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In the first years of the SARS-CoV-2 pandemic, published observational data were quite optimistic about the course of infection in the pediatric population [1]. The share of infection with this virus in the children's population remains constant during the pandemic, fluctuating within 10%, which cannot be said about the severity of the course, which is progressively increasing. The latter is obviously explained by the appearance of new, more virulent variants of the virus [2]. Of course, most children recover, but some of them, according to various data, from 1/4 to 1/10 depending on the size of the cohort, methodology and definition of the term, have persistent symptoms after the infection [3]. These symptoms of COVID-19, which persist for a long time or recover some time after the end of the acute process, are called differently: post-acute effects of COVID-19, remote, chronic or long-lasting COVID syndrome, post-COVID-19 syndrome [4, 5] . In addition, it is reported that the risk of autoimmune diseases increases after experiencing COVID-19 [6, 7]. Regardless of how these manifestations are called after the transfer of COVID-19, they are new, repeated or persistent health problems that occurred 4 or more weeks after the onset of the root of the viral infection caused by SARS-CoV-2 [8]. The American Academy of Physical Medicine and Rehabilitation has already created a multidisciplinary consensus guideline for the assessment and treatment of post-acute consequences of SARS-CoV-2 infection (PASC) in children and adolescents [9]. However, published reports demonstrate ambiguity in the analysis and assessment of symptoms in children who have contracted COVID-19, as half of healthy children also indicated the presence of the same symptoms [10, 11]. So, despite the huge volume of research conducted on the study of the pandemic coronavirus and the disease it causes, there are still enough gaps in our knowledge, and many questions still need to be answered. The question of differentiation of certain long-term symptoms, their involvement in the transferred corona virus infection and the pathogenetic basis of their occurrence remains open.

sprouting.

**Purpose:** to generalize and specify the effect of vitamin D on the course of COVID-19 and the post-covid period in children.

An electronic search of scientific studies was carried out in the well-known databases PubMed, Scopus, ResearchGate, Wiley Online Library and Google Scholar from 2019 to February 2023. The keywords for the search were: Long COVID, Post COVID, COVID-19, Pediatrics, Children , Adolescents, Postacute sequelae of SARS CoV-2 infection (PASC), Vitamin D. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [12] were used to analyze the selected publications. The criteria for inclusion of articles for possible consideration was the presence of the above keywords in their texts. In the process of automatic search, 127 articles were selected from the PubMed database, 82 from Scopus, 13 from ResearchGate, 3 from Wiley Online Library, 291 from Google Scholar, that is, the total number of selected items was 516. The exclusion criteria were: duplicated, devoted exclusively to adults or those in whose persons were not verified by age, those who analyzed only acute COVID-19. The analysis included studies of the post-covid period in children and adolescents, which contained the results of assessing the level of vitamin D in the serum of children and adolescents. A total of

227 articles were duplicated in at least one of the selected databases, 16 — separate chapters of one monograph, 38 — acute COVID-19, 8 — the influence of vitamin status on the course of acute COVID-19 in adults, and 15 — in the general population without indication of dependence on age, 7 — editorial reviews on acute COVID-19 and vitamin D, 4 — hypotheses, 2 — Russian articles (no access to review), 4 — concerns about the reliability of the reported results and conclusions and about the non-disclosure of competing interests, 4 — journalistic or editorial, 6 — long COVID in the general population, 19 — long COVID in children, 21 — causes of long COVID, 69 — long COVID in adults, 9 studied changes in the vitamin status of children after a period of social distancing caused by the pandemic COVID-19, 27 — the influence of vitamin status on the course of acute COVID-19 in children, 8 — the influence of vitamin D on the development of an infectious disease, that is, 484 articles were excluded from the review. The remaining 38 publications: 13 — influence on the course of COVID-19, 12 — correlation of the severity of corona virus infection with the level of vitamin D in adults and children, 2 — preventive effect of vitamin D on the course

COVID-19, 11 — Efficacy of Vitamin D in the Treatment of COVID-19.

# Results and discussion

***The effect of vitamin D on the course of COVID-19***

Among the risk factors for starting a certain pathogenetic chain in the formation of long-term health disorders, one of the important places is hypovitaminosis D. The biological role of vitamin D in the body is primarily reduced to ensuring the regulation of innate and adaptive immune responses [13]. Approximately 75% of the functions of the human immune system depend on vitamin D and the presence of vitamin D metabolites (vitamin D and 25(OH)D) in concentrations sufficient to enter immune cells from the bloodstream [14]. Calcitriol (1,25-dihydroxyvitamin D3 ), as an active form of vitamin D, also has antioxidant and anti-inflammatory properties, therefore hypovitaminosis D, reducing the ability of the immune system to adequately respond to infection, contributes to an increase in the level of infectious diseases [15, 16] . This vitamin has a very significant effect on the activity of the innate immune response in acute respiratory pathology caused by the microflora most common in childhood: *Streptococcus pneumoniae,* respiratory syncytial virus, and influenza virus [17, 18]. A serum vitamin D level below 50 nmol/L increases the risk of community-acquired pneumonia by 64% and affects the clinical outcome of pneumonia in COVID-19 [19, 20]. Published meta-analyses put forward the hypothesis of a relationship between vitamin D insufficiency and the deterioration of the functioning of the immune system in people infected with the pandemic coronavirus, which increases the risks

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severe course of illness and death [21–26]. An analysis of 17 observational studies with 2756 patients associated vitamin D deficiency with higher mortality, higher rates of hospitalization, and longer duration of hospitalization [27]. A causal relationship between hypovitaminosis D and poor cognitive function was revealed [28].

All children requiring treatment in the intensive care unit of Birmingham Children's Hospital, Birmingham, UK, had suboptimal 25(OH)D concentrations [29]. However, in individuals with sufficient or higher serum 25(OH)D levels before the pandemic, a reduction in the incidence of COVID-19 has been reported, and the reduction in risk reaches a plateau at 25(OH)D values ~ 100 nmol/L [30, 31].

A number of observational studies, both exclusively in adult patients and adults combined with children, report inverse correlations between the concentration of 25-hydroxyvitamin D in the blood serum of patients with COVID-19 and the severity of the disease and death [32–44]. However, large-scale randomized clinical trials investigating the effectiveness of vitamin D in the treatment of this disease and prevention of its consequences are still ongoing, and the results are yet to be published [45].

The UK-Biobank data [46] testify to the positive effect of prophylactic vitamin D application on the eve of the pandemic on reducing the incidence rate.
SJ Wimalawansa (2022) estimated that with the presence of sufficient vitamin D metabolites in the body on the eve of the SARS-CoV-2 pandemic, 50% of hospitalizations (and associated health care costs) and a third of deaths from COVID could have been prevented to prevent [14].

Social distancing and long-term isolation of the child population during the SARS-CoV-2 pandemic led to an insufficient level of insolation, which became a prerequisite for the formation of vitamin D deficiency. A systematic review conducted until November 2020, which included an analysis of 39 studies with clarification and generalization of the relationship between the concentration of 25-hydroxyvitamin-D and the risk of development and consequences of COVID-19 in children showed the presence of a higher risk of SARS-CoV-2 infection in the group with vitamin D deficiency [47]. A 6-month retrospective study of COVID-19 in 144 hospitalized children at Abuzar Hospital (Ahwaz, Iran) found a relationship between serum vitamin D concentration and disease severity [48]. An open-label, randomized, controlled, blinded clinical trial of hospitalized patients aged 1 month to 17 years with moderate severity of COVID-19 requiring supplemental oxygen demonstrated the efficacy and safety of adding vitamin D to a standard treatment protocol [49]. A 15-month clinical experience in the treatment of patients infected with the SARS CoV-2 virus confirms the effectiveness of the use of vitamin D [50–52]. However, the accumulated published data at the end of 2022 are pilot and still remain controversial, as there are individual studies that did not find probable positive effect or it was doubtful [53–55]. These are studies in which high doses of vitamin D were used. Therefore, it is worth considering that high doses cause a short-term blocking effect on the production of calcitriol. Similarly, high doses of periodic bolus vitamin therapy

D are ineffective in preventing rickets, a condition clearly caused by vitamin D deficiency, because high doses induce prolonged expression of the catabolic enzyme 24-hydroxylase and fibroblast growth factor 23 (FGF 23), both of which have an inactivating effect for vitamin D [56]. . But treatment with 25(OH)D does not cause such adverse effects. Its use in this infection demonstrated a reduction in the need for intensive care and a reduction in mortality [57]. "To clarify the effectiveness and safety of vitamin D supplements for people with COVID-19, additional randomized controlled trials are needed" — this is the conclusion of the 2022 Cochrane review [58]. That is, the question of vitamin D and the disease caused by SARS-CoV-2 remains open and encourages further study of the role of this vitamin in the pathogenesis of coronavirus infection, the legality of including it in the protocol of its treatment, as well as in post-coronavirus processes [18, 59, 60].

### *Vitamin D and long COVID*

18 patients with SARS-CoV-2-associated multisystem inflammatory syndrome (MIS-C) in children at a UK children's hospital were found to be deficient in vitamin D compared to a group of COVID-19 patients who did not have the syndrome. Obviously, low concentrations of 25-hydroxyvitamin D due to the negative effect on cytokine regulation and immune response did not directly contribute to the development of a severe, complicated course of infection [29]. Among 68 pediatric patients with COVID-19, a higher prevalence of vitamin D deficiency occurred in sick children with MIS-C [61]. The observation of the relationship between the level of vitamin D and the clinical severity of the long-term inflammatory syndrome in 103 children and adolescents with COVID-19 allowed the authors to recommend prophylactic administration of vitamin D, especially in adolescence [62]. The potential role of hypovitaminosis D in the formation of long-term health disorders after acute COVID-19 is also still under permanent study [63]. The study of the influence of serum vitamin D levels in children and adolescents on the course of COVID-19 and its consequences remains relevant, as the available data are promising but controversial.

**Conclusions**

The analysis of literature sources showed that insufficiency and deficiency of vitamin D increase the risk of a severe course of COVID-19, including in the pediatric population, and also lead to higher rates of hospitalization, its duration, and mortality from SARS-CoV 2 infection. Vitamin D deficiency was also more likely to affect the development of MIS-C. At the same time, the influence of non-

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the sufficiency of vitamin D on the development of other symptoms of three-dimensional COVID-19 is under study, as is the effect of vitamin D supplementation on the course of SARS-CoV-2 infection and its consequences.

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## The role of vitamin D in the course of SARS-CoV-2 infection and long COVID in children (literature review)

**Abstract.** Long-term observation of the SARS-CoV-2 pan demic in the pediatric population revealed the presence of per sistent symptoms in 1 : 4 to 1 : 10 children four or more weeks after the onset of this infection. The question about the role of vitamin D in the course of COVID-19 and the development of long-term health conditions is still debatable. The purpose of this review is to generalize and clarify the effect of vitamin D on the course of COVID-19 and the post-COVID period in chil dren. Electronic search for scientific publications was done in the PubMed, Scopus, ResearchGate, Wiley Online Library and Google Scholar databases from 2019 to February 2023. Analysis of studies on COVID-19, the post-COVID period, and the im pact of hypovitaminosis D on their course attests to the ambiguity of published results in the pediatric cohort. A number of resear chers have linked vitamin D deficiency to higher mortality, higher hospitalization rates, and longer hospital stays. Hypovitaminosis D impairs the functioning of the immune system in an organism infected with the pandemic coronavirus, which increases the risk of severe course and mortality. But this hypothesis still needs in depth study to understand the essence of the effect of vitamin D supplementation on the course of the coronavirus infection and long COVID. The hypothesis about the relationship between hy povitaminosis D and immunosuppression during infection with a pandemic coronavirus and its potential role in the formation of long-term health conditions after acute COVID-19 is still under permanent study.

**Keywords:** COVID-19; long COVID; SARS-CoV-2; vitamin D; children