Pediatr Pol 2023; 98 (1): 140-144
DOI: https://doi.org/10.5114/polp.2023.128067
Submitted: 04.08.2022, Accepted: 18.12.2022, Published: 14.06.2023

PEDIATRIA Polska
Polish Journal of PAEDIATRICS

REVIEW PAPER

Effect of vitamin D level on COVID-19 and the risk of complications in children

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ABSTRACT

The immunomodulatory and pro-apoptotic role of vitamin D is still being investigated and the relationship between its deficiency and the development of many diseases is widely described. Vitamin D deficiency, which is prevalent in the world population, is under investigation, especially in the current epidemiological situation and the risk of complications from COVID-19, including multisystem inflammatory syndrome in children. Recommendations regarding the norms of vitamin D levels in children suggest monitoring of its concentration in groups at risk of deficiency and supplementation to the optimal level. Studies on the relationship of vitamin D deficiency with the severity of COVID-19 and an increased risk of complications after the disease suggest strong associations. At the same time, the literature review also noted data that indicated no or only a small effect of vitamin D on the morbidity of the studied population.

KEY WORDS:

COVID-19, vitamin D, vitamin D deficiency, MIS-C, 25(OH)D.

INTRODUCTION

The available data indicate that vitamin D deficiency is an alarming problem in the general population, irrespective of latitude, age, gender and race. Vitamin D deficiency is a global public health problem. About one billion people worldwide are clinically diagnosed with vitamin D deficiency, while 50% of the population are mildly deficient in this vitamin [1–3]. In Poland, vitamin D deficiency of varying severity was found in 90% of adults, children and adolescents [4]. Due to the lack of explicit recommendations for educating the society about the role of vitamin D in the health of the population, the problem of vitamin D deficiency is common, and the data on the scale of the problem related to its deficiency may be underestimated.

The guidelines regarding the principles of vitamin D supplementation are regularly updated. In 2017, the Main Board of the Polish Society of Pediatric Endocrinology and Diabetology verified the recommendations for the prevention and treatment of vitamin D deficiency, both for the general population and risk groups. In cooperation with the European Society of Vitamin D, a Team of Experts was established, which, based on a review of the current literature, own clinical experience and a critical discussion, developed current guidelines on recommendations for prophylactic supplementation in groups at risk of vitamin D deficiency and treatment principles in the event of a diagnosis of vitamin D deficiency [5].

THE ROLE OF VITAMIN D IN THE BODY

Calcitriol [1.25(OH)2D] is the active form of vitamin D and is one of the hormones associated with target proteins. Calcitriol synthesis is related to the availability of the 25(OH)D substrate, a metabolite of vitamin D, referred to as the level of vitamin D.

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Vitamin D is the prohormone that defines ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). Vitamin D_2 is found in plants and fungi, while vitamin D_3 is produced from provitamin D_3, which under the influence of UVB solar radiation is converted into pre-vitamin D_3, undergoing isomerization to vitamin D_3. Although some foods (e.g. fatty fish, eggs, milk, mushrooms) contain small amounts of vitamin D, cutaneous synthesis is the most effective source of vitamin D. The main metabolite of vitamin D is 25(OH)D, which reflects the amount of vitamin D in the body from these two sources [6, 7].

Vitamin D is a fat-soluble vitamin that plays an important role in many physiological mechanisms. It participates in calcium homeostasis and bone metabolism, as well as in modulating regulatory processes and systems related to immune-repair mechanisms in the body. Vitamin D's metabolic functions include inhibition of lipid accumulation in adipocytes, influencing the total composition of adipose tissue in the body [8, 9]. Vitamin D acts as a modulator of the immune system, preventing over-expression of pro-inflammatory cytokines that damage the lining of the lungs and lead to serious infection. Its action is based on the induction of cathelicidins and defensins, which may reduce the rate of viral replication [10, 11].

Vitamin D deficiency is endemic and associated with many civilization diseases [12, 13]; it is as common in the world as excess body weight, and both are the result of adverse lifestyle changes. In the United States, in the group of children aged 6–18 years, vitamin D deficiency was found in 21% of children with normal body weight, 34% of overweight and obese children, and 49% of subjects with severe obesity [14]. Treatment of children and adolescents with diagnosed vitamin D deficiency improves the functioning of the cardiovascular system by lowering the blood pressure of patients with essential hypertension [9].

However, the prophylactic dosage of vitamin D should be individualized depending on the age, weight, season, diet and lifestyle of children and adolescents, and in groups at risk of deficiency it is advisable to determine the concentration of 25(OH)D and select the optimal dose to balance its level [4].

Widely described mechanisms of cell cycle regulation by 1.25(OH)2D_3 include inhibition of mitogenic signals transmitted by growth factors, stimulation of transforming growth factor pathways and insulin-like growth factor binding proteins [15]. It has also been shown that 1.25(OH)2D_3 can inhibit the activity of prostaglandins, which act as stimulators of cell growth. Calcitriol's ability to stimulate apoptosis has been demonstrated in various neoplastic cells, including breast, colon and prostate cancer, which proves the anti-cancer effect of vitamin D.

There is therefore a link between vitamin D deficiency and chronic diseases, including caries in children, autoimmune disorders, infectious diseases, cardiovascular diseases and cancer [3, 16, 17].

ASSOCIATION OF VITAMIN D DEFICIENCY WITH INFECTIOUS DISEASES

The immunomodulatory effect of vitamin D is very well described for many diseases, including respiratory system infections, infectious and neoplastic diseases [18]. However, acute respiratory infections are the most common infections in the world. It has been reported that in previously healthy children, the most common cause of acute respiratory infections was respiratory viruses (mainly rhinoviruses – 42.2% and influenza virus – 15.8%) [18, 19]. In England, a significant inverse correlation was observed between the incidence of flu and temperature, which is strongly related to solar radiation during the winter season. The relationship of vitamin D deficiency with influenza morbidity (including seasonality of the disease) seems to be confirmed [10, 20].

However, in a meta-analysis of attempts to estimate the effect of vitamin D supplementation on the occurrence of acute respiratory infections, a statistically small level of reduction of the risk of infection with vitamin D supply was detected compared to the control samples [21]; the protective effect of vitamin D was associated with the administration of daily doses of 400–1000 IU for up to 12 months adjusted to the age of the studied children and adolescents. As a limitation of the research, the authors noted the significant heterogeneity of the group, which could lead to underestimating the protective effect of vitamin D supplementation on reducing the risk of acute respiratory infections. The significance of the above data in the context of COVID-19 is not fully known and requires further research [21].

Recent studies also suggest the influence of viral infections on the mean volume of platelets, which is associated with low vitamin D levels, creating an inflammatory process in the body [18, 19]. Vitamin D deficiency is associated not only with the intensification of respiratory diseases [18, 22, 23] but also with an increase in the incidence of sepsis in children and adults, which may be a complication of these diseases [24, 25].

The administration of 150,000 IU of cholecalciferol to children with vitamin D deficiency and sepsis at one time resulted in a significant reduction in the frequency of septic shock (20% vs. 7%) [26]. Although vitamin D levels have been shown to be related to mortality in critically ill adults [24], no statistically significant effect on mortality in children with sepsis has been demonstrated, which requires further studies.

Studies conducted in pediatric intensive care units (PICUs) have shown that vitamin D deficiency in severely ventilated patients may lead to increased mortality, increased incidence of multi-organ dysfunction and a generally worse clinical course of the disease [25, 27, 28].

VITAMIN D DEFICIENCY AND COVID-19 COURSE

The coronavirus (COVID-19) pandemic has not only changed the global healthcare system, but also verified the current priorities of the population. Clear recommendations regarding social isolation, including work and distance learning, limiting exposure to sunlight, increasing stress levels and an improperly balanced diet increased the risk of vitamin D deficiency [29].

Recent studies have unequivocally identified a relationship between the severity of COVID-19 infection and vitamin D deficiency based on observations in the northern hemisphere – with lower vitamin D levels due to reduced exposure to sunlight [30–32].

Preliminary reports identified the pediatric population as a low-risk group for COVID-19 infection [33, 34], whose typical symptoms were very subtle or absent. Only a positive antigen test result diagnosed COVID-19 infection. Infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in children were usually milder [35] and concerned a population of various age groups [36].

Children are at risk of COVID-19, but the rate of severe disease is lower than in adults – so far, studies have been reported in which the pediatric population was infected with mild SARS-CoV-2 [37, 38].

The pediatric population is often asymptomatic and difficult to identify, which may result in a silent carrier of the virus. At the same time, children with comorbidities such as respiratory diseases, immunodeficiencies, chronic heart diseases, metabolic diseases and cancer are extremely susceptible to SARS-CoV-2 infection [39].

Treatment of the pediatric population was largely replicated from adult studies, but management focused on prevention of transmission. Due to the lack of data on vitamin D levels in the SARS-CoV-2 positive pediatric population, the focus was on discussing the relationship in the COVID-19 infected adult population.

Clinical publications indicate that the most dangerous is severe COVID-19 infection associated with viral pneumonia caused by acute respiratory distress syndrome (ARDS) [40]. All adult ARDS patients were found to have low serum vitamin D levels (< 50 nmol/l). Moreover, patients with serum vitamin D < 20 nmol/l had a statistically significantly higher probability of ARDS ($p = 0.040$) [41]. Other studies showed that vitamin D deficiency was present in 90% of ARDS patients [42]. A review of the effect of hypovitaminosis D on COVID-19 patients showed that people with severe COVID-19 exhibit a 65% greater vitamin D deficiency compared to mild cases of the disease [43].

Severe COVID-19 infection culminates in cytokine storm syndrome, in which many COVID-19 patients report with an exaggerated inflammatory response, leading to multiple system failure and lung damage [44].

Therefore, it seems justified to monitor the level of vitamin D in children and adolescents who are at risk of deficiency and supplementation with the optimal dose in accordance with the current guidelines. Despite the huge role of vitamin D on the body's immunostimulation processes, its impact on the morbidity and course COVID-19 disease is still being investigated and the obtained results are inconclusive, as evidenced by two studies.

The first study, conducted in the United Kingdom in May–October 2021, was an attempt to assess the protective role of vitamin D against COVID-19. Participants were tested for vitamin D levels; people who had a blood concentration of 25(OH)D < 75 nmol/l were supplemented with vitamin D. It was found that none of the doses of vitamin D had an effect on the incidence of COVID-19. However, only 1.2% of participants had been vaccinated at the start of the studies, while 89.1% had received at least one dose at the end of the study. It is therefore possible that vaccination masked any effect of vitamin D. It is also worth noting that in the unvaccinated group COVID-19 was less common among participants taking 3200 IU/day [45].

The second study was conducted in Norway from November 2020 to June 2021 using cod liver oil as a substitute for low dose (400 IU/day) vitamin D – no effects of vitamin D supplementation were found. As a limitation of the study, the authors mentioned that participants were young and healthy people and 86.3% had an optimal vitamin D level at baseline, which clearly suggests a positive effect of vitamin D on the health of people with D hypovitaminosis [45].

VITAMIN D AND THE RISK OF COMPLICATIONS OF MULTISYSTEM INFLAMMATORY SYNDROME

Preliminary reports identified the pediatric population as a low risk group for COVID-19 infection [33, 34]. However, in the last few months, systemic symptoms of inflammatory infection, a complication of COVID-19, have been identified as a life-threatening condition in the pediatric population [46–49], which were directly related to the previous COVID-19 infection or exposure to SARS-COV-2.

Of the many complications associated with past COVID-19 infection, the most dangerous was the multisystem inflammatory syndrome in children (MIS-C) due to hyperinflammatory states, varied course and acute condition of patients upon admission to the hospital [35].

At the start of the pandemic, several names were used to describe this disorder, such as pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) and MIS-C, which was ultimately approved and defined by the Centers for Disease Control and Prevention and the World Health Organization [50]. The clinical picture of MIS-C differed in the severity

of the course; some patients had mild symptoms, some required intensive care, and some of them unfortunately died despite treatment [51–53].

In a study of the pediatric population diagnosed with MIS-C in March–July 2020, a serious deficiency of vitamin D (< 10 ng/ml) was found within 48 hours of admission to the Emergency Department (ED) in as many as 1/3 of the examined children. 90% of them were diagnosed with a severe course of MIS-C, which extended hospitalization time. In the group of patients with severe complications, all patients required inotropic support, 42.8% required invasive mechanical ventilation, and 14% required support for extracorporeal membrane oxygenation. Moreover, the study found that a single dose of vitamin D given to children with vitamin D deficiency may reduce the incidence of septic shock in certain patient populations [27]. The etiology of this compound may be related to the immunomodulatory role of vitamin D [9, 11, 51, 53, 54].

Previous studies in critically ill children have shown an association between severe, immediate life-threatening diseases requiring admission to the PICU and vitamin D deficiency [25]. The article also mentions studies that have shown only a slight effect of vitamin D on the risk and course of COVID-19. Given the role of vitamin D in the development of immunity, screening critically ill children for vitamin D levels and implementing effective supplementation strategies in line with current guidelines are certainly recommended. However, it should be remembered that the prevention of COVID-19 should take place in many aspects and supplementation with vitamin D should be treated only as an auxiliary measure.

This article describes the potential relationship between vitamin D deficiency and the severity of COVID-19 in children and the occurrence of complications. Future research should aim at a more precise connection of these two issues, as vitamin D deficiency in patients admitted to the PICU may lead to increased mortality, higher incidence of multi-organ dysfunction and an overall worse clinical course of the disease [28].

CONCLUSIONS

The pathophysiological role of vitamin D in COVID-19 is crucial and consists in active immunostimulation by strengthening the immune system and the body's repair functions, and immunosuppression that reduces excessive reactions leading to a cytokine storm. An extremely important aspect is the assessment of vitamin D levels in children and adolescents at risk of deficiency and dedicated supplementation for patients diagnosed with hypovitaminosis D and children and adolescents with a severe course of COVID-19. The level of 25(OH)D in the serum of children with a positive COVID-19 test result should be assessed and treated as a predictor of a severe course of COVID-19 and a higher risk of serious health complications (MIS-C). Prevention of vitamin D deficiency may contribute to increasing the health potential of children as well as reducing the risk of many diseases, including the severe form of COVID-19, especially in the group at risk of vitamin D deficiency. Due to the lack of studies unequivocally showing a direct influence of vitamin D on the incidence and course of COVID-19 in children and adolescents, supplementation with vitamin D should be initiated only after determining the level of 25(OH)D and should be treated as an adjunct in the treatment of the disease.

DISCLOSURE

The authors declare no conflict of interest.

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