну D3 та підвищенням тяжкості інфекції COVID-19 у педіатричних пацієнтів. Ці результати свідчать про те, що вітамін D3 слід призначати, щоб потенційно мати можливість зменшити тяжкість інфекції COVID-19 у педіатричній популяції пацієнтів або як профілактика інфекції COVID-19. Однак, рівень вітаміну D3 у сироватці крові має бути визначений, щоб показати, скільки його потрібно для зменшення тяжкості COVID-19.

Висновки. У хворих із поєднаним перебігом ІХС та ожиріння знайдено високі рівні індексу HOMA, що свідчить про інсулінорезистентність. Визначення показників вуглеводного обміну (глюкози, інсуліну, індексу Нома) доцільно для своєчасної діагностики інсулінорезистентності та призначення лікування за коморбідності метаболічних порушень.

Ключові слова: *вітамін D3, 25-гідроксихолекальциферол, інфекція COVID-19, педіатричні пацієнти.*

Introduction. In recent years, the interest in the extraskeletal effects of vitamin D, especially its immunomodulatory effects, has increased. Moreover, this interest has increased during the pandemic as the association of Vitamin D and infections has previously been reported [1]. The studies of a new coronavirus infection SARS-CoV-2 (COVID-19) have reported a high incidence of cases of COVID-19 for elderly patients and those with serious health conditions such as diabetes mellitus and cardiovascular diseases, many countries' data showed that COVID-19 infection in children might be less severe than in adults. Vitamin D3 supplementation (25-hydroxyvitamin D3) has been shown to reduce a wide variety of components in the innate and adaptive immune response. Studies have shown that Vitamin D3 supplementation reduces severity in several diseases including COVID-19 [2].

As published recently, the molecular mechanism of action of vitamin D could be to lower oxidative stress and prevent the fusion of viral SARS-CoV-2 protein with the host cell receptor. Regulation of oxidative stress has a direct impact on COVID-19 infection. Vitamin D elaborated on its role in maintaining cellular redox status by regulating the expression of antioxidant enzymes like Glutathione peroxidase. When vitamin D status is adequate, many of the intracellular oxidative stress-related activities are down-regulated [3].

The mechanism of viral SARS-CoV-2 infection includes the merge of S-protein of SARS-CoV-2 with the angiotensin-converting enzyme 2 (ACE2) receptors, transmembrane serine protease 2 cleaves ACE2 and allows the virus particles to enter the host cell, replicate, and have cell-to-cell transmission. In vitro studies demonstrated a direct correlation between the expression of ACE2 and increase in the infection of the lungs and other tissues by SARS-CoV-2. Additionally, as viral glycoproteins bind with the ACE2 receptor, this interaction reduces the ability of ACE2 to convert Angiotensin II (Ang II) to Angiotensin 1–7. This leads to lung injury and pneumonia because of the accumulation of Ang II, a hormone that can increase the presence of reactive Oxygen species in the body, which in turn also increases oxidative stress in the body [4]. The interplay between ACE2 and Vitamin D has been reported [5].

Vitamin D is a key nutrient for both healthy children and those with chronic illnesses. Understanding its roles in health and disease has become one of the most important issues in the nutritional management of children. Half of all children admitted to intensive care units are vitamin D deficient (< 20 ng/ml); more studies are needed to assess the benefit of vitamin D supplementation [6].

As reported, the school-aged children (6–12 years) and adolescents (12–18 years) are at risk of Vitamin D deficiency and insufficiency in both the pre-pandemic and pandemic periods in Turkey. Moreover, pandemic-related restrictions have caused significant decreases in Vitamin D levels in these age groups. Thus, the study suggests that children and adolescents should be given Vitamin D supplementation in order to maintain sufficient levels of Vitamin D [7].

Purpose of the study. This secondary research

aims to execute a search in the literature to identify the data regarding vitamin D3 supplementation and the severity of COVID-19 infection in children aged 1-18. This will allow us to determine if there is any correlation with vitamin D3 supplementation at higher doses with a reduction in COVID-19 mortality, duration of infection, etc.

Materials and methods. Scientific literature related to the subject was explored across databases such as PubMed and Google Scholar. The search was limited to studies published in English. The search criteria included the disease COVID-19 and keywords such as Vitamin D, children, and severity. Furthermore, a system of manual examination of the studies' data regarding Vitamin D3 levels and COVID-19 infection severity and/or symptoms was carried out to compile the data. The studies' sample sizes were also examined to include studies which had a decent study power.

Selection and inclusion/exclusion criteria: Only the studies that meet the following inclusion criteria were included in this review: (i) Children aged 1–18 years, (ii) Children diagnosed with COVID-19, (iii) The serum Vitamin D3 levels during ongoing COVID-19 infection, (iv) studies published in the English language. Studies were excluded if they (1) involved a sample size that was too small to have broader relevance, or (2) involved subjects older than 18 years, or (3) did not specifically concern serum Vitamin D3 levels with COVID-19 infections. The articles went through assessment by all authors and the correlating data pertaining to Vitamin D3, sample size, and severity and/or duration of COVID-19 infection was extracted.

We created a tool called the PRISMA Flow Diagram (Figure) that is used to record different stages of the literature search. These steps are broken down specifically from Identification to Analysis filtering out information that is not needed.

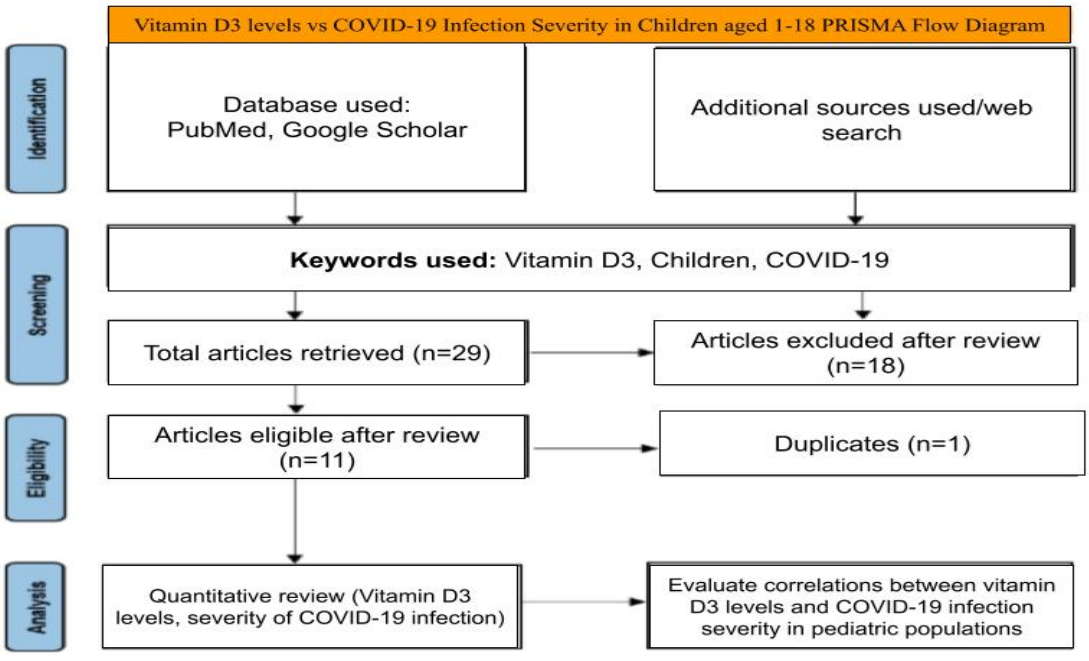

Figure. PRISMA Flow chart of the literature search.

Results and discussion. A manual literature search compiled 29 total studies. After a review process, 10 unique studies were included in our narrative review and 18 did not meet the inclusion criteria and 1 included study was a duplicate which was ultimately excluded. Included studies consisted of cross-sectional, evaluation, retrospective cohort, and retrospective case-series. All studies included in our narrative review explored serum Vitamin D3 levels in COVID-19 infected pediatric patients.

Serum concentration of 25(OH)D is currently the main indicator of Vitamin D status. It reflects Vitamin D produced endogenously and that obtained from foods and supplements [1]. In serum, 25(OH)D has a fairly long circulating half-life of 15 days [1]. Serum concentrations of 25(OH)D are reported in both nanomoles per liter (nmol/L) and nanograms per milliliter (ng/mL). One nmol/L is equal to 0.4 ng/mL, and 1 ng/mL is equal to 2.5 nmol/L [8].

In contrast to 25(OH)D, circulating 1,25(OH)2D is generally not a good indicator of Vitamin D status because it has a short half-life measured in hours, and serum levels are tightly regulated by parathyroid hormone, calcium, and phosphate [1]. Levels of 1,25(OH)2D do not typically decrease until vitamin D deficiency is severe [4].

According to the National Institute of Health [9], children of all ages are recommended to take prophylactic doses of Vitamin D, which are prescribed without determining its level in the blood.

If the child needs to be prescribed therapeutic doses of Vitamin D, then the doctor prescribes this test in order to choose the right dose of the drug.

Blood levels of Vitamin D (25(OH)D): absolute toxic level: > 200ng/mL; possible toxicity level: > 100ng/mL; norm: 30–100 ng/mL; insufficiency: 21–29 ng/mL; deficiency: less than 20 ng/mL [10].

The studies cited in this narrative review revealed a relationship between serum Vitamin D3 levels of pediatric patients and the severity of COVID-19 infection. It also revealed that pediatric patients who were infected with COVID-19 were more likely to be Vitamin D3 deficient or insufficient. This suggests that pediatric patients who are Vitamin D3 deficient or insufficient are likely more susceptible to COVID-19 infections. This also suggests to us that vitamin D3 supplementation for the pediatric population can be used as a prophylaxis to prevent severe COVID-19 infection. This retrospective study found more children infected with COVID-19 had Vitamin D deficiency or insufficiency than sufficiency. Key findings from each study were summarized and tabulated (Table).

Table. Summary of Studies

Study Citation/ Country	Study design	Sample size	Study period	Vitamin D3 serum levels	Results
Karimian P. et al., 2022 / Iran [11]	Cross-sectional analytical study	99	September 2020 to October 2021	Levels (ng/ml): Severity Score ≤ 4; 5–7; > 7 > 10: 0% 25% 5% 10–20: 0% 33% 66.7% 21–30: 3.8% 61.5% 34.6% > 30: 35.3% 58.8% 5.9%	Vitamin D can be effective in reducing COVID-19 severity.

Continuation of the table

Karakaya, M. G. et al., 2021 / Turkey [12]	Evaluation study	49	15 May 2020 to 15 June 2020	Vitamin D deficiency (< 20ng/ml): 54% of patients Vitamin D severe deficiency (< 10ng/ml): 28% of patients	Vitamin D deficiency was the most common vitamin deficiency present in a significant percentage of pediatric patients infected with COVID-19
Bayramoğlu et al., 2021 / Turkey [13]	Retrospective cohort	103	March 2020 to May 2020	COVID-19 Severity Asymptomatic (n = 29) Vitamin D: Deficiency: 5 Insufficient: 17 Normal: 7 Mild (n = 40) Vitamin D: Deficiency: 14 Insufficient: 17 Normal: 9 Moderate-to-Severe (n = 34) Vitamin D: Deficiency: 24 Insufficient: 7 Normal: 3	This study revealed an association between Vitamin D deficiency and clinical severity of COVID-19 in infected children.
Elif, S. et al., 2021 / Turkey [14]	Retrospective descriptive study	112	March 2020 to April 2020	COVID-19 positive group (n = 30): Median Vitamin D: 8.9 ng/ml Control group (n = 82): Median Vitamin D:18.5 ng/ml	In this study 28 out of the 30 children infected with COVID-19 had Vitamin D replacement due to deficiency or insufficiency
Aysegul A. et al., 2021 / Turkey [15]	Retrospective cohort	155	25 May 2020 to 24 December 2020	COVID-19 patients (n = 75) Vitamin D: Deficiency: 33 Insufficient: 30 Normal: 12 Control group (n = 80) Vitamin D: Deficiency: 14 Insufficient: 39 Normal: 27	Vitamin D can be beneficial in reducing the severity of COVID-19 infection.

Continuation of the table

Heidari S. et al., 2022 / Iran [16]	Retrospective cohort	144	April to September 2021	COVID-19 Severity Mild (n = 43) Vitamin D (ng/ml): 29 ± 12 Moderate (n = 49) Vitamin D (ng/ml): 26 ± 14 Severe (n = 52) Vitamin D (ng/ml): 17 ± 9	The study indicated an association between Vitamin D levels and COVID-19 severity.
Nadiger M. I. et al., 2021 / USA [17]	Retrospective case series	14	Mean hospital stay was 10.8 days with a range of 3-27 days.	Premorbid conditions were present in 9 of patients; and 7 of those were Vitamin D deficient patients. Pulmonary failure was present in 7 of them and 6 of them were Vitamin D deficient.	Majority of pediatric patients infected with COVID-19 needing ICU admission were vitamin D deficient. It is important to screen and supplement vitamin D to those with low levels.
Yılmaz K., & Şen, V., 2020 / Turkey [18]	Retrospective case series	85	Not available	COVID-19 infected group (n = 40) Vitamin D were 13.14 Healthy control group (n = 45) Vitamin D were 34.81	There were statistically significantly lower levels of Vitamin D ($p < 0.001$) in children with COVID-19 than those in the control group.
Abdelrazic M. I. et al., 2023 / Egypt [19]	Cross sectional	56	July 2021 to December 2021	COVID-19 Severity Moderate (n = 24) Vitamin D (ng/ml): Median: 55 Normal: n = 21 Insufficiency: n = 1 Deficiency: n = 2 Severe (n = 32) Vitamin D (ng/ml) Median: 17 Normal: n = 13 Insufficiency: n = 9 Deficiency: n = 10	Low serum vitamin D levels at the time of COVID-19 infection was associated with severe clinical course and higher mortality rate in children.
Ozden A. et al., 2022 / Turkey [20]	Retrospective cohort	74	March 2020 to September 2020	Children infected with COVID-19 (n = 74) Serum vitamin D levels: Sufficient: 20 (27.1%) Insufficient: 32 (43.2%) Deficient: 22 (29.7%)	This retrospective study found more children infected with COVID-19 had Vitamin D deficiency or insufficiency than sufficiency.

The findings of this narrative review support Vitamin D3 supplementation in the pediatric population to prevent the susceptibility and severity of COVID-19 infections. The results of the studies compiled in our narrative review demonstrate children aged 1–18 years who had an ongoing COVID-19 infection were likely to be Vitamin D3 deficient or insufficient. The posted results of some studies also showed a correlation between lower serum Vitamin D3 levels and more severe COVID-19 infection in children aged 1–18 years [21–25]. The relevance of this narrative is high as we still continue to encounter COVID-19 infected patients, years after the pandemic. This narrative review is also applicable as we make the transition to clinical practice and will certainly encounter COVID-19 infected patients who might be Vitamin D3 insufficient or deficient as well.

In the cross-sectional analytical study by Karimian P. et al. it was shown that Vitamin D can be effective in reducing COVID-19 severity. The study included 99 pediatric patients infected with COVID-19 and classified into three groups each given a severity score level according to their symptoms. The average of children was 2.85 ± 0.85 years. Severity scores and group included: < 4, 5–7, > 7. The Vitamin D serum levels of each group was taken and it found the more severe COVID-19 infection the lower the serum Vitamin D3 levels. Low oxygen saturation was observed in 35.3% of infected children. Clinical signs in cases with deficient and sufficient Vitamin D levels were more severe in terms of tachypnea and tachycardia ($p = 0.01$). Children with Vitamin D lower than 10 ng/ ml showed more frequency ($p = 0.02$). Cases with moderate Vitamin D had fewer gastrointestinal complications ($p = 0.03$). Also, oxygen levels were lower in children who had low levels of Vitamin D ($p = 0.02$). Vitamin D levels were associated with levels of involvement, tachycardia, tachypnea, clinical signs, gastrointestinal problems, and O_2 levels. The authors concluded that the moderate Vitamin D levels in children are a critical issue that should be considered [11].

In the evaluation study by Karakaya M. G. et al. the Vitamin D deficiency was present in a significant percentage of pediatric patients infected with COVID-19. The authors concluded that it is possible that Vitamin D deficiency increases susceptibility to the infection while Vitamin B12, Vitamin C, Ferritin, Vitamin A, Vitamin E, and Folate deficiency were less common [12].

The retrospective study by Bayramoğlu E. et al. associated the serum Vitamin D level with clinical severity and markers of inflammation in children and adolescents with COVID-19. The more severe groups had progressively lower Vitamin D3 serum levels. These associations were observed especially when there was a deficiency (i.e., 25(OH)D < 12 ng/mL). The authors also suggest "that considering the ongoing lockdown measures, prophylactic Vitamin D supplementation may be considered especially for the adolescent age group during the COVID-19 pandemic as a health policy" [13].

In the retrospective descriptive study by Elif S. et al. 28 out of the 30 children infected with COVID-19 had Vitamin D

replacement due to deficiency or insufficiency. In this study there were 2 groups: a healthy control group of 82 participants and asymptomatic infected group of 30 pediatric patients. The COVID-19 infected group had a median Vitamin D serum level of 8.9 ng/ml versus the healthy control group with a median Vitamin D serum level of 18.5 ng/ml. The authors concluded that even though 28 out of the 30 children infected with COVID-19 had Vitamin D replacement due to deficiency or insufficiency, "it is difficult to say that this favorable clinical response is contributed to Vitamin D supplementation because they also had supportive and medical therapy". Because of lack data about Vitamin D supplementation in children with COVID-19 they implemented oral Vitamin D 3000 IU for less than 12 years old and 6000 IU for more than 12 years old patients according to algorithms of 'Global Consensus Recommendations on Prevention and Management of Nutritional Rickets'. All the children in their study cured and showed good clinical improvement [14]. In COVID-19, cytokine storm is problematic and Vitamin D may play a role in COVID-19 by reducing proinflammatory cytokines [14].

According to the retrospective cohort study by Aysegul A. et al., Vitamin D can be beneficial in reducing the severity of COVID-19 infection. The study had two groups: 75 COVID-19 infected pediatric patients and 80 healthy controls. It was found that the group infected with COVID-19 had only 12 patients out of the 75 who had Vitamin D serum levels in the normal range (> 30 ng/ml) versus 27 out of 80 patients in the healthy control group. Most patients in the COVID-19 infected group had either deficient (< 20 ng/ml) or insufficient (< 30 ng/ml) Vitamin D3 serum levels [15].

In the retrospective cohort by Heidari S. et al. subjects were divided into two groups. Group 1 had significantly lower levels of serum Vitamin D, calcium, and lymphocytes, as well as higher fibrinogen, D-dimer, and C-reactive protein levels compared with those in Group 2 ($p < 0.001$). Group 1 also had significantly higher dry cough, fever, chest radiographic findings, respiratory rate, and longer hospital length of stay than patients in Group 2. The authors came up with their study indicated associations between severity COVID-19 infection and serum Vitamin D levels [16].

In the retrospective case-series by Nadiger M. I. et al. the majority of COVID-19 infected children admitted to the ICU were obese and Vitamin D deficient adolescents. The authors concluded from their cohort that it is important to screen for and supplement Vitamin D in children with low (< 30 ng/ml) levels [17].

Posted by Yılmaz K. and Şen V.: children patients with COVID-19 had significantly lower Vitamin D levels 13.14 μg/L (4.19–69.28) than did the controls 34.81 (3.8–77.42) μg/L ($p < 0.001$). Patients with COVID-19 also had significantly lower serum phosphorus (4.09 ± 0.73 vs. 5.06 ± 0.93 vs. (U/L) ($p < 0.001$)) values compared with the controls. The symptom of fever was significantly higher in COVID-19 patients who had deficient and insufficient Vitamin D levels than in patients who had sufficient vitamin D levels ($p = 0.038$). There was a negative correlation found between fever symptom and Vitamin D level ($r = -0.358$, $p = 0.023$). These results suggest that Vitamin D values may

be associated with the occurrence and management of the COVID-19 disease by modulating the immunological mechanism to the virus in the pediatric population [18].

In a cross-sectional study of Abdelrazic M. I. et al. the total of 56 children whose PCR test revealed COVID-19 were included in the study, 24 in the moderate group, and 32 in the severe group. Vitamin D serum levels and laboratory markers were measured in all patients. Fever was the most common associated symptom in both groups. No significant difference in the suspicion level of COVID-19 infection at clinical presentation before confirming by PCR tests between the two groups while there were significant differences in the disease course and outcome between both groups with lower scores of respiratory distress, and survival rates in the severe group with 100% mortality in this group. On analyzing the demographic data of the cases, the ages of the children ranged from 1 month to 18 years with a median age of 6 months with a non-significant difference between moderate and severe positive PCR cases. This finding suggests that all ages of childhood were susceptible to COVID-19 [19]. Although the effects of 25 OH Vitamin D on the immune system are quite complex, the available information support that adequate Vitamin D levels improve the defense process against bacterial and viral infections and prevent hyperinflammation. In this study, it has been shown that low serum Vitamin D level in the body at the time of infection was associated with severe clinical course and higher mortality in children and adolescents with COVID-19 [19].

Ozden A. et al. suggested that serum 25OHD concentration may play a role in lymphocyte count in children with COVID-19. This study shows that SARS-CoV-2 infection in children is related with a low lymphocyte count as in adult patients and that serum 25OHD concentration may affect lymphocyte count. The positive correlation between serum 25OHD level and lymphocyte count supports this idea. Additionally, the negative correlation between serum 25OHD and PTH levels can be considered an indirect finding indicating the true state of 25OHD in the patients. In this study, the patient's age was negatively correlated with serum 25OHD level and lymphocyte and platelet counts. These findings suggest that as children with COVID-19 grow older, serum 25OHD decreases, and these cell counts decrease accordingly [20]. Many of the children infected with COVID-19 posted in this narrative review are Vitamin D deficient (< 20 ng/ml) or insufficient (< 30 ng/ml).

Children from 6 to 18 years are at risk of Vitamin D deficiency and insufficiency in both the pre-pandemic and pandemic periods because of pandemic-related restrictions according to a study conducted in Turkey. The study suggests that children and adolescents should be given Vitamin D supplementation to maintain sufficient levels of vitamin D [7]. Our narrative review provides a strong correlation between lower Vitamin D3 levels and a higher susceptibility to infection or a more severe course of infection with COVID-19 in children aged 1–18 years. This research so might help to manage the care of COVID-19 infected children.

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Conclusions. The literature we reviewed demonstrates a negative correlation between serum Vitamin D3 levels and COVID-19 infection susceptibility and severity in children aged 1-18 years. Studies show that blood levels of Vitamin D3 in children are associated with susceptibility and severity of COVID-19 infection. Most hospitalized children with COVID-19 have inadequate Vitamin D3 levels. Supplementing with Vitamin D3 may help reduce the risk of the disease and improve its course. Physicians should pay attention to Vitamin D3 levels in pediatric patients to maintain adequate levels and reduce susceptibility to COVID-19 infection. However, the causality of this correlation remains the subject of further target values, a systematic review and meta-analysis of the compiled studies should be done. Our narrative review is also limited by the fact that it does not prove causality but rather it provides a correlation between vitamin D3 deficiency and insufficiency with more severe COVID-19 infections in children.

Limitations. This narrative review has limitations. The literature searches were only examined in two databases. Included studies were limited to those published in the English language and no gray literature was included. Expanding the search and inclusion criteria could add more information to our study's final report. To establish more precise findings, such as research.

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