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REVIEW ARTICLE

VITAMIN D IN SARS-COV-2 INFECTION

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ABSTRACT

Background. SARS-CoV-2 virus is one of the largest RNA viruses, included in the coronavirus group, showing tropism to airway epithelial cells. SARS-CoV-2 causes an acute respiratory infectious disease, Covid-19. According to WHO reports, mortality due to Covid-19 is higher in the elderly and in those burdened with comorbidities such as diabetes, obstructive pulmonary disease, coronary artery disease, cancer, hypertension, hepatitis B, obesity or chronic kidney disease.

Objective. The aim of the study was to review the current literature on the influence and importance of vitamin D levels on the course of SARS-CoV-2 infection.

Material and method. A systematic review of studies published from January 1, 2009 to June 31, 2021 has been performed. For this purpose, bibliographic databases such as PubMed and Scopus were searched. The following keywords and combinations were used: Covid-19, vitamin D, 25-hydroxy-vitamin D, vitamin D supplementation, SARS-CoV-2.

Results. It has been shown that vitamin D plays an important role in the mechanisms of the innate immunity in the course of the acute respiratory infections. The overlapping factors of the severity of COVID-19 disease, vitamin D deficiency, and the prevalence of obesity, age scare, ethnicity, has led some researchers to hypothesize that vitamin D supplementation may be promising as a preventive or therapeutic measure for COVID-19.

Conclusions. A very important factor that has an immunomodulatory character is vitamin D, the adequate supplementation of which can be a preventive or therapeutic measure in case of SARS-CoV-2 infection, especially in elderly people, with obesity and other chronic diseases.

Key words: *Covid-19, SARS-CoV-2, vitamin D3, supplementation*

STRESZCZENIE

Wstęp. Wirus SARS-CoV-2 to jeden z największych wirusów RNA, zaliczany do grupy koronawirusów, wykazujący tropizm do komórek nabłonka dróg oddechowych. SARS-CoV-2 powoduje ostrą chorobę zakaźną układu oddechowego, Covid-19. Według doniesień WHO śmiertelność z powodu Covid-19 jest wyższa u osób starszych i obciążonych chorobami współistniejącymi, takimi jak cukrzyca, obturacyjna choroba płuc, choroba wieńcowa, nowotwory, nadciśnienie, zapalenie wątroby typu B, otyłość czy przewlekła choroba nerek.

Cel. Celem pracy był przegląd aktualnej literatury dotyczącej wpływu i znaczenia poziomu witaminy D na przebieg zakażenia SARS-CoV-2

Materiał i metody. Przeprowadzono systematyczny przegląd badań opublikowanych od 1 stycznia 2009 r. do 31 czerwca 2021 r. W tym celu przeszukano bazy bibliograficzne, takie jak baza PubMed i baza Scopus firmy Elsevier. Zastosowano następujące słowa kluczowe i kombinacje: Covid-19, witamina D, 25-hydroksy-witamina D, suplementacja witaminą D, SARS-CoV-2.

Wyniki. Wykazano, że witamina D odgrywa ważną rolę w mechanizmach odporności wrodzonej w przebiegu ostrych infekcji dróg oddechowych. Nakładanie się czynników ciężkiego przebiegu choroby COVID-19, niedoboru witaminy D oraz występowania otyłości, straszy wiek, pochodzenie etniczne, doprowadził niektórych badaczy do hipotezy, że suplementacja witaminy D może być obiecująca jako środek zapobiegawczy lub terapeutyczny w przypadku COVID-19.

Wnioski. Bardzo ważnym czynnikiem o charakterze immunomodulującym jest witamina D, której odpowiednia suplementacja może być środkiem zapobiegawczym lub terapeutycznym w przypadku zakażenia SARS-CoV-2, zwłaszcza u osób starszych, z otyłością i innymi chorobami przewlekłymi.

Słowa kluczowe: *Covid-19, SARS-CoV-2, witamina D3, suplementacja*

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INTRODUCTION

SARS-CoV-2 virus is included in the coronavirus group, showing tropism to airway epithelial cells. SARS-CoV-2 causes the acute respiratory infectious disease - Covid-19. The first case of the disease was diagnosed in December 2019 in Wuhan, China. On 11 March 2020, the World Health Organization declared a Covid-19 pandemic, recognising that it is a seriously life-threatening disease to public health with international reach [26]. Penetration of the virus occurs through the receptor, which is located in the nasal mucosa, while the average incubation time is 5 days, but can reach up to 14 days. Most often, the course of the disease is asymptomatic or with slight fever, cough and dyspnoea [49]. In the advanced form, interstitial inflammatory lesions in the lungs appear, while severe forms develop acute respiratory failure, which progresses to multiple organ failure and eventually death of the patient. According to WHO reports, higher mortality rates have been reported in the elderly and those diagnosed with comorbidities such as diabetes, obstructive pulmonary disease, coronary artery disease, cancer, hypertension, hepatitis B, obesity, and chronic kidney disease [21]. Therefore, there is a need to implement a rapid, accessible and effective therapy to limit the spread of the virus and save lives. More and more studies and static studies are emerging that present the clinical course of this disease. In many countries around the world, preventive measures are being taken to limit the number and rapid growth of cases, so that the health care system remains viable. Great hopes are placed in the natural defence mechanisms of our organism, and their effectiveness depends on ourselves. Therefore, many scientists in the world are studying the influence of various factors that may significantly affect the body's response to the SARS-CoV-2 infection, with the aim of preventing or reducing its effects [22]. Vitamin D has been shown to play an important role in the mechanisms of innate immunity in the course of acute respiratory infections. Supplementation with this vitamin has also been shown to reduce the risk of respiratory infection [3].

The aim of this study was to review the current literature on the influencet and importance of vitamin D in the course of the SARS-CoV-2 infection.

VITAMIN D METABOLISM

Vitamin D, along with vitamins A, E, K is classified as a fat-soluble vitamin, now called a prohormone. One of the most important known functions of vitamin D is its role in calcium phosphate metabolism and thus in bone growth and mineralisation processes [15]. In the human body, provitamin D3, under the influence of solar UVB radiation is converted to previtamin D3, then isomerised to vitamin D3 under the influence of heat. The vitamin, which is formed in the deeper layers of the epidermis, which are close to blood and lymph vessels, is completely bound by DBP, a protein that is characterised by its high capacity and strength to bind vitamin D [13]. When the skin is overexposed to UV radiation, there is no intoxication with this vitamin, as the biologically inactive compounds lumisterol and tachysterol are formed. These biologically inactive photoproducts lack DBP's ability to bind them and are therefore systematically removed from the body with exfoliating epidermis [33]. In foods, vitamin D is found in two forms: vitamin D2 called ergocalciferol and D3 called cholecalciferol. Vitamin D2 is found in plants and mushrooms, while D3 is synthesised by animal organisms [47].

The exogenous and endogenous form of vitamin D is inactive in the human body and requires two steps of hydroxylation to convert it into a biologically active form. The first step takes place by 25-hydroxylase in a liver to produce 25-hydroxyvitamin D (calcidiol), which is a substance of moderate biological activity that is the main form of vitamin D in the bloodstream. The second step occurs among others in the kidney with the participation of 1-α-hycroxidase and leads to the formation of the active metabolite 1,25-dihydroxyvitamin D (calcitriol), which is widely considered as the most active form of vitamin D [8].

SOURCES OF VITAMIN D

Vitamin D occurs naturally in a small number of dietary products and it is estimated that 10-20% of the daily requirement comes from the diet. Vitamin D2 is supplied to the body only by eating products of plant origin and mushrooms (oyster mushroom, champignon, shitake mushroom). Sources of vitamin D3 in products of animal origin are fatty fish, eggs, milk and dairy products [5, 29]. A significant part of vitamin D3 found in the body (about 80%) comes from dermal synthesis. It has been shown that under Polish conditions, exposure on a sunny day, a minimum of 18% of the body surface from 10 AM to 15 PM for 15-20 minutes, results in adequate synthesis of vitamin D, without the use of sunscreens. Factors that reduce vitamin D synthesis up to 80% include: increased melatonin, use of UV filter creams, body weight, age, and skin pigmentation [25]. In Poland, there is a limited possibility to obtain the recommended serum 25OHD concentration through dermal synthesis due to its geographical location [24].

DETERMINATION OF VITAMIN D SERUM CONCENTRATION

Vitamin D deficiency is assessed by determination of plasma concentrations of the main circulating metabolite 25-hydroxycholecalciferol, which will reflect the actual state of the body's supply of this vitamin. However, in order to provide the best assessment of the metabolism occurring in the body, it is also advisable to determine 1,25-dihydroxycholecalciferol, which will allow tracing the activity of 1-alpha-hydroxylase in the kidney and the production of active metabolites [36].

Many studies conducted in Poland and worldwide have shown that vitamin D deficiency is an increasingly common health problem for people living at higher latitudes, in all age groups. The main reasons for this condition are: staying most of the day indoors, diet poor in the aforementioned vitamin, not using supplementation and low active lifestyle [28]. The requirement for vitamin D should be considered in close relation to its concentration in the blood, by determining the blood metabolite 25-hydroxycholecalciferol. Despite the heterogeneous terminology and ongoing discussion about this concentration, currently most experts around the world adopt the following classification: optimal concentration 30-50 ng/ml, suboptimal 20-30 ng/ml, deficiency 10-20 ng/ml and severe deficiency 0-10 ng/ml [25].

According to the nutrition standards for the Polish population developed at the adequate intake (AI) level, the vitamin D intake for all population groups is 15 μg cholecalciferol/person/day, except for newborns for whom AI =10 μg [25].

Since 2013, Guidelines for vitamin D supplementation for Central Europe have been in force in Poland, where the indications for determination of vitamin D serum levels, the principles of supplementation and treatment of vitamin D deficiency are included [43].

BODY FUNCTIONS

Vitamin D plays an important role in maintaining calcium phosphate metabolism, but also has an important function in insulin secretion when conditions of increased demand for this hormone occur in the body, which is linked to the presence of the VDR (vitamin D receptor) also in the beta cells of the pancreas. Vitamin D deficiency may adversely affect insulin secretion and glucose tolerance in people with type 2 diabetes [49]. Vitamin D is also important for the normal development of nervous system tissue, as its metabolite 1,25(OH)2 D3 is produced locally in brain tissue and its receptors are found in the cerebellum, brainstem, hippocampus, forebrain, spinal cord, perivascular tissue, among others [46]. Vitamin D also exhibits anticancer effects by inhibiting excessive cell proliferation, stimulating apoptosis and cell differentiation, as well as regulating mRNA expression and modelling signalling pathways to inhibit inflammatory processes [1]. The anti-cancerogenic effect of vitamin D is also supported by the expression of 1α-hydroxylase in many extraskeletal tissues, as well as reduced synthesis of this enzyme in the course of various cancers, resulting in reduced calcitriol concentrations. The immunomodulatory properties of vitamin D in the prevention and treatment of autoimmune diseases, such as type 1 diabetes, inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, vitiligo or multiple sclerosis, are increasingly being highlighted [29]. Vitamin D by regulating the expression of specific neurotrophins can stimulate neuronal growth. Another important function is to influence the maintenance of the normal epidermal barrier, by regulating calcium concentration, keratin gene expression, promoting their differentiation into corneocytes [23].

The result of calcium deficiency in the body is elevated parathormone levels, which will be an exponent of low vitamin D concentrations. Parathormone increases the production of calcitriol in the intestines and kidneys, which has a negative impact on the cardiovascular system and causes endothelial dysfunction, increased aortic stiffness, aortic valve calcification, the development of hypertension and dyslipidaemia. It has been shown that higher parathormone levels increase the risk of death from cardiovascular disease [20].

In a review by *Stefanowski* et al [45] it was shown that there is a lot of literature available showing the effect of vitamin D deficiency on the occurrence of depression and the severity of depressive symptoms.

INFECTIONS VERSUS VITAMIN D

In addition to the effects of vitamin D on bone metabolism and calcium balance, vitamin D has been shown to model the response of macrophages and monocytes against bacteria, viruses and microorganisms. In cases of visceral disease, inflammatory bowel disease, or pancreatic and liver diseases there are disorders of vitamin D absorption and metabolism leading to vitamin D deficiency in the body [29].

Several scientific publications have shown that vitamin D plays an important role in the body's innate response [44]. Through metabolism in the kidney and liver, the active Vitamin D metabolite - dihydroxycholecalciferol (1,25(OH)2D) interacts with numerous tissues through the VDR receptor.

It has been detected on monocytes, dendritic cells, macrophages, NK cells (natural killer cells – NK), T and B lymphocytes [39]. VDR activation results in the production of cytokines that inhibit the activation of the T helper cells (Th), while stimulating the activation of the regulatory T cells (Treg). The active metabolite of vitamin D also causes changes in dendritic cells, where an acceleration of their maturation, differentiation and migration is observed [15]. The role these cells play in stimulating lymphocytes and in the early detection of microorganisms indicates that an adequate supply of vitamin D may influence the speed of the immune response after contact with a foreign antigen. Vitamin D, by enhancing the phagocytic activity of macrophages and stimulating NK cells, has a direct effect on the body's ability to destroy microorganisms. In viral infections, lung epithelial cells convert inactive vitamin D into its active form, thus stimulating the production of the antimicrobial peptide, helping to fight the ongoing infection [10].

In a study conducted by *Ginde* [19], among 18,883 people aged over 12 years old, a correlation was found between vitamin D levels and the occurrence of upper respiratory tract infections. It was shown that serum vitamin D concentrations were inversely related to the occurrence of these infections. This relationship was even higher in patients with respiratory diseases (asthma and chronic obstructive pulmonary disease). It has been concluded that vitamin D supplementation can reduce the prevalence of upper respiratory tract infections and also reduce the severity of respiratory diseases. A study conducted in 2010, among 198 people, found that levels of this vitamin D≥38 ng/ml were associated with twice the frequency of the occurrence of the upper respiratory tract infections and also a shorter duration of infection [25]. Other researchers have assessed the effects of vitamin D on lung function in 10,000 Korean adults. The authors showed a positive correlation between lung function and 25 (OH) D concentration with regard to age, sex, height and season, and it was higher in patients with a history of tuberculosis [9].

VITAMIN D VERSUS COVID-19

The new disease entity Covid-19 is caused by SARS-CoV-2, which is responsible for severe acute respiratory distress syndrome. In the majority of cases infected with Covid-19, the disease is mild and there are no complications afterwards. In approximately 14% of all patients, the course of Covid-19 requires hospitalisation, oxygen therapy and has a severe nature, while 5% of patients require admission to an intensive care unit [48]. If the course of the disease is severe, complications may arise in the form of acute respiratory distress syndrome (ARDS), sepsis and septic shock, multi-organ failure including heart and kidney failure [52].

Given the dangerous course of Covid-19 infection, particularly among patients with coexisting respiratory, cardiovascular and diabetic diseases, there is a need for a vaccine to prevent infection, but also for therapeutic steps to help reduce the risk of contracting the disease and also to reduce the symptoms of an already existing infection [4, 32]. A very important factor that is immunomodulatory in nature is vitamin D, the adequate supplementation of which can be a preventive or therapeutic measure for SARS-CoV-2 infection, especially among the elderly, those with obesity and other chronic diseases [30]. Since the outbreak of the pandemic, many studies have been published that have investigated the association between vitamin D and Covid-19. These have been mostly observational, cross-sectional, retrospective and prospective cohort studies and randomised control trials [50].

A study by *Faniyi* et al [16] at the end of the first wave of the epidemic (n=392) among staff at NHS University Hospitals Birmingham showed that of the Covid -19 positive staff (55%), 15.6% (n=16) were vitamin D deficient. It was also shown that there were significantly lower levels of this compound among those from BAME groups (Black, Asian and Minority Ethnic), men and those with a higher BMI. Similar results were obtained in a study by *Maghboola* et al [31] conducted at Boston University School of Medicine, where vitamin D levels were measured in 235 patients hospitalised for coronavirus infection. They found that patients who had at least 30 ng/mL of 25-hydroxyvitamin D were significantly less likely to experience severe illness, including unconsciousness and hypoxia. A lower mortality rate was also achieved in this group. Patients with sufficient vitamin D levels had significantly lower blood levels of the inflammatory marker CRP and had a higher total blood lymphocyte number, suggesting that adequate vitamin D improved their immune function. Another small study of 107 patients in Switzerland also found that serum vitamin D levels were lower among patients with positive Covid-19 [11].

A review of recent findings by *Rhodes* et al [42] indicates that there is a lot of literature available demonstrating a beneficial effect of vitamin D on the course of Covid -19 infection. Vitamin D deficiency has been shown to be more prevalent in obese individuals, those with type 2 diabetes, hypertension, and most among ethnic minorities in Europe and North America - where darker skin pigmentation reduces skin synthesis, resulting in up to eight times higher prevalence of vitamin D deficiency. Greater vitamin D deficiency is observed, also among people placed in institutions, including prisoners and those

in nursing homes. These results may suggest that UV radiation, and thus indirectly vitamin D, may be beneficial in reducing the prevalence of Covid-19. However, it should be noted that UV exposure also has a number of vitamin D-independent mechanisms such as a reduction in the number and activity of dendritic cells and macrophages which translates into impaired activation of T lymphocytes in the skin [6]. A survey of Italian patients (n=1486) diagnosed with *Parkinson's* disease showed that those taking vitamin D were less likely to have Covid-19 [17].

Another study conducted at Wuhan Hospital found that the prevalence of vitamin D deficiency was higher among Covid-19 patients (n=335), compared to a control group (n=560) studied in 2018-2019 (65.1% vs 40.7%; p <0.0001). In a linear regression analysis, age was directly associated with length of hospital stay, whereas serum 25(OH)D concentrations, gender, comorbidities, BMI or smoking were not associated with duration of hospitalisation. Serum 25(OH)D concentrations were significantly lower in the group of patients with severe Covid-19 symptoms than in the group with a mild course [30].

A study of 7807 patients in Israel found that suboptimal serum vitamin D levels may be a potential risk factor for Covid-19 infection, at high risk of hospitalisation, regardless of demographic characteristics and medical conditions [35]. A US observational study based on test data from Quest Diagnostics is the largest observational study to date, involving 191,779 patients aged 40-65 years found that higher incidence of Covid-19 was among patients with vitamin D deficiency (<20 ng/ml) than patients with optimal levels (30-34 ng / ml) and patients with values ≥ 55 ng / ml [27].

Low serum vitamin D concentrations are associated with hypocalcaemia. This condition has been frequently described in the course of other epidemics [51], as well as in 80% of Italians who were hospitalised for SARS-CoV-2 infection [14]. The causal relationship between serum vitamin D concentrations and the risk of SARS-CoV-2 infection and the severity of Covid-19 has not been definitively established. Age as well as comorbidities may play a greater role than vitamin D levels in fatal cases of Covid-19. In the long term, low vitamin D levels may be the determinant of the patient's comorbid condition and therefore a more or less direct determinant of Covid-19 severity [7].

Exposure to sunlight is one of the factors that is involved in endogenous biosynthesis of the vitamin D. The few published studies, which mainly refer to the first wave of the pandemic, describe a significant association between disease outbreak and latitude [42]. From an analysis, over 108 days, in 152 countries, *Moozhipurath* et al [37] found that a sustained unit increase in ultraviolet index was associated with a 1.2% decrease in the daily rate of increase in cumulative deaths from Covid-19 and a 1.0% decrease in the daily case fatality rate. A recent paper whose authors considered both the first and second waves of the pandemic (1 March to 30 April 2020 and 1 October to 30 November 2020, respectively), an analysis based on 40996 25(OH)D determinations, found no direct association between serum vitamin D levels, presumed UV dose and risk of SARS-CoV-2 infection [18].

During the pandemic, the recommendations regarding vitamin D supplementation in Poland have not changed. The key question is whether short-term vitamin D supplementation can be tested and also be a test for disease risk. In studies in people with a positive SARS-CoV-2 test result and vitamin D deficiency (25(OH)D ng/ml), a follow-up response to the result (60,000 biliary response or placebo for 7 days, no to the number of participants, including tests over 21 days [40].

Achieving adequate serum vitamin D concentrations in the population is a good clinical practice in preventing the adverse effects of vitamin D deficiency, which may also affect the course of Covid-19. Currently, there are no reliable intervention data available on vitamin D supplementation among patients hospitalized for COVID-19 [34]. There are also studies in which it has been shown that vitamin D supplementation did not improve the clinical outcomes of the studied patients [38].

CONCLUSIONS

The outbreak of the Covid-19 pandemic has created a global public health crisis and therefore preventive health measures are urgently needed that can reduce the risk of infection, progression and severity of this disease. Numerous studies have shown that vitamin D is an immunomodulatory hormone with proven efficacy in acute respiratory infections. Supplementation with this vitamin influences the immune system, and recent studies may suggest that a deficiency of this vitamin may have a significant impact on the course of Covid-19. In addition, attention is drawn to the fact that factors associated with higher mortality from Covid-19 (age, ethical background, obesity diabetes, hypertension) overlap with the risk of vitamin D deficiency. Vitamin D deficiency in the blood may impair immune function but, may also have a negative influence on Covid-19 treatment.

Although there is currently insufficient evidence to recommend vitamin D supplementation to reduce the risk of Covid-19, it is advisable to maintain concentrations of vitamin D in the blood at optimal levels. Further intervention studies are needed to confirm the hypothesis that vitamin D supplementation

may be helpful in the prevention and treatment of Covid-19.

Author contributions

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. All authors provided substantial contribution to the design and implementation of this study and to the generation of the manuscript. The contributions of each author are as follows: *A. Decyk* conceived the design and purpose of the work. *A. Decyk, M. Kobylińska, K. Antosik, K. Kurowska* analyzed the data and interpreted the results based on the available literature. *M. Kobylińska and A. Decyk* drafted the manuscript. *A. Decyk, M. Kobylińska, K. Antosik and K. Kurowska* provided critical revisions and final approval of the version submitted.

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