Vitamin D and COVID-19: how close are they? (Analytical review of the literature)

Abstract. The analytical review includes an analysis of current literature on the possible effects of vitamin D on the immune system functioning (innate and acquired immunity), as well as its impact on the risk of infectious diseases of the upper respiratory tract (IDURT) and COVID-19. Available clinical trial data evaluated in current meta-analyses on the effects of vitamin D on the risk and course of COVID-19 and related hospitalization, mortality, and disease recovery rates were analyzed. Despite conflicting data on the positive effects of vitamin D on the IDURT risk in general and COVID-19 particularly, most clinical studies and meta-analyses demonstrated this positive effect, pointing to certain limitations associated with heterogeneity of study populations, doses and forms of vitamin D etc. Current researches show the same bioequivalence of different forms of vitamin D (capsules, drops, tablets) in terms of their quality production and the need to correct vitamin D deficiency and deficiency in order to prevent IDURT in general and COVID-19 disease in particular.

Keywords: vitamin D; immune system; COVID-19; acute respiratory infections; pneumonia; clinical trials; meta-analyses; review

Introduction

For today, the coronavirus disease 2019 (abbreviation – COVID-19) remains an important infectious disease with catastrophic medical and social consequences for the entire society of the planet, the cause of which was the SARS-CoV-2 coronavirus, the circulation of which in the human population was unknown until 2019. First time it was detected in humans in December 2019 in the city of Wuhan (Central China), COVID-19 already had reached pandemic status in March 2020. Currently, the disease is associated with a high risk of mortality and complications, a high level of need for hospitalization and intensive therapy. Up to the end of November 2021, more than 253 million people in the world have been confirmed to fell ill with COVID-19, more than 5 million of whom have died [1]. In accordance with the data of the Public Health Center of the Ministry of Health of Ukraine, for the 20-th of November of 2021, almost 3,5 million people were confirmed to fell ill with COVID-19 in Ukraine, and more than 80,000 Ukrainians died from this disease [2].

Currently, there are no effective methods of treating of COVID-19, and concerning that, numerous studies are ongoing as for the learning of the prophylactic and therapeutic possibilities of medicines of various groups. A special discussion continues around the study of the possibilities of vitamin D due to its multifaceted effect on various body systems. On the one hand, there are numerous experimental and clinical studies that have been conducted during recent years that demonstrate the probable effect of vitamin D on the functioning of the immune system [3-6] and reducing the risk of respiratory infections [7, 8], on the other hand, not all meta-analyses [9] confirm this effect.

The evidence of the potential effect of vitamin D on the risk of COVID-19 was the fact, that the outbreak of the disease occurred in winter, when the concentration of vitamin D in human blood has the lowest level, and at the beginning of the pandemic, the frequency of the disease was much lower in the Southern Hemisphere, especially in late summer. However, it should be noted, that often the risk factors for the development of severe COVID-19 are the same as the factors for the development of vitamin D deficiency, so it is difficult to assess whether vitamin D deficiency is an independent risk factor for COVID-19, in particular, its severe course.

Currently, it is generally known that vitamin D is a number of biologically active fat-soluble substances (more than 6 vitamins and 50 metabolites), which are formed in the skin under the action of ultraviolet rays of the “B” range, and also enter the body with food, among which the most significant are vitamin D₂ (ergocalciferol) and D₃ (cholecalciferol) [10].

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In accordance with the definition of the International Institute of Medicine and the Committee of Endocrinologists for the creation of guidelines for clinical practice, vitamin D deficiency in children and adults is a clinical syndrome caused by a low level of the main metabolite of vitamin D – 25-hydroxyvitamin D (25(OH)D) in blood serum. Limit values of 25(OH)D in blood serum are defined as deficiency (< 50 nmol/l or < 20 ng/mg), insufficiency (50–75 nmol/l or 20–30 ng/mg) and norm (75–125 nmol/l or 30–50 ng/mg).

For today, the effects of vitamin D are divided into classical (the influence on the calcium-phosphorus metabolism) and non-classical (pleiotropic, effect on the other organs and systems of the body). The classical effects consist of increased absorption of calcium and phosphates in the gastrointestinal tract (GI), influencing the synthesis of parathyroid hormone, promoting the mobilization of calcium from bone, reabsorption of calcium and phosphates in the kidneys, influencing the differentiation and functioning of bone tissue cells (osteoblasts and osteoclasts). The extraskeletal effects of vitamin D are realized through receptors in other organs and systems, which, for this moment, have been identified in almost 40 organs and tissues. The implementation of the mechanisms of action of vitamin D is ensured both at the level of cell nuclei (affects the transcription of about 3% of the entire human genome), as well as cell membranes (modulates gene expression and the intensity of various biochemical processes) and reveals both immunomodulatory, antibacterial, anticytokine (anti-inflammatory) and antiproliferative, antidepressant, anabolic, lipolytic, normoglycemic, hypotensive, analgesic, and other effects.

The purpose of the article is to evaluate the existing data from literary sources regarding the possible mechanisms of action of vitamin D on the state of the immune system and its potential influence on the risk and course of infectious diseases of the upper respiratory tracts and COVID-19.

Analytical review of literary sources was carried out using a systematic approach, in particular, using methods of information analysis. The databases Medline (using the Pubmed interface), Web of Science and Scopus, Embase, Google Scholar and the Cochrane Central Register of Controlled Trials (CENTRAL) during 2011-2021 had been searched using the keywords “vitamin D”, “immune system”, “COVID-19”, “acute respiratory infections”, “pneumonia”, “clinical studies”, “meta-analyses”.

Vitamin D and the immune system

Up to now, the numerous studies have proven the effect of vitamin D on the immune system both at the level of congenital and acquired links of immunity [3-6]. Thus, vitamin D receptors (VDR) are found on almost all immunocompetent cells, in particular, antigen-presenting cells (APCs), in particular, macrophages and dendritic cells, neutrophils, immature lymphocytes of the thymus, activated T-lymphocytes, mature CD8-cells, B-lymphocytes. The level of VDR changes in different directions during the maturation of cells of the immune system (lymphocytes and monocytes, macrophages and dendritic cells), and the expression of VDR during activation of CD4-lymphocytes can be increased up to 5 times.

Currently, it has been established that the synthesis of the active form of vitamin D (1,25-dihydroxyvitamin D, 1,25(OH)2D), except the kidneys, also occurs in macrophages, dendritic cells, T- and B-lymphocytes due to the expression of CYP27B1-1α-hydroxylase, the activity of which is regulated not by parathyroid hormone (as under the conditions of synthesis in the kidneys), but by cytokines, in particular, interferon-γ (IFN-γ). It was also established that the level of 1,25(OH)2D in cells that are located in the center of inflammation, is significantly higher compared to that in the healthy cells of the same organ [3]. The immunomodulatory effects of 1,25(OH)2D are ensured by increasing the chemotaxis and phagocytosis of monocytes and macrophages, increasing the synthesis of antimicrobial peptides (cathelicidin, defensin), suppressing the expression of TLR-2 and TLR-4 molecules, MHC II (HLA-DR, HLA-DP, HLA-DQ) on APC and co-stimulatory molecules and proteins inducing their maturation. In addition, 1,25(OH)2D inhibits the differentiation of monocytes into dendritic cells (DCs) and their maturation, stimulates the synthesis of interferon-γ (IFN-γ), inhibits the expression of TLR-1-10 and CCL22 (Th2 and Treg formation, tolerogenic phenotype) and inhibits the release of IL-12, IL-23 from DCs. An important influence, that allows the anti-inflammatory effect to be realized in the human body is inhibition of 1,25(OH)2D, synthesis of anti-inflammatory cytokines (IL-1α, IL-1β, IL-2, IL-6, TNF-α, IFN-γ) in APC and inhibition of cyclooxygenase-2 activation.

The positive influence on the main links of the specific (acquired) immunity consists of the effect on both, T- and B-lymphocytes. The effects of 1,25(OH)2D consist in reducing the synthesis of some cytokines by T-helpers of type 1 (Th1), that are responsible, in particular, for the formation of a cellular immune response (IL-2, IFN-γ), and increasing the synthesis of a number of cytokines (IL-4, IL-5, IL-10, IL-13) by T-helpers of type 2 (Th2), reducing the synthesis by T-helpers of type 17 (Th17) IL-17, thus, reducing the severity of both, inflammation in general, and autoimmune reactions in particular [3, 5, 6]. Moreover, it has been proven for today the influence of 1,25(OH)2D in slowing down of the differentiation of B-cell precursors into plasma cells and reducing the synthesis of immunoglobulins (Ig) G and M.

Vitamin D and respiratory tract infections (RTIs)

For today, sufficient data as for the influence of vitamin D on the risk and course of infectious diseases of the respiratory system have been accumulated, both, in one-time and prospective studies, which have been analyzed in several meta-analyses that were published in recent years [7-9].

The results of a meta-analysis [11] of 5 randomized controlled clinical trials (RCTs) confirmed a reduction of the cases of RTIs in individuals with additional intake of vitamin D compared to the control group (odds ratio (OR): 0.582; 95% confidence interval (CI): 0.417-0.812; p = 0.001). The positive effect of intake of vitamin D supplements on reducing the risk of RTIs was observed both in the pediatric (OR = 0.579; 95% CI: 0.416-0.805; p = 0.001) and in the adult population (OR = 0.65; 95% CI: 0.47-0.90; p = 0.01) when using a fixed model for the analysis, although this
influence did not become significant when using a random model in the group of adults (OR = 0.54; 95 % CI: 0.28–1.06; p = 0.075) while the effect among the children had been preserved (OR = 0.579; 95 % CI: 0.416–0.805; p = 0.001). These differences are explained by the authors by the possibility of publication prejudgment, the small number of studies, the different doses of vitamin D and the heterogeneity of participants, as well as the small number of the studies that had been analyzed.

One more meta-analysis [12], which included the results of 11 RCTs with the participation of more than 5,500 people (the average age is 16 years, from 6 months up to 75 years), also had demonstrated that intake of vitamin D significantly reduced the risk of RTIs (OR = 0.64; 95 % CI: 0.49–0.84; p = 0.001), while the positive effect of vitamin D was greater in studies with the use of single daily doses (300–2000 IU/d) (OR = 0.51; 95 % CI: 0.39–0.67) compared to its less frequent use with the application of high doses (100,000 or 200,000 IU/month or every 3 months) (OR = 0.86; 95 % CI: 0.62–1.20).

The results of the meta-analysis of 25 RCTs with the participation of more than 11,000 people aged from 0 up to 95 years from 14 different countries of the world [7] revealed a reduction of the risk of, at least, one acute RTIs in total for 12 % (relative risk (RR) = 0.88, 95 % CI: 0.81–0.96; p < 0.001) with additional intake of vitamin D, herewith, this positive effect was confirmed in the group of people who received vitamin D on a daily or weekly basis (without bolus doses): OR = 0.81; 95 % CI: 0.72–0.91), but not among those who received one or more bolus doses (≥ 30,000 IU): OR = 0.97; 95 % CI: 0.86–1.10; p = 0.05. Among the subjects that had been receiving vitamin D on a daily or weekly basis, the effects were stronger at the baseline low level 25(OH)D (< 25 nmol/l: OR = 0.30; 95 % CI: 0.17–0.53) than in those with a serum level 25(OH)D above 25 nmol/l (OR = 0.75; 95 % CI: 0.60–0.95; p = 0.006). However, the positive effect of additional intake of vitamin D also had its age characteristics (it was reliable in children aged 1–16 years (OR = 0.60; 95 % CI: 0.46–0.77; p < 0.001), but not in persons aged 16–65 years and people older than 65 years [7], herewith the authors noted a significant heterogeneity of the effect when analyzing the data included in the meta-analysis.

This year, the results of another meta-analysis were published, which included the results of 46 RCTs, 43 of which were included in the authors' final analysis [13] (more than 48,000 participants in the age from 0 up to 95 years). The authors demonstrated a significantly lower risk of one or more episodes of acute respiratory illnesses (ARI) in the group of people who took vitamin D compared to the placebo group (OR = 0.92; 95 % CI: 0.86–0.99; p = 0.02). No likely positive impact of additional intake of vitamin D on the risk of one or more ARI was found for any of the subgroups defined by the outgoing concentration 25(OH)D, but protective effects of vitamin D supplementation were observed in studies in which vitamin D was administered on a daily basis (OR = 0.78; 95 % CI: 0.65–0.94; 19 studies), with daily dose equivalents of 400–1000 IU (OR = 0.70; 95 % CI: 0.55–0.89; 10 studies), within 12 months or less (OR = 0.82; 95 % CI: 0.72–0.93; 29 studies), as well as for the persons in the age of 1.0–15.9 years old at the moment of inclusion in the study (OR = 0.71; 95 % CI: 0.57–0.90; 15 studies).

The authors had made a conclusion that, despite the evidence of considerable heterogeneity across the studies, vitamin D supplementation was safe and, overall, reduced the risk of ARI compared with placebo, although the reduction of the risk was small. The protection was associated with the giving of daily doses of 400–1000 IU during the period up to 12 months and age of inclusion in the study of 1.0–15.9 years old. The relevance of these conclusions to COVID-19 is unknown and requires further investigation.

In connection with the high frequency of pneumonia development in COVID-19, the question of the possible role of additional vitamin D intake in reducing the risk of pneumonia deserves a special attention. In a meta-analysis of 8 observational studies [14] in which it had been involved more than 20,000 people, an increased risk of non-hospital pneumonia was found in patients with vitamin D deficiency (< 20 ng/ml: RR = 1.64; 95 % CI: 1.00–2.67) and a significantly lower level of vitamin D in blood serum (by 5.63 ng/ml) in patients with non-hospital pneumonia (95 % CI: 9.11–2.14). For the patients with vitamin D deficiency, the effect was not reliable (RR = 1.37; 95 % 0.81–2.32), but it was most pronounced among the people with severe vitamin D deficiency (RR = 6.65; 95 % 2.58–17.96). Thus, for today, the majority of the existing studies and meta-analyses confirm the positive influence of additional vitamin D consumption in reducing the risk of RTIs, in particular, ARI and pneumonia.

**Vitamin D and COVID-19: data of the clinical trials**

For today, more and more data is accumulated in the literature sources regarding the possible influence of vitamin D on the risk and course of COVID-19 and associated with this hospitalization, mortality, and recovery rates from the disease [14–23].

Thus, in the meta-analysis published by Liu N. and co-authors [14], in which the results of 10 studies with the results of more than 36 thousand people had been analyzed, was demonstrated that vitamin D deficiency or insufficiency is associated with an increased risk of COVID-19 (OR = 1.43, 95 % CI: 1.00–2.05, fixed effect model). Moreover, the patients with COVID-19 had significantly lower serum 25(OH)D levels than those with a negative SARS-CoV-2 test (mean differences (MD) = -0.37, 95 % CI = -0.52 – -0.21), although the authors had noted significant heterogeneity of the samples when analyzing the results.

In a recently published meta-analysis [15] of 318 publications with the analyzing of 14 studies with the involvement of more than 91,000 patients there was assessed the influence of the level of vitamin D on the risk of COVID-19. The results of the analysis had demonstrated that the individuals with vitamin D deficiency were 80 % more likely to be infected with SARS-CoV-2 compared to those with sufficient vitamin D level (RR = 1.80; 95 % CI: 1.72–1.88). The analysis in the groups, depending on the study design, showed that the corresponding indicator in cohort studies was 1.54...
Another recent meta-analysis [16] of 30 studies had analyzed the influence of 25(OH)D levels on the risk of SARS-CoV-2 infection and the severity of COVID-19. The authors had found that serum levels 25(OH)D were significantly lower in patients with SARS-CoV-2 infection than in healthy individuals (MD: -3.99: 95 % CI: -5.34 to -2.64; p < 0.00001). In addition, they were significantly lower in patients with severe course of the disease (MD: -6.88; 95 % CI: -9.74 to -4.03; p < 0.00001) and in those who died of COVID-19 (MD: -8.01; 95 % CI: -12.50 to -3.51; p = 0.0005). The patients with vitamin D deficiency had a higher risk of severe disease course (OR = 4.58; 95 % CI: 2.24-9.35; p < 0.0001), but not a higher risk of death (OR = 4.92; 95 % CI: 0.83-29.31; p = 0.08). Unfortunately, the authors, as in most previous analyzes of the influence of vitamin D on the risk of RTIs, confirm the great heterogeneity of the studies included in the analysis, that are associated with different criteria for the inclusion of patients in the study (age, body mass index, ethnicity, comorbidities, the country where the subjects live, other factors that affect serum level of 25(OH)D and the criteria that were used to confirm the severity of COVID-19). They also note that, unfortunately, it is currently impossible to establish a causal relationship between the level of 25(OH)D and COVID-19, even considering that 25(OH)D is a marker of acute inflammation, so the use of vitamin D can be considered in the primary prevention of the disease and its complex treatment.

For today, the studies and meta-analyses concerning the links between the risk of death from COVID-19 and the status of vitamin D are of particular interest. Thus, a meta-analysis of 24 observational studies that had involved more than 3.5 thousand people [17] confirmed a reliable link between the level of 25(OH)D and the risk of death from COVID-19. A low level of vitamin D in a blood serum was statistically associated with a higher risk of death (RR = 1.60; 95 % CI: 1.10-2.32), a higher risk of the development of severe COVID-19 pneumonia (RR: 1.50; 95 % CI: 1.10-2.05). Another meta-analysis [18] based on the data of one population-based and seven clinical studies confirmed the link of the level of 25(OH)D in the blood on the eve of COVID-19 or on the day of hospitalization with the risk of mortality (r = -0.415, p = 0.077). For the united data, the median (IQR) of 25(OH)D levels was 23.2 ng/ml (17.4-26.8) on condition of a significant correlation (r = -0.40, p = 0.02), at the same time, the theoretical zero level of mortality for the level of 25(OH)D was 50 ng/ml. The authors made a conclusion that low level of D₃ is a predictor, rather than just a side effect of COVID-19 and recommend, despite the vaccination, to increase 25(OH)D level in blood serum to the level above 50 ng/ml to reduce the possibility of recurrent disease that is associated with new mutations of the virus or a decrease of the activity of specific antibodies.

The first pilot randomized study [19] as for the efficacy of calcifediol (25(OH)D₃) in the treatment of patients with COVID-19 was conducted in Spain in 2020. 76 hospitalized patients with COVID-19, that was radiologically confirmed by viral pneumonia and a positive polymerase chain reaction for SARS-CoV-2 received standard complex treatment (within the hospital protocol) a combination of hydroxychloroquine (400 mg every 12 hours during the first day and 200 mg every 12 hours during the next 5 days) with azithromycin (500 mg orally during 5 days) and were divided into 2 groups depending on the additional intake of oral calcifediol (0.532 mg on the day of randomization and 0.266 mg on the 3-rd and 7-th days. Then every week until discharge or hospitalization in the intensive care unit (ICU). The results of the study had demonstrated a significantly lower need for ICU transfer (2 and 50 %, respectively, in the calcifediol or placebo group, p < 0.001, OR: 0.02; 95 % CI: 0.002-0.17). The odds ratio for ICU hospitalization (adjusted for concomitant hypertension and type 2 diabetes) was 0.03 (95 % CI: 0.003-0.25). None of the patients who had received calcifediol died, and everyone was discharged without complications. 50 % of patients who did not receive calcifediol and were not hospitalized in intensive care unit were discharged. Among the remaining 50 % who had been hospitalized to intensive care unit, 15.4 % died and the rest were discharged, and on that basis the authors concluded that high-dose of calcifediol had a positive influence in reducing the need for ICU treatment in patients with COVID-19.

In a recently completed 2-center, double-blind, randomized research [20] that had been conducted in Brazil, Murai I. H. and co-authors studied the influence of a single oral dose of vitamin D₃ (200,000 IU) versus placebo among 240 patients that had been hospitalized because of moderate up to severe course of COVID-19. The average age of the patients (SD) was 56.2 (14.4) years old; 43.9 % of them were women; the initial level of 25(OH)D was 20.9 (9.2) ng/ml. The results of this study have demonstrated that despite a significant increase of 25(OH)D in blood serum after a single dose of vitamin D₃ compared to placebo (44.4 vs. 19.8 ng/ml; difference 24.1 ng/ml; 95 % CI: 19.5-28.7; p < 0.001), the duration of hospitalization because of COVID-19 was not significantly different between the groups (vitamin D₃: 7.0 (95 % CI: 4.0-10.0) days and placebo: 7.0 (95 % CI: 5.0-13.0) days, p = 0.59; unadjusted risk factor for hospital discharge 1.07 (95 % CI: 0.82-1.39; p = 0.62). The authors did not establish probable differences in hospital mortality rates (7.6 vs. 8.1 %, respectively; p = 0.43), admission to the intensive care unit (16.0 vs. 21.2 %; p = 0.30) or the need for artificial lung ventilation (7.6 vs. 14.4 %; p = 0.09). Only one of 120 patients in the group of active treatment had a side effect in the form of vomiting, which was associated with vitamin D₃ intake. The authors made a conclusion regarding the absence of a positive effect of a single administration of a high dose of vitamin D₃ (200,000 IU once) with the aim of improving mortality rates and the duration of hospital treatment in patients with a moderate and severe course of COVID-19 and the lack of expediency of using a high dose of vitamin D₃ for the patients of this category.

One of the most recent meta-analyses about the links between vitamin D supplementation and COVID-19 appeared in October 2021 [22] and had analyzed the results.
of 11 cohorts (involving more than 536,000 people) and 2 RCTs. The authors did not confirm the reliable influence of deficiency (< 20 ng/ml) or insufficiency (< 30 ng/ml) of vitamin D on the increased risk of infection with COVID-19 (for < 20 ng/ml: RR = 1.61, 95 % CI: 0.92–2.80) or hospital mortality (for < 20 ng/ml: RR = 2.18, 95 % CI: 0.91–5.26; for < 30 ng/ml: 3.07, 95 % CI: 0.64–14.78). The increasing of the level of vitamin D in blood serum for each 10 ng/ml was not associated with a significant reduction of the risk of COVID-19 infection (OR = 0.92, 95 % CI: 0.79–1.08) or death (OR = 0.65, 95 % CI: 0.40–1.06). Additional vitamin D supplementation did not reduce mortality indicators (OR = 0.57) or treatment in ICU (OR = 0.14) among the patients with COVID-19. However, the authors note that the overall quality of evidences (graded by the GRADE system) for the risk of COVID-19 and related with it death, depending on additional vitamin D supplementation was very low, that requires a further studying of this question in multicenter, prospective, well-designed studies.

Researches concerning the rates of recovery of the patients after suffering from COVID-19 against the background of additional intake of vitamin D seem to be interesting for today. Thus, in the study of Caballero-García A. and co-authors [23] with the participation of 30 patients of the older age group who had been ill with COVID-19, half of whom additionally took 2000 IU/d of cholecalciferol, a monitoring of biochemical blood parameters was conducted and functional tests of the subjects before the treatment and 6 weeks after of vitamin D intake were evaluated. In the group of patients who additionally had taken vitamin D, a significant decrease in serum levels of creatine kinase (compared to the comparison group) and a tendency for the better results of functional testing against the background of the absence of the differences in other biochemical blood parameters (liver tests, creatinine, inflammatory markers) were established, which, according to the author’s opinion, confirms the fact that additional vitamin D intake reduces the rates of muscle damage during COVID-19, which may improve patients’ health and the quality of life during the recovery process.

**Vitamin D and COVID-19: recommendations of the experts from international societies**

During the last 2 years, the infection of COVID-19 prompted various international societies to develop algorithms, protocols and recommendations for the optimal use of vitamin D for the patients with COVID-19 [24-26].

One of the first protocols for the treatment of critical states when COVID-19 was proposed by the Eastern Virginia Medical School [24] in April 2020, in which it was noted that, in addition to other components of effective prevention and treatment of COVID-19, the additional use of vitamin D is recommended: in case of prevention of COVID-19 — 1000-3000 IU/d, outpatient treatment — 2000-4000 IU/d, inpatient treatment of mild forms of SARS-CoV-2 infection — 20000-60000 IU (single dose) with further appointment of 20000 IU weekly until discharge from the hospital. Over the past 1.5 years, this protocol has been revised several times, but the prescription of vitamin D has remained unchanged.

In July 2021, experts from 6 international medical societies (American Society for Bone and Mineral Research (ASBMR), American Association of Clinical Endocrinologists (AACE), Endocrine Society, European Calcified Tissue Society (ECTS), National Osteoporosis Foundation (NOF) and International Osteoporosis Foundation (IOF)) published consolidated recommendations as for the use of vitamin D during the COVID-19 pandemic [26]. It was noted that up to now, the clinical trials investigating the potential influence of vitamin D in the prevention and treatment of COVID-19 are currently incomplete. Modern data do not provide any evidence that vitamin D supplementation will help to prevent or to treat COVID-19 infection, but these recommendations do not exclude the need for further study of the potential impact of vitamin D on the risk and course of COVID-19. The experts recommend to the most of people over the age of 19 years old to get vitamin D with food and/or with supplements (consumption depends on age and gender) in a dose of 400–1000 IU/day. In addition, they note that existing researches demonstrate that vitamin D may play a certain role in a strengthening of the immune response, that’s why further research as for the possible influence of vitamin D supplementation during COVID-19 is justified.

In May 2021, a Cochrane expert opinion about vitamin D and COVID-19 [27] was published, which concluded that, at the time of the review, there were insufficient high-quality evidences to assess whether vitamin D is an effective and safe way of treatment for the adults with COVID-19. Some studies demonstrate that the individuals who are hospitalized to the medical institutions for the hospital treatment with severe COVID-19 also have low level of vitamin D (deficiency), but the risk factors for severe COVID-19 are the same as those for the development of vitamin D deficiency, therefore, it is difficult to assess whether vitamin D deficiency alone is a risk factor for severe COVID-19. The experts note that 21 studies on this issue are currently going, after receiving the results of which, their conclusion will be updated.

**Vitamin D: what to choose?**

The group of vitamin D and its metabolites/analogos is currently presented in the form of cholecalciferol (D<sub>3</sub>), ergocalciferol (D<sub>2</sub>), calcifediol (25(OH)D), calcitriol (active hormonal form of vitamin D), alphacalcidol (1α-hydroxyvitamin D<sub>3</sub>), requires 25 -hydroxylation to obtain the active hormonal form of vitamin D<sub>3</sub>, doxercalciferol (vitamin D<sub>2</sub>, transformed into the active hormonal form after 25-hydroxylation with a lower calcemic effect than calcitriol), paricalcitol (an analogue of vitamin D<sub>3</sub> that does not require the activation, with a limited calcemic effect), 22-oxacalcitriol (an analogue of vitamin D<sub>3</sub> with a limited calcemic effect). Some of them are presented in the form of medicines (calcidiol, calcitriol, alfalcaldiol), others — in the form of dietary supplements, although not all of them are available in Ukraine. Dietary supplements of vitamin D are used to correct its deficiency and insufficiency,
while metabolites/analogues of vitamin D (in the form of medicines) are used for the patients with severe renal impairment (chronic renal failure of stage 4-5, in patients that are on hemodialysis or after kidney transplantation).

The questions often arise, which types of release forms (fat- or water-soluble forms, capsules, tablets, drops) of vitamin D are more suitable for the use in clinical practice?

It is well known that the assimilation of fats and fat-soluble vitamins, which, in particular, includes vitamin D, occurs in the gastrointestinal tract with the participation of bile acids and enzymes (in particular, lipase). Up to 30% of fats are broken down in the stomach mechanically and by emulsification with the participation of gastric lipase, about 70% – at the level of the duodenum due to the creation of micelles with the help of pancreatic lipase and bile acids. In persons with physiological digestion and normal bile secretion, micellization of fats and fat-soluble vitamins occurs in sufficient volume. Other strategies for the absorption of fats and fat-soluble vitamins are needed in the case of gastrointestinal tract pathology (impaired liver, gall bladder, and pancreas function), among which nanotechnologies (additional micellization or addition of disintegrants, in particular, crosarmellose) [28, 29] have been increasingly implemented in recent years.

Different oral dosage forms (tablets, capsules, and oral solutions) are known to have different rates of absorption, and the rate of oral absorption of conventional vitamin D₃ is approximately 50% of the dose that enters to the body. With the use of nanotechnology or disintegrants, it is currently possible to increase significantly the bioavailability of the agents, that are administered, in particular, vitamin D₃.

A comparative assessment of the bioavailability of vitamin D in capsules and oil solution (drops) was carried out in a cross-sectional open randomized study among 18 nuns at the age from 20 up to 75 years (who are living in a closed group with a low level of solar insolation). The concentration of 25(OH)D in blood serum was determined before the randomization procedure and after 4, 8, 12 and 24 hours and 90 days after taking capsules or drops (the dose of vitamin D₃ was 66,000 IU). The indicators of the maximal concentration (Cmax) of vitamin D in the blood and the area under the curve (AUC) were evaluated. The authors have demonstrated that the overall bioequivalence indicators did not differ when using both forms, however, under the conditions of using the capsule form of vitamin D, the Cmax and AUC indicators (0-24 hours) were 5.78 and 0.76%, respectively, than when using an oil solution in drops [30].

In an open-label randomized study conducted by Krishnakumar M. Nandgaye and co-authors [31] with the participation of 70 people, the authors compared the relative bioavailability of vitamin D₃ for oral intake in solution with the use of nanotechnology, tablets or capsules with a one-time administration of 60,000 IU by evaluating of Cmax, AUC (0-28 days) and Tmax indicators. The authors confirmed the bioequivalence of all three forms of vitamin D₃, although when using an oral solution using nanotechnology, the Cmax and AUC indicators were higher compared to the indicators when using tablets or capsules, which proves the possibility and feasibility of the using of different forms of vitamin D under the conditions of accordance with the technological standards of the production. Among this, compliance issues are extremely important in these conditions, which are determined by patient/consumer convenience and more infrequent dosing regimens (on daily or weekly basis).

Conclusions

Thus, for today, the data from modern literary sources demonstrate extraskeletal influences of vitamin D, in particular, on the functioning of congenital and acquired immunity (influence on chemotaxis/phagocytosis of monocytes and macrophages, synthesis of antimicrobial peptides, expression of TLR molecules, MHC, synthesis of interleukins and cyclooxygenase, differentiation of T – and B-lymphocytes, etc.). Despite the conflicting data as for the positive influences of vitamin D on the risk of URTIs in general and on COVID-19 in particular, the majority of conducted clinical studies and meta-analyses confirm the presence of this positive effect despite the heterogeneity of the studied populations, the doses and forms of vitamin D administration. Modern studies demonstrate the same bioequivalence of different forms of vitamin D (capsules, drops, tablets) under the conditions of their quality production and the need to correct the deficiency and insufficiency of vitamin D in order to prevent URTIs in general and COVID-19 disease in particular.

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Вітамін D і COVID-19: наскільки тісний зв’язок?
(Аналітичний огляд літератури)

Резюме. Аналітичний огляд містить аналіз сучасних літературних джерел щодо можливого впливу вітаміну D на функціонування імунної системи (ланок вродженого й набутого імунітету), а також його впливу на ризик інфекційних захворювань верхніх дихальних шляхів (ІВДШ) і COVID-19. Проаналізовано доступні дані кінічних досліджень, оцінені в сучасних метааналізах, щодо впливу вітаміну D на ризик і перебіг COVID-19 і пов’язані з ним показники госпіталізації, смертності й темпів одужання від недуги. Незважаючи на суперечливі дані щодо позитивних впливів вітаміну D на ризик ІВДШ загалом і COVID-19 зокрема, більшість проведених клінічних досліджень і метааналізів констатують наявність цього позитивного ефекту, вказуючи на невелику обмеженість, пов’язану з неоднорідністю досліджуваних популляцій, форм введення вітаміну D тощо. Сучасні дослідження демонструють однакову біоеквівалентність різних форм вітаміну D (капсули, краплі, таблетки) за умови їх правильного вживання, виходячи з індивідуальних потреб, а також складності розуміння і невизначеності рівня дефіциту вітаміну D у популяції.

Ключові слова: вітамін D; імунна система; COVID-19; гострі респіраторні інфекції; пневмонія; клінічні дослідження; метааналіз; огляд

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