REVIEW ARTICLE

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Role of vitamin D3 in selected pulmonary diseases with particular emphasis on lung fibrosis

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Abstract

Introduction and Objective. For many years vitamin D3 was known only as a regulator of the calcium-phosphate and water-electrolyte balances. Recent studies have paid special attention to other biological effects of calcitriol (the bioactive form of vitamin D3) with particular emphasis on its influence on immune function. Thus, any alterations, especially deficiencies, in the physiological level of calcitriol have serious health consequences. The aim of the study was to summarise the current state of knowledge concerning the role of vitamin D3 in selected pulmonary diseases.

Review methods. The review was based on data obtained from articles published in PubMed between 2000–2022. Papers were reviewed for scientific merit and relevance.

Brief description of the state of knowledge. In the reviewed literature, much attention was paid to clinical studies focused on the role of vitamin D3 in the pathogenesis of selected respiratory diseases. As revealed in research over the last two decades, vitamin D3 deficiency increases the risk and worsens the course of asthma, cystic fibrosis, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, as well as COVID-19. Surprisingly, vitamin D supplementation has not always proved to be an effective therapeutic strategy. The review also presents the unique concept of the possibility of using vitamin D3 in the prevention and treatment of pulmonary fibrosis in the course of hypersensitivity pneumonitis.

Conclusions. Due to the multiplicity and variety of factors that affect the metabolism of vitamin D3, effective counteracting, and even more eliminating the negative consequences of disorders in the level and activity of calcitriol in the respiratory tract, seems to be a breakneck action. On the other hand, only a deep understanding of the role of calcitriol in the pathogenesis of lung diseases provides the chance to develop an effective therapy.

Key words

calcidiol, calcitriol, asthma, cystic fibrosis, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, sarcoidosis, COVID-19, hypersensitivity pneumonitis

INTRODUCTION

The colloquial term 'vitamin D' refers to vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). Vitamin D2 is present in plants and mushrooms, whereas vitamin D3 is characteristic of animals, which endogenously synthesize it following skin exposure to ultraviolet B (UVB) radiation [1]. Furthermore, animals can supplement vitamin D with food, and depending on their origin (plant, animal), they are supplied with ergocalciferol or cholecalciferol, respectively. Both the ergocalciferol and cholecalciferol forms are fat-soluble secosteroid prohormones that differ by the presence of a double bond and a methyl group (Fig. 1) [2]. Both forms of vitamin D need further enzymatic conversion to their active forms, a process identical in both cases, despite the indicated differences in the chemical structure of mentioned compounds [3].

The major natural source of vitamin D3 is its synthesis in the skin in response to the sun. During sun exposure, 7-dehydrocholesterol absorbs ultraviolet B radiation, producing previtamin D3. This unstable steroid undergoes non-enzymatic conversion into cholecalciferol in the lower layers of the skin. Afterward, vitamin D3 is transported to the adipose tissue for storage or to the liver for activation. In liver cells, 25(OH)-vitamin D3 (calcidiol) is generated with the help of several cytochrome P450 enzymes. Calcidiol, with a

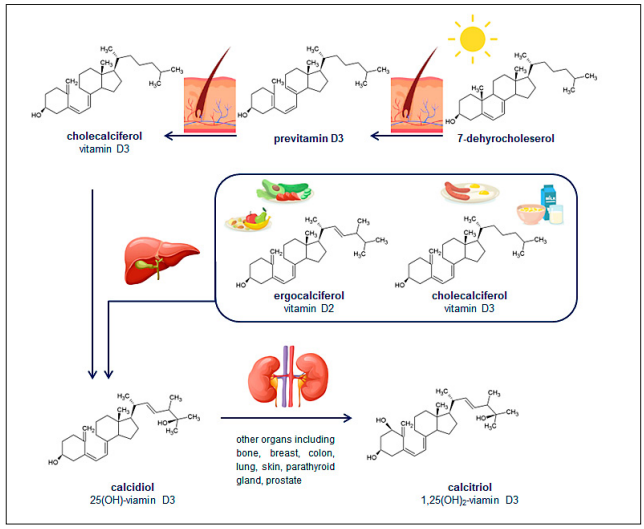

Figure 1. The synthesis of biologically active form of vitamin D3 (calcitriol)

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half-life of 2–3 weeks, is the major circulating form of vitamin D3 in the human body and its concentration in serum has been used to determine vitamin D3 levels. The 25(OH)-vitamin D3 undergoes an additional transformation in the kidneys with the use of another cytochrome P450 enzyme (CYP27B1). The calcidiol is hydroxylated to its biologically-active form – 1,25$(OH)_2$-vitamin D3 (calcitriol), with a half-life of 4–6 h [3]. The same calcidiol to calcitriol transformation also occurs in extrarenal sites, including bone, breast, colon, immune system, lung, skin, prostate or parathyroid gland [4]. Nevertheless, extrarenal CYP27B1 activity is highly substrate dependent, thus the local production of calcitriol is limited when the serum concentration of calcidiol is below 25 ng/ml [5]. It needs to be highlighted that cholecalciferol derived from food undergoes the same transformations as vitamin D3 synthesized in the skin, finally creating calcitriol [3]. The simplified calcitriol synthesis scheme is provided in Figure 1.

Despite two independent ways of obtaining vitamin D3 by the human body (endogenous synthesis accounts for 80% of the resources, while 20% of vitamin D3 is assumed with diet) [6], its deficiency is a global health issue that afflicts more than one billion children and adults worldwide. Several factors can affect vitamin D levels in a population and in individuals, of particular importance are sunlight exposure and modulators of this (clothing, sunscreen usage, time of exposure), dietary and lifestyle [7]. Therefore, the norms defining the physiological and pathological concentrations of vitamin D3, as well as recommendations for its supplementation, may be slightly different in individual countries. A Polish cross-sectional study conducted by Rusińska et al. revealed vitamin D3 deficiency in 90% of adults with a concentration of 25(OH)-vitamin D3 below 30 ng/ml [8]. Furthermore, the above-mentioned report determines the norms of the organism's vitamin D3 requirements (Table 1) as well as provided recommendations for daily vitamin D3 supplementation according to age (Table 2) [8].

The actions of the vitamin D3 hormone (calcitriol) are mediated by the vitamin D receptor (VDR), a ligand-activated transcription factor. Activation of the VDR through direct interaction with 1,25$(OH)_2$-vitamin D3 prompts the receptor's rapid binding to regulatory regions of target genes [9]. According to the latest research, calcitriol can control over 200 different genes including this responsible for cell growth, proliferation and differentiation; bone metabolism and remodelling; energy metabolism; as well as immune response. VDR presence has been proven in almost every nucleated cell in our body, which explains the pleiotropic action of calcitriol [10, 11]. Because vitamin D3 acts through VDR, changes in this molecule e.g., as a result of polymorphisms occurring in the *VDR* gene, may have a key influence on the vitamin D concentration in the circulation, and the final biological activity. The most common single nucleotide polymorphisms (SNP) in the gene *VDR* are Apa-1 (rs7975232), Bsm-1 (rs1544410), Fok-1 (rs2228570), and Taq-1 (rs731236) [12, 13].

Next to VDR, the correct function of vitamin D3 is applied via proper transport in circulation by vitamin D-binding protein (VDBP), which is often called group-specific component (GC) protein, or GC-globulin. Gene *VDBP*/*GC* is well known for its single nucleotide polymorphisms and three of its allelic variants, namely GC1F, GC1S, and GC2 (denoted as rs4588 and rs7041) are crucial for the biological activity of coding protein [14]. Al-Daghri et al. study revealed that the basic serum level of 25(OH)-vitamin D3 is higher among people with the major homozygous rs7041 genotype, while after supplementation calcidiol concentration is higher in people carrying major homozygous rs4588 and rs7041 genotypes [15].

For many years vitamin D3 was known only as a regulator of the calcium-phosphate and water-electrolyte balances. Recent studies have paid special attention to other biological effects of calcitriol with particular emphasis on its influence on innate and adaptive immune function, which are the key to understanding the role of vitamin D3 in the development of many disorders, including lung diseases [16]. Therefore, before the presentation of the role of vitamin D3 in particular lung disease, its immunomodulatory properties are described in the light of the function of the respiratory system.

Table 1. Diagnostic cut-offs of concentrations of vitamin D3 in human serum

Vitamin D3 status	Concentration of 25(OH)-vitamin D3 [ng/ml]	Concentration of 25(OH)-vitamin D3 [nmol/l]
Overdose	≥150	≥375
Optimal	30–50	75–125
Insufficiency	20–30	50–75
Deficiency	10–20	25–50
Severe deficiency	<10	<25

Source: based on data presented in the paper by Rusińska et al. [6]

Table 2. Recommended daily dose of vitamin D3 according to age group in the Polish population

Age group	Dose [IU/day]
Neonates born at term and infants (0–6 months)	400
Infants (6–12 months)	400–600
Children (1–10 years)	600–1000
Adolescents (11–18 years)	800–2000
Adults (19–75 years)	800–2000
Seniors (>75 years)	2000–4000

Source: based on data presented in the paper by Rusińska et al. [6

IMMUNOMODULATORY FUNCTION OF VITAMIN D3 IN THE RESPIRATORY SYSTEM

There are growing evidences showing the immunomodulatory properties of vitamin D3, which next to the direct impact on the immune cells, also regulate the inflammatory response as well as the production of immune peptides [17, 18]. As mentioned before, calcitriol biological activity appears after binding to the receptor VDR. Its presence has been proven in almost every nucleated cell in the human body, including epithelial cells, lymphocytes, monocytes, and antigen-presenting cells (APCs), such as macrophages and dendritic cells [10, 11]. Furthermore, many of these cells produce enzyme 1α-hydroxylase (CYP27B1), which catalyses the last and limiting step in the synthesis of the biologically-active form of vitamin D3 [19].

Calcitriol stimulates the differentiation of monocytes to macrophages. Vitamin D3 deficiency is disturbing the maturation of monocytes by decreased activity of lysosomal enzymes and release of hydrogen peroxide, factors necessary for their anti-microbial effects. Thus 1,25$(OH)_2$-vitamin

D3 enhances the chemotactic and phagocytotic potential of macrophages [20]. Furthermore, calcitriol significantly lowers the expression and reduces the secretion of matrix metalloproteinases: MMP-7, MMP-9 and MMP-10 also enhances the level of TIMP (tissue metalloproteinase inhibitor) by monocytes in response to an infection, consequently protecting the interstitial tissue of the lungs from damage [21]. Calcitriol reduced the expression of TLR2 and TLR4 (toll-like receptors) in monocyte cultures in response to PAMPS (pathogen-associated molecular patterns), which suggests inhibition of the inflammatory process in the late stages of infection [22]. In addition, it has also been shown that $1,25(OH)_2$-vitamin D3 inhibits the expression of some pro-inflammatory cytokines, i.e. TNF-α (tumour necrosis factor α), IL-1, IL-6, IL-8, IL-12 [23]. Calcitriol inhibits dendritic cell differentiation, maturation, and function, mostly to reduce unnecessary reactivity of the immune system [24]. The $1,25(OH)_2$-vitamin D3 modulates the expression of dendritic cells cytokines or chemokines, mainly inhibiting the secretion of IL-12 and IL-23 (stimulating Th1 and Th17 differentiation), as well as increasing the release of anti-inflammatory IL-10 (inhibiting both Th1 and Th2 immune responses). Braking the production of IL-12 by the mature dendritic cells is the result of suppression of the transcription factor NF-κB (nuclear factor kappa B), which contributes to the development of cells with a suppressive phenotype. At the same time, calcitriol increases the production of the CCL22 (C-C motif chemokine 22), which is capable of recruiting Treg [25, 26]. Furthermore, calcitriol decreases the expression of MHC class II and co-stimulants molecules reducing both macrophages and dendritic cells abilities to present antigens, and stimulate T lymphocytes, leading to inhibition of the activation of pathogenic effector T cells and an increasing number of cells with suppressor properties [23, 25].

Vitamin D3 not only affects lymphocytes indirectly via its effects on dendritic cells, as described above, but also has direct effects on T-cells and B-cells. Vitamin D3 is responsible for the transition of Th lymphocytes to an active form. In the absence of calcitriol, Th lymphocytes cannot recognise microorganisms that actively cause infections. Vitamin D3 affects the differentiation of lymphocyte T by restraining the release of IL-12 by dendritic cells, while cytokines trigger the development of Th1 while inhibiting Th2 [27]. Calcitriol inhibited the proliferation of Th1 lymphocytes and the secretion of cytokines, i.e. IFN-γ (interferon gamma), IL-2, which play a large role in supporting the cellular response (IL-2 stimulates lymphocyte cytotoxicity, while IFN-γ participates in the activation of macrophages). On the other hand, $1,25(OH)_2$-vitamin D3 increases the secretion of cytokines produced by Th2 (IL-3, IL-4, IL-5, and IL-10) with suppressor functions, especially against Th1 lymphocytes and cell-type responses. In addition, vitamin D3 inhibits the expression of Th17 effector molecules, i.e. IL-23R and CCR6, and pro-inflammatory cytokines IL-17 and IL-21 [28, 29]. It has also been shown that after binding calcitriol to the VDR on T lymphocytes, the profile of secreted cytokines changes in the direction of inhibiting the activation of effector T lymphocytes and inducing regulatory T lymphocytes. This mechanism protects against the excessive intensification of the inflammatory process during episodes of active immune response [30]. Vitamin D3 also plays a pivotal role in maintaining B cell homeostasis by inhibition their proliferation and differentiation. Additionally, calcitriol suppresses the production of immunoglobulins G and M (IgG and IgM) by plasma cells; however, totally differentiated memory B cells and antibody-secreting cells are resistant to calcitriol inhibitory influence [16, 31].

Calcitriol is also responsible for the regulation of expression of defence peptides cathelicidin and defensin in respiratory epithelium, monocytes, macrophages or neutrophils, which are the key for the response of the innate immune system to both wounds and infection of various origins [32, 33, 34, 35]. These peptides are able to directly kill enveloped viruses, fungi, bacteria and parasites by perturbing their cell membranes [36, 37, 38]. Moreover, cathelicidin and defensin enhance the immune cells' natural abilities to recognise and fight infections in various ways, including their attraction of immunocompetent cells, stimulation synthesis and release of pro-inflammatory compounds and intensification of phagocytosis [36, 38, 39]. Furthermore, in order to improve the host response to pathogens, defence peptides increase the proliferation and migration of epithelial cells and promote wound closure, which altogether play the pivotal role in the preservation of tissue homeostasis by supervising the healing processes [40].

It should be emphasized that the immunomodulatory properties of calcitriol in the respiratory tract are also expressed by its influence on airway epithelium. First of all, calcitriol increases the expression of genes for tight cell connections enhancing the epithelial function as a physiological barrier against pathogens [35]. Furthermore, calcitriol generated by airway epithelium in response to infection, increases the transcription of genes responsible for the recognition and killing of pathogens, such as pattern recognition receptors (TLR2, NOD2; nucleotide-binding oligomerization domain containing 2), the CD14 (cluster of differentiation 14), a co-factor for TLR4, as well as the above-mentioned antimicrobial peptides [33, 35, 41].

THE ROLE OF VITAMIN D3 IN SELECTED PULMONARY DISEASES

Asthma. Asthma is one of the most common chronic diseases, characterized by varying and recurring symptoms of airflow obstruction and bronchial hyper-responsiveness in inflammation. The disease typically begins in childhood and usually lasts throughout life, with periods of exacerbation and remission. Factors influencing asthma development include genetic and environmental factors, such as air pollution, smoking, and viral or bacterial infections. Asthma can have an atopic basis associated with excessive production of immunoglobulin E (IgE) in the body (atopic or allergic asthma) or a non-atopic basis, with normal levels of IgE (non-atopic, non-allergic). Abnormal production of IgE is one of the most important triggers of airway remodelling, which refers to airway changes (both thickened and narrowing airway walls) caused by the comprehensive interaction of epithelium, immune cells and mediators of inflammation [42]. Among the immune cells involved in airway remodeling, macrophages, mast cells, eosinophils, neutrophils and lymphocytes T cells have to be emphasized. These cells release chemokines, prostaglandins, histamine, leukotrienes, and cytokines, including TNF-α, IL-1, IL-4, IL-5 IL-13, which are the key players in the above-mentioned pathological changes [42]. An effective strategy to prevent asthma does

not yet exist, but appropriate treatment can limit the attack frequency and severity.

Since the biological actions of vitamin D3 are mediated by the receptor VDR, changes in this receptor may modify calcitriol activity causing various pathological conditions, including asthma. Very interesting conclusions have been provided in the systematic review by Zhao et al. that focused on the connections between polymorphisms in the gene *VDR* and asthma susceptibility, with particular emphasis on the ethnic factor. The study revealed that Asian ethnicity with ApaI (rs7975232) polymorphism increased the risk of asthma progression. At the same time, FokI (rs2228570) polymorphism may play a particular role in childhood asthma in the Caucasian population, while BsmI (rs1544410) polymorphism marginally contributes to asthma susceptibility in this ethical group. Simultaneously, there was no association between the risk of childhood asthma development and TaqI (rs731236) polymorphism [43].

As mentioned previously, calcitriol biological activity is determined by genetic variations of the vitamin D binding protein, which is also true in the case of asthma although the results are ambiguous. Nasiri-Kalmarzi et al. have shown that the serum level of 25(OH)-vitamin D3 was significantly lower in asthmatic patients (n=110; 16.26±6.76 ng/ml) than in healthy individuals (23.05 ± 10.57 ng/ml). Simultaneously, increased serum levels of VDBP recorded were in patients compared to the control group (1044.6±310.82 μg/ml vs 545.95±121.73 μg/ml). Discussed studies reveal that a decrease in calcidiol concentration is associated with a high level of VDBP, phenomena which are risk factors for asthma progression. Moreover, the studies reported that the progression of asthma in the Kurdish population was higher among patients carrying the rs7041 GG genotype [44]. Fawzy et al. examined 192 Egyptian children (equal groups of healthy and asthmatic children) and found that rs7041 GG genotype and G allele enhanced the risk of childhood bronchial asthma, while the rs4588 AA genotype and A allele were reported to be protective agents [45]. The research by Paraskakis et al. on a Greek cohort of 111 asthmatic children and 96 healthy individuals indicated elevated incidences of the rs7041 G allele in children with controlled asthma, while frequency of the rs4588 A allele was a negative correlation with asthma control [46]. The importance of rs7041 with the GC1S haplotype in asthma development also supported data reported by Randolph et al. Their case-control study on 465 infants from The Netherlands, hospitalized because of bronchiolitis induced by RSV (respiratory syncytial virus), and 930 healthy individuals, revealed that rs7041 with the GC1S haplotype increased the risk of the mentioned bronchiolitis and development of asthma in future. Furthermore, they also demonstrated that GC1S haplotype carriage is correlated with elevated VDBP levels, leading to the reduction of the amount of available vitamin D3, and thus may intensify its deficiencies [47].

In addition to studies on the impact of genetic changes in the molecules regulating the biological activity of vitamin D3 on the course of asthma, most clinical studies focus on the analysis of serum vitamin D3 levels in the context of respiratory efficiency in asthmatic patients. A cross-sectional study performed in Puerto Rico on 560 6–14-year-old children with asthma (n=287), as well as healthy individuals (n=273) showed that insufficiency of vitamin D3 was observed in 44% and 47% of the children, respectively. Nevertheless, multivariate analyses revealed the connection between deficiency of vitamin D3 and a higher probability of at least one severe asthma exacerbation during a single year, as well as a lower FEV1 (forced expiratory volume in 1 second)/FVC (forced vital capacity) ratio; however, the discovered correlation was independent of the time spent outdoors, as well as African racial ancestry.

Moreover, the above-mentioned association was greater in non-atopic than atopic asthma, which suggested that vitamin D impact on the pathogenesis of severe asthma exacerbations occurs independently of modulation of allergic immune responses [48]. In another study on a cohort of 75 Italian children with asthma, only 9.4% of patients had a sufficient serum level of 25(OH)-vitamin D3 (30 – 40 ng/ml). Performed studies showed a positive correlation between calcitriol concentration and FVC, as well as FEV1. Additionally, serum levels of 25(OH)-vitamin D3 were substantially higher in children with well-controlled asthma than in children with a partially controlled or non-controlled diseases, which indicated the presence of a correlation between the lower concentration of calcidiol and worse control of asthma [49]. Similarly, studies conducted on 160 adult asthma patients in Turkey also demonstrated the association between vitamin D3 deficiencies and decreased pulmonary function, as well as reduced asthma control. 66% of investigated asthmatics had a severe deficiency of vitamin D3 (< 10 ng/ml), which correlated with lower absolute FEV1 values. Furthermore, asthmatics with severe deficiency of vitamin D3 were characterized by substantially higher usage of inhaled corticosteroids than the patients with a serum level of calcidiol over 10 ng/ml [50]. A study by Korn et al. in a German cohort of 280 adult asthma patients demonstrated that vitamin D3 deficiency (< 30 ng/ml) was common in asthmatic patients (67%). In addition, they revealed the correlation between calcidiol serum levels and both asthma severity (severe – 24.0 ± 11.8 ng/ml, moderate – 26.5 ± 12.0 ng/ml, mild – 27.3 ± 11.9 ng/ml, intermittent – 31.1 ± 13.0 ng/ml), as well as disease control (uncontrolled – 24.2 ± 11.8 ng/ml, partly controlled – 25.9±10.8 ng/ml, controlled – 29.5±12.5 ng/ml). Furthermore, comparison of results from asthmatic patients with serum levels of calcidiol under 30 ng/ml vs over 30 ng/ml showed that the deficiency of vitamin D3 was associated with lower FEV1 values (2.3±0.9 l vs 2.7±1.0 l, respectively), and higher concentrations of exhaled NO (45± 6 ppb vs 31± 37 ppb, respectively) [51].

A randomized, placebo-controlled two months study by Tachimoto et al. on 89 Japanese schoolchildren with asthma, revealed significant improvements in disease control in the children (n=54) who were administered vitamin D3 supplements in the amount of 800 IU/day. Furthermore, beneficial effects were discovered, defined as a lower frequency and severity of asthma, which even persisted for four months after stopping vitamin D3 administration. Moreover, six months after the beginning of the examination, the number of children with a peak expiratory flow under 80% was noticeably larger in the placebo group (12/35: 34%) than in the group supplemented with vitamin D3 (8/54: 15%) [52].

While discussing the correlation between vitamin D3 concentration and asthma development, it is also worth mentioning the retrospective evaluation of results obtained from a cohort of Western Australian Pregnancy (n=2834) performed by Zosky et al. The study reported vitamin D3

deficiency (calcidiol level under 50 nmol/l) and insufficiency (calcidiol between 50 – 75 nmol/l) in 34.9% and 46.3% of investigated pregnancy population, respectively. Additionally discovered were positive associations between maternal serum level of 25(OH)-vitamin D3 at 16 – 20 weeks gestation and postnatal lung function (FVC Z-scores), in children aged six as well as 14-year-old girls. Reported plethysmography alterations were correlated with an increased risk of wheezing (both genders) and asthma (boys only) development at the aged of six. The presented results proved that maternal vitamin D3 status influences both lung development and their function in the offspring [53].

The significance of calcitriol in preventing upper respiratory tract infections in adult patients with asthma was also studied. Denlinger et al. conducted a randomized, placebo-controlled, double-blind, clinical study on 408 USA adults with mild to moderate asthma, whose calcidiol serum level was lower than 30 ng/ml, and who received low doses of inhaled corticosteroids, the amount of which was decreased during the studies. The study revealed that restoration of the physiological level of vitamin D (patients received at the beginning 100,000 IU cholecalciferol, followed by 4,000 IU/day for 28 weeks) did not influence the severity of colds in asthmatics undergoing corticosteroid dose reduction. The intervention surprisingly increased the rate of colds in African Americans patients with the lowest baseline levels of vitamin D3 [54].

Cystic fibrosis (CF). Cystic fibrosis is a monogenic disease common among Caucasians, inherited in an autosomal recessive way. CF is caused by a mutation in the gene *CFTR* (Cystic Fibrosis Transmembrane Conductance Regulator). The product of *CFTR* translation is located at the apical membrane of ciliated airway epithelial cells and in the submucosal glands. This protein acts as an ion channel, regulating the flow of both water and ions of chloride through cell membranes. Numerous mutations of the *CFTR* gene lead to the pathological production of large quantities of thick, viscous mucus that gathers in the respiratory tract and digestive systems [55].

Currently, there is no cure for CF; however, numerous available treatments allow control of the symptoms and reduce the risk of complications. One such strategy seems to be maintaining the vitamin D3 concentration at the appropriate level, especially in the light of studies that revealed a deficiency of vitamin D3 is frequent in patients suffering from CF, and ranges from 40% – 90%, dependent on age [56, 57, 58]. The cross section-study conducted in the UK by Elkin et al. on 107 adults (aged 18–60) with CF demonstrated that serum levels of 25(OH)-vitamin D3 in 36% of patients were lower than 25 nmol/l in spite of vitamin D supplementation (800–900 IU/day) [56]. At the same time, a cross-sectional study on a Canadian cohort of 81 CF patients who had been clinically stable for at least three months, revealed a suboptimal vitamin D3 status in 95% of individuals [57]. Neville and Ranganathan who examined the level of vitamins in 58 Australian infants diagnosed with CF, discovered vitamin D3 deficiencies in 37% of individuals, and the obtained results were independent of gender, month of birth, pancreatic status or levels of vitamins A and E [58].

A comprehensive review by Daley et al. indicated several causes of vitamin D3 deficiency in cystic fibrosis, including limited sun exposure, insufficient vitamin D intake, vitamin D malabsorption caused by exocrine pancreatic insufficiency and impaired hydroxylation of vitamin D [59].

The multitude of factors that disturb calcitriol levels in cystic fibrosis patients partly explains the failure of vitamin D supplementation in this population. Furthermore, it should be highlighted that 85–90% of people suffering from CF have pancreatic insufficiency leading to fat malabsorption of fats, as well as fat-soluble vitamins including vitamin D [60]. A prospective clinical study involving 134 USA adults (aged 19–64) with CP, among whom 81.3% had serum levels of 25(OH)-vitamin D3 under 30 ng/ml, demonstrated that only 8.0% of patients who received ergocalciferol in the amount 50,000 IU/week for eight weeks, improved their calcidiol status, reaching the concentration of 30 ng/ml or greater [61]. Green et al. performed a similar study in a group of 262 USA paediatric patients (under 21-years- old) with CP. Despite the fact that ergocalciferol supplementation once, twice, or three times weekly for eight weeks in the amount 50,000 IU improved the serum levels of calcidiol in 33%, 26%, and 43% of patients, respectively, the investigated treatment did not noticeably increase the number of patients who achieved the recommended calcidiol levels of over 30 ng/ml. On the other hand, the study revealed a correlation between the serum level of calcidiol and age of the CF patients (individuals older than 12 years were more at risk of vitamin D3 deficiency than children under the age of five years), season (risk of vitamin D3 deficiency was higher in autumn than in spring and summer months) and FEV1 volume (higher FEV1 correlated with higher levels of calcidiol) [62].

On the contrary, an investigation conducted by Rovner et al. on a group of white patients with CF (n=101; aged 8–25) receiving 800 IU/day of vitamin D, and healthy subjects (n=177; aged 6–21), revealed a lack of association between serum level of 25(OH)-vitamin D3 and FEV1 volume or function of liver in the cystic fibrosis patients. Furthermore, they did not observe any evident associations between the food intake of vitamin D and the calcidiol serum level in either of the groups. The mean serum level of 25(OH)-vitamin D3 was 20.7±6.5 ng/ml in patients with CF and 26.2±8.6 ng/ml in the investigated healthy individuals, while calcitriol concentration reached the following values: 36.1±8.1 pg/ml and 43.0±4.8 pg/ml, respectively. Vitamin D3 deficiency (calcidiol concentration under 11 ng/ml) was recorded in 7% of CF patients and 2% of healthy individuals, while insufficiency (calcidiol concentration under 30 ng/ml) was observed in 90% and 74% of subjects, respectively [63].

Among trials focused on the supplementation of vitamin D in CP patients, most of them were not able to restore the physiological level of calcidiol (30 ng/ml); however, studies conducted by Gronowitz and Khazai provided encouraging results [64, 65]. The aim of their open-label-controlled trial was to verify the possibility of using UVB light to improve vitamin D3 status in the period October – April in CF patients in Sweden. The study involved 30 individuals and (aged 9–40), who routinely supplemented vitamin D (400–2250 IU daily), divided into a control (mean calcidiol level = 21 ng/ml) and a research group (mean calcidiol level = 22 ng/ml) exposed to UVB radiation for one to three times a week during six months (time of single exposure – one minute; the time was gradually increased up to 10 minutes). The study showed that 25(OH)-vitamin D3 serum concentrations reached the level of 44 ng/ml after eight weeks, and subsequently 50 ng/ml after 24 weeks of UVB radiation, while in the reference group in

the corresponding times the following concentrations were observed: 19 ng/ml and 25 ng/ml, respectively [64].

Khazai et al. extended the concept of Gronowitz and examined the effectiveness of cholecalciferol, ergocalciferol, and UVB radiation in maintaining or increasing 25(OH)-vitamin D3 levels to the recommended 30 ng/ml. The open-label-controlled USA trial was conducted on 30 patients with CF (aged 16–70) randomized to ten-member research groups, wherein the first and second received 50,000 IU of vitamins D2 or D3 per week for 12 weeks, while the third group was exposed five times a week to UVB for three to 10 minutes (dependent on skin pigmentation) for 12 weeks. The treatment with cholecalciferol and ergocalciferol increased the serum level of calcidiol from a mean of 21.2±0.18 to 47.1±20.5 ng/ml (100% of subjects crossed the level 30 ng/ml), and 24.4±10.3 to 32.7±9.7 ng/ml (60% of subjects crossed the 30 ng/ml level). UVB therapy failed, probably because 45% of patients did not follow the study protocol [65].

Because of the concept of the study, it is worth mentioning the Grossman et al. investigation. They performed a randomized, placebo-controlled, double-blinded pilot study focused on the influence of vitamin D3 therapy on antimicrobial peptide LL-37 (cathelicidin) concentrations and expression markers of inflammation. The USA study involved 30 CF adult patients hospitalized because of pulmonary exacerbation, randomized to a placebo group or a group receiving a single dose of 250,000 IU cholecalciferol. Unfortunately, 12 weeks after vitamin D3 intervention, they demonstrated only a decrease in serum level of IL-6 and TNF-α, other investigated molecules: IL-1β, IL-8, IL-10, IL-18-binding protein, NGAL (neutrophil gelatinase-associated lipocalin), and LL-37, were not affected [66]. A retrospective longitudinal study conducted on 130 USA children between the ages six and to 18 years, sufferuing from CF, demonstrated a slow increase in the frequency of vitamin D3 deficiency (calcidiol <20 μg/l) as well as insufficiency (calcidiol between 20 μg/l to 29 μg/l) through adolescence. Furthermore, it was also revealed that they had higher serum levels of 25(OH)-vitamin D3, associated with lower rates of pulmonary exacerbations and, in adolescents, higher values of FEV1. Simultaneously, they did not record any differences in pulmonary function or incidence of first *Pseudomonas aeruginosa* infection in the investigated vitamin D3 groups: sufficient, insufficient, deficient [67].

Research by Polish scientists also focused on *Pseudomonas aeruginosa* infection among a CF population. Their randomized, placebo-controlled, double-blind study on 23 CF patients chronically infected by *P. aeruginosa* showed that three months of daily supplementation with calcitriol (0.5 mcg daily) or cholecalciferol (1000 IU daily) decreased the airway level of IL-17A and IL-23, which inhibited inflammatory responses to bacteria [68].

Chronic Obstructive Pulmonary Disease (COPD). This is a group of progressive pulmonary diseases that include chronic bronchitis and emphysema. Obstructive bronchiolitis refers to inflammation in the bronchial tube lining, while emphysema is shortness of breath caused by alveolar sac destruction. These two factors are responsible for breathing problems and poor airflow to the lungs leading to impaired gas exchange. COPD development is associated with a local, abnormal inflammatory response in the lung tissue, which is the body's response to inhaled harmful substances and occurs in predisposed individuals. One of the most important causes of COPD is tobacco smoking. Among other risk factors, pollution and exposure to occupational irritant substances such as organic dust have to be mentioned [69].

Several studies indicated the relationship between vitamin D3 deficiency and COPD; however, two issues musth be emphasized: first of all, the serum level of calcidiol decreases with age which, in turn, is a risk factor for developing COPD [70]. Furthermore, the co-morbidities associated with COPD, e.g. cancer, osteoporosis, cardiovascular disease or skeletal muscle dysfunction, may be also associated with the mentioned deficiency [71]. Results published by Malinovschi et al. for a group of 97 Italian patients with COPD, revealed that 96% of them had a calcidiol serum level lower than 30 ng/mL, while in 36% of subjects severe vitamin D deficiency (calcidiol level lower than 10 ng/ml) was observed. A strong relationship was also shown between a low concentration of 25(OH)-vitamin D3 and acute exacerbations, and hospitalization due to exacerbation [72]. Førli et al. demonstrated that among 46 Norwegian patients with advanced COPD waiting for lung transplantation, the majority had a calcidiol serum level under 20 ng/ml [73]. Similarly, data from a Belgian cohort of 414 ex-smokers aged over fifty and not supplementing with vitamin D, demonstrated that COPD patients more often suffered from vitamin D deficiency than healthy smokers, in particular, 60% of COPD patients in GOLD stage III and 77% of patients with GOLD stage IV had serum levels of 25(OH)-vitamin D3 under 20 ng/ml. The discussed data additionally showed a correlation between calcidiol concentration and FEV1 value [74]. Comparable findings were found in a Norwegian study involving 433 patients with COPD (GOLD stage II-IV), as well as 325 healthy individuals. The study showed an increased risk for vitamin D3 deficiency (calcitriol <20 ng/mL) in COPD patients, compared to controls after adjustment for age, smoking, seasonality and BMI. It should be emphasized that the cited study also indicated a few variables associated with lower serum levels of 25(OH)-vitamin D3 in the COPD cohort, including depression, obesity, smoking, and GOLD stages III-IV [75].

A hospital-based case-control study performed by Fu et al. on 303 Chinese individuals among whom 101 were patients with newly diagnosed COP, is also worth mentioning. The study revealed that serum levels of 25(OH)-vitamin D3 gradually decreased in COPD patients with the advancement of the disease, which indicated vitamin D3 as a key mediator of disease progression. In addition, the results also demonstrated that serum concentration of calcidiol is inversely correlated with serum levels of inflammatory mediators, including CRP (C-reactive protein), TNF-α, and MCP-1 (monocyte chemoattractant protein-1) [76].

As mentioned before, deficiency of vitamin D3 is common in patients with COPD because of many causes, including a lower efficiency of vitamin D synthesis in aging skin, lower outdoor activity and therefore sun exposure, as well as limited food intake [7]. The reasons indicated suggest that vitamin D3 supplementation with a recommended daily dose of 800 – 1,000 IU, which restores the physiological level of calcidiol in the general adult population, may be insufficient in patients with COPD. A randomized, placebo-controlled, double-blinded study New Zealand focused on the influence of vitamin D supplementation on health outcomes (442 adults, aged 50–84 years) provided very interesting data from participants suffering from COPD or asthma (60

patients). This clinical trial revealed that high-dose vitamin D3 supplementation (200,000 IU in the first month of the trial, followed by monthly 100,000 IU doses of vitamin) over an average of 1.1 years, corrected lung function (FEV1 and FEV z-score) in ever-smokers with vitamin D3 deficiency, as well as patients suffering from asthma/COPD [77]. Another randomized, double-blinded, placebo-controlled clinical study dedicated on Iranian COPD patients (n=63) showed that the consumption of vitamin D3 in the amount of 50,000 IU once a week for eight weeks, and then once a month for four months, improved their quality of life assessed by CAT questionnaire (COPD assessment test). Furthermore, a significant increase of 25(OH)-vitamin D3 serum level (from 19.33 ng/ml to 51.83 ng/ml) was also reported. At the same time, there were no noticeable differences among FEV1, FEV1/FVC, and the frequency of exacerbations in COPD patients [78].

In contrast to the above-mentioned data, Zendedel et al., in a randomized, double-blinded, placebo-controlled trial, also performed on Iranian patients with severe and very severe COPD (n=88), revealed a beneficial effect of vitamin D3 supplementation (six months treatment with 100,000 IU of oral vitamin D per month) on the rate of exacerbations among patients with calcidiol serum level under 25 nmol/l. The study also indicated that vitamin D3 intake improved FEV1 (an increase from 31.9 to 51.6) in the investigated cohort of COPD patients [79]. Nevertheless, three other randomized, double-blind placebo-controlled studies investigating the effects of vitamin D3 supplementation on the risk of COPD exacerbation, reported no impact [80, 81, 82]. A trial by Lehouck et al. was carried out on 182 Belgian patients suffering from moderate to very severe COPD, who received vitamin D3 in the amount of 100,000 IU monthly for one year [80]. A study by Martineau et al. involving 240 UK patients with COPD, who received three mg of vitamin D3 every two months for one year [81]. A study by Rafiq et al. included 50 Dutchman patients with COPD, who receive 1,200 IU of vitamin D3 per day for six months [82].

Discussing correlations between vitamin D3 and COPD, the genetic variants of gene *VDBP* coding the vitamin D-binding protein has to be mentioned. The previously-mentioned Belgian study by Janssens et al., demonstrated that the serum level of calcidiol is reduced by 25% in homozygous carriers of the rs7041 T allele. The study also showed that 76% and 100% of COPD patients with GOLD stages III and IV homozygous for the rs7041 T allele, demonstrated 25(OH)-vitamin D3 serum levels lower than 20 ng/ml, which indicated the discussed genetic variant as a risk factor for COPD [74].

A cross-sectional case-controlled study by Li et al., who investigated 250 participants from Thailand, including 116 COPD patients with a smoking history and 134 healthy smokers, demonstrated that the individuals suffering from COPD were at high risk of vitamin D3 deficiency, and the severity of diseases was inversely correlated with the serum level of calcidiol. Furthermore, the homozygous carriers of the rs7041 T allele were independently related to the serum concentration of 25(OH)-vitamin D3 and susceptibility to COPD [83]. A meta-analysis, case-control study examining 531 COPD patients and 1,181 healthy individuals among Asians and Caucasians, indicated the GC2 allele as a preventive factor of COPD development, especially for Asians. The study also demonstrated, in the recessive model, that the GC1F allele was a risk factor for COPD [84]. A meta-analysis by Khanna et al. also indicated the GC1F allele and GC1F/1F genotype as a COPD risk factor, regardless of race, while GC1S/1S was indicated as a risk only in Europeans [85]. Another investigation in a group of 361 COPD patients and 219 controls from the Japanese population, exhibited that individuals carrying the C allele at rs4588, revealed a greater susceptibility for COPD, higher frequency of exacerbations, and tendency for the rapid decline of airflow obstruction [86].

Idiopathic Pulmonary Fibrosis (IPF). IPF is a progressive and irreversible pulmonary disease of unknown etiology, and a mean life expectancy of only three to five years [87]. Pulmonary fibrosis involves a gradual exchange of normal lung parenchyma with fibrotic tissue, which is the pathological wound-healing response for chronic lung injuries and/or infection. The replacement of normal lungs with scar tissue eliminates pathologically changed areas from the gas exchange, causing hypoxia and in advanced cases – death [88]. The therapeutic options for IPF remain limited to antifibrotics nintedanib and pirfenidone, which can only slow down the disease progression [89]. Simultaneously, the most effective therapy – lung transplantation – is available to a minority of patients [90]. Therefore, the key goal in IPF treatment is to preserve lung function, decrease disease progression, and the development of new drugs which, first of all, modulate the inflammation process responsible for aggravating and accelerating fibrosis development.

Over the last few years, the correlation between vitamin D3 and lung fibrosis has been extensively evaluated. Studies revealed that vitamin D3 may beneficially influence each of the four steps of fibrosis development, including wound clotting, the inflammatory phase, fibroblast migration and differentiation phase, as well as tissue remodelling [91]. In the first step, in response to harmful/injured agents, epithelial cells release inflammatory mediators and activate an antifibrinolytic coagulation cascade. This process is mediated by protease-activated receptors (PARs), and operating through them, tissue factor (TF) which, together with factor VIIa, initiates the coagulation cascade leading to the activation factor IX. The anti-fibrotic effect of vitamin D3 is based on the inhibition of TF expression as well as the stimulation of the production of a TF pathway inhibitor (TFPI) [91, 92]. During the inflammatory phase of wound healing, injured epithelial and/or endothelial cells produce mediators leading to infiltration of immune cells releasing several cytokines (TNF-α, TGF-β, IL-1, IL-6, IL-8, IL-10, IL-13, IL-17), which promote the inflammation and fibrosis. Vitamin D3 is able to decrease the serum level of all the above-mentioned cytokines inhibiting the expansion of the inflammatory response and further fibrosis development [91, 93]. Because of the pivotal role of TGF-β in fibrosis induction, the inhibitory effect of vitamin D3 on this molecule has to be highlighted. Modulation of the TGF-β pathway by vitamin D3 decreases the expression of fibronectin and collagen, as well as attenuating epithelial to mesenchymal transition involved in pathological wound healing phenomena like the migration, proliferation and differentiation of fibroblasts [91, 94, 95].

Despite the fact that the molecular mechanism of vitamin D3 anti-fibrotic activities has been quite well-described, there are only a few clinical studies focused on the influence of this compound on IPF progression. In one clinical trial

performed in northern Italy, vitamin D3 deficiency (<20 ng/ml) and insufficiency (20–30 ng/ml) were reported in 35 (40.2%) and 14 (16.1%) patients, respectively, in a cohort of 90 patients with IPS. However, as indicated in the study, laboratory examination of vitamin D3 concentration was not conducted in 24 patients (27.6%), thus the obtained data should be interpreted with caution [96].

A study by Tzilas et al. focused on both patients with IPF (n=93) and patients with other interstitial lung diseases (n=40), revealed vitamin D3 deficiency in the investigated Greek cohorts. However, there were no evident differences between mean concentrations of calcidiol in the indicated research groups (18.76 ± 8.36 vs 18.54 ± 8.39 ng/ml). Furthermore, it was discovered that serum concentration of 25(OH)-vitamin D3 below the level of 17.9 ng/ml may indicate IPF patients with an elevated probability of mortality, compared to those with a higher level of calcidiol [97]. Yang et al. investigated the serum level of the biologically- active form of vitamin D3 in a Chinese cohort of 72 patients with IPF, and proved that concentrations of $1,25(OH)_2$-vitamin D3 at baseline were higher in IPF patients with stable disease (n=31; 16.62 pg/ml), than in those with acute exacerbation (n=41; 11.58 pg/ml). It was additionally discovered that a low concentration of calcitriol was a negative mortality prognostic factor [98].

As presented above, several studies examined the vitamin D status among IPF patients, but research focused on vitamin D3 supplementation is missing. In the light of this lack of knowledge, it seems worth mentioning an Iranian clinical trial that nvestigated the effects of co-supplementation with vitamins C, D, and E on inflammatory and respiratory responses in 33 patients with IPF. Research participants received 200 IU of vitamin E per day, 250 mg of vitamin C every other day for twelve weeks, and 50,000 IU of vitamin D3 per week for eight weeks. The results indicated that supplementation vitamins in patients with IPF may positively influence respiratory function, in particular, increasing the values of TLC (total lung capacity), FEV1 (forced expiratory volume in the first second), IRV (inspiratory reserve volume) and RV (residual volume). Simultaneously, there were no significant changes in ERV (expiratory reserve volume), FVC (forced vital capacity), VC (vital capacity), and FEV1/FVC in response to the treatment. The trial also proved that vitamin supplementation that silenced the inflammation state in IPF patients, was manifested by a significant decrease in the level of TGF-β, ESR (erythrocyte sedimentation rate) and hs-CRP (high-sensitivity C-reactive protein) [99].

Coronavirus disease (COVID-19). COVID-19 is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease may lead to acute severe respiratory distress syndrome (ARDS), which seriously threatens human health and life. COVID-19, as a multiorgan disease which in addition to lung involvement, is often associated with an uncontrolled immune response, which largely determines the severity of the course of the disease [100]. The potential beneficial role of vitamin D3 may be due to its effect on the renin-angiotensin pathway and may result in a reduction of the body's inflammatory response; it is also thought that vitamin D3 has a beneficial effect on the gut microbiome, which is involved in the fight against infection. Vitamin D3 further strengthens the antioxidant defence system by regulating the activity of enzymes responsible for neutralising free radicals [101].

One of the most important studies, due to the size of the study group, was the Kaufman et al. case-control study conducted on 191,779 USA patients with SARS-CoV-2 test results and matching 25(OH)-vitamin D3 data. The SARS-CoV-2 infection rate was higher in patients with a calcidiol concentration under 20 ng/ml (n= 39 190; 12.5%) than patients with a 25(OH)-vitamin D3 level of around 30–34 ng/ml (n= 27 870; 8.1%), or a calcidiol concentration equal to or higher than 55 ng/ml (n=12 321; 5.9%) [102]. Merzon et al., in a cohort of 7,800 Israel patients, observed that the mean serum vitamin D3 level was significantly lower in patients with COVID-19 (19.00 ng/ml) than in uninfected individuals (20.55 ng/ml). Moreover, studies indicated that a 25(OH)-vitamin D3 concentration below the level of 30 ng/ml was an independent risk factor for COVID-19 infection and hospitalization [103]. A retrospective study from 107 Swiss patients also demonstrated a significantly lower serum level of 25(OH)-vitamin D3 in PCR-positive SARS-CoV-2 patients (11.1 ng/ml), compared to negative, uninfected individuals (24.6 ng/ml) [104]. Abdollahi et al, in a case-control study of 201 Iranian patients with COVID-19 and 201 healthy individuals, also demonstrated a negative correlation between calcidiol concentration and vulnerability to COVID-19. In the mentioned study, the serum level of 25(OH)-vitamin D3 in infected cases and controls was 24 (21–35) ng/ml and 26 (21–35) ng/ml, respectively [105].

The prevalence of vitamin D3 deficiency in patients infected with SARS-CoV-2 suggests that its supplementation may be used prophylactically as an affordable and safe strategy that could be added to the existing standard treatment of COVID-19. However, the results of clinical trials dedicated to this issue, are inconclusive. The beneficial effect of vitamin D3 supplementation was reported by Nogues et al., who conducted an observational study among 838 Spanish patients with COVID-19, who had not previously used any vitamin D3 supplements. In the study, 447 individuals received calcifediol (on day one – 532 μg, and on day two – 266 μg, and the same dose on days three, seven, fifteen and thirty), while 391 were untreated. The study revealed that calcifediol administered shortly after hospitalization reduced the admission time to the intensive care unit (ICU) from 21% to 4.5%, and decreased mortality by more than 50%. A negative correlation was also discovered between 25(OH)-vitamin D3 levels and COVID-19 exacerbation and mortality [106].

Another interesting piece of data was provided in a multicentre, double-blind, randomized, placebo-controlled trial conducted on 240 Brazilians patients suffering from moderate to severe COVID-19, who received a single dose of 200,000 IU vitamin D3 or placebo. Despite the fact that the serum levels of calcifediol significantly increased after supplementation from 19.8 ng/ml to 44.4 ng/ml, the differences in need for mechanical ventilation, time of hospitalization, or risk of death, were not statistically significant [107]. Similar observations provided a multicentre, randomized, double-blind, placebo-controlled clinical study conducted in Argentina on 218 adult patients suffering from mild to moderate COVID-19, and burdened with risk factors for disease progression. Patients received a single dose of 500,000 IU vitamin D3 or a placebo. There were no significant differences in the length of hospitalisation, frequency of intensive care unit admissions, and in-hospital mortality [108].

It is also worth mentioning the conclusions of both the meta-analysis and systematic review by Bassatne et al., which

indicated that the association between vitamin D3 deficiency (calcidiol serum level lower than 20 ng/ml) and frequency of SARS-CoV-2 infections, risk of COVID-19 mortality, the need for both mechanical or non-invasive ventilation, and ICU admission, were not statistically significant. Nevertheless, the review revealed that serum levels of 25(OH)-vitamin D3 were 6 ng/ml lower in COVID-19 patients than in uninfected individuals. Furthermore, after redefining the vitamin D3 deficiency (calcidiol serum level lower or equal than 30 ng/ml), the investigation showed the existence of dependencies between low vitamin D3 levels and increased risk of SARS-CoV-2 infection and COVID-19 mortality. Simultaneously, there were no correlations between the risk of disease severity and occurrence of acute respiratory distress syndrome (ARDS), and length of hospital stay [109].

Sarcoidosis. Sarcoidosis is an inflammatory disease characterized by the formation of granulomas (small clusters of inflammatory cells) in one or more organs of the body. The disorder can affect almost any organ, but 90% of granuloma depositions are observed in the lungs. The typical pulmonary symptoms are cough, dyspnea, and chest pain. The most common areas of sarcoidosis manifestation are the lung interstitium and respiratory tract. Interstitial disorders can lead to restrictive disease, while granulomas formation in the airways can lead to their obstruction. Other chest manifestations include pulmonary hypertension and weakness in pulmonary muscle. Furthermore, lung fibrosis in the course of sarcoidosis is also very common [110].

Although the cause of sarcoidosis is unknown, over the years some causative agents have been indicated. Among them, the most commonly postulated disease causes are infectious agents (e.g. *Mycobacterium tuberculosis*, *Chlamydia pneumoniae*, *Borrelia burgdorferi*, *Propionibacterium acnes*, herpes virus, retrovirus), exposure to environmental irritants (e.g. silica, soil, tree pollen, insecticide), and/or abnormal immune reaction to the above-mentioned agents observed in genetically-predisposed people [111, 112, 113].

Discussing the role of vitamin D3 in sarcoidosis, it is worth mentioning the review by Targowski and Locke who indicated several key causes of disturbances in vitamin D metabolism observed in this disease. First of all, they drew attention to the cells forming granulomas (macrophages, multinucleated giant cells, macrophages) and their ability to autonomously synthesize the biologically-active form of vitamin D3 from calcidiol, a phenomenon additionally enhanced by IFN-γ and TNF-α produced by lymphocytes and macrophages presented in sarcoidal granulomas. Furthermore, they paid attention to the fact that the synthesis of hydroxylase CYP24A1, responsible for the conversion of calcitriol into an inactive metabolite, by alveolar macrophages, in contrast to the same enzymes presented in the kidneys, required very high concentrations of $1,25(OH)_2$-vitamin D3 – which promote calcitriol accumulation in the pulmonary granulomas [114, 115].

The specificity of vitamin D3 metabolism in patients with sarcoidosis is clearly demonstrated in the study conducted by Baughman et al. on a cohort of 261 sarcoidosis USA patients (50% Caucasians) with monitored serum levels of both calcidiol and calcitriol. The study revealed that 83.5% of patients had low 25-(OH)-vitamin D3 levels, while the calcitriol deficiencies were recorded only in one of the investigated patients (0.4%) and elevated in 11% of investigated individuals [116]. Similar observations were revealed in study by Saidenberg-Kermanac'h et al. on 142 patients with sarcoidosis (Caucasians 60%, Caribbeans 38%, Indians 2%). The mean serum concentration of 25(OH)-vitamin D3 was lower than physiological (14.5 ng/ml), while the mean calcitriol level was normal (137.4 pmol/l). It needs to be highlighted that the study indicated an inverse correlation between serum level of calcidiol and sarcoidosis flares, and the severity of the pulmonary involvement. The simultaneous statistical examination did not show a correlation between serum level of $1,25(OH)_2$-vitamin D3 and chronicity of the disease, despite the presence of positive correlation between concentrations of indicated vitamin D3 metabolites [117].

The above-mentioned data correspond with results obtained by Kavathia et al. during the examination of 59 sarcoidosis patients (African-American – 85%, Caucasian – 15%), which revealed a deficiency level of 25(OH)-vitamin D3 (mean value – 11.3 ng/ml), and physiological serum concentration of $1,25(OH)_2$-vitamin D3 (mean value – 42.2 pg/ml). The study also revealed a lack of correlation between calcitriol concentration and sarcoidosis severity; however, an elevated level of $1,25(OH)_2$-vitamin D3 was associated with increased odds of the chronic phenotype (71% of individuals with calcidiol level over 51 pg/ml required chronic immunosuppressive treatment) [118].

A retrospective study conducted in The Netherlandson a sarcoidosis cohort which included 301 patients, also shown calcidiol deficiencies in 63% of patients (mean value – 16.8 ng/ml), while 89% of examined patients revealed a normal calcitriol level mean value – 114 pmol/l). At the same time, 8% of tested patients had elevated levels of calcitriol. Moreover, similar to previously presented data, Kamphuis et al. reported a negative correlation between 25-(OH)-vitamin D3 and severity of disease activity [119].

Discussing the role of vitamin D3 in sarcoidosis development, following facts must be noted: 1) several independent studies revealed a seasonal clustering of sarcoidosis in winter and early spring when vitamin D3 concentration is the lowest [120, 121, 122]; 2) some scientific reports have indicated a higher Afro-Americans than Caucasians predisposition to sarcoidosis development, which is associated with decreased skin synthesis of vitamin D3 in people with darker skin [118, 123, 124, 125, 126].

In view of the above-described scientific reports, vitamin D3 supplementation in order to increase the unphysiological serum level of calcidiol seems to be justified. Nevertheless, because of the fact that an elevated level of calcitriol observed in sarcoidosis patients has been perceived for a long time as an inducer of hypercalcaemia and hypercalciuria, research into the role of vitamin D supplementation in sarcoidosis has been hampered. Nevertheless, there are some studies that addressed this issue.

Next to earlier presented data from a cohort of 261 patients with sarcoidosis [116], Baughman et al. conducted independent research on 1,606 sarcoidosis patients in order to examine the influence of vitamin D3 supplementation on the prevalence of hypercalcaemia. Sarcoidosis-associated hypercalcaemia (SAHC) was discovered in 6% of investigated patients. Additional studies conducted on 21 of 97 SAHC patients who declared vitamin D3 supplementation, revealed hypercalcaemia improvement in response to the withdrawal of calcium and vitamin D supplementation [116]. On the contrary, research conducted by Saidenberg-Kermanac'h

et al. demonstrated that vitamin D3 supplementation for six months in a wide range of concentrations (the following treatment groups were distinguished: 1–100, 000, 100,000–200,000 and over 200,000 units of vitamin D3) did not impact on either the calcitriol or calcium serum levels, but in a dose-dependent manner increased the concentration of calcidiol [117].

The previously described retrospective study by Kamphius et al. also included an examination of the influence of both calcium (500 mg) and vitamin D3 (400 IU) daily supplementation on sarcoidosis, as well as the development of hypercalcaemia. The investigated treatment did not impact on the serum level of calcidiol and calcitriol. Among 104 patients with replenished calcium and vitamin D3 deficiencies, only five developed hypercalcaemia, but none of them had elevated $1,25(OH)_2$-vitamin D3 levels, which suggested the safety of the tested supplementation [119]. Interesting results were obtained in a randomized, placebo control study on the group of 27 normocalcaemic sarcoidosis patients with a calcidiol serum level below 50 nmol/l (European – 77%, Indian – 8%, Other – 8%). Patients were treated with cholecalciferol 50,000 IU weekly for four weeks, and then for the next 11 months received the same dose monthly. The study revealed a significant increase in both calcidiol and calcitriol serum levels, from 40 nmol/l to 80 nmol/l and from 109 pmol/l to 141 pmol/l, respectively (there were no significant changes in these parameters in the placebo group). Examination of the pulmonary function test did not show any improvements in response to the treatment. Although vitamin D3 supplementation did not affect the serum or urine calcium levels, it induced a significant level in hypercalcaemia in one tested individual [127].

Worth mentioning are also the data obtained by Capolongo et al. from 86 sarcoidosis patients (African-American – 85%, Caucasian – 15%), wherein insufficient calcidiol levels (<75 nmol/l) were observed in 73.8% of investigated individuals; 16 of 86 patients with vitamin D3 deficiencies were treated with ergocalciferol at a dose 50,000 IU once a week for 12 weeks. Vitamin D supplementation significantly increased the serum level of calcidiol from 42 nmol/l to 82 nmol/l, while at the same time decreasing the calcitriol serum level from 101 pmol/l to 52 pmol/l. Similar to Bolland's study, there was no impact on pulmonary function in the response to tested treatment. Disadvantages of vitamin D3 supplementation were observed in three of 16 patients who developed increased serum and/or urine calcium indices, but these alterations were mild, asymptomatic, and reversible.

It has to be highlighted that the presented data also revealed inhibition of the angiotensin-converting enzyme which, according to the authors, suggests suppression of granulomatous immune activity. Furthermore, the authors connected the observed decline of calcitriol level in response to vitamin D3 supplementation with the inhibition of autonomous production of $1,25\text{-}(OH)_2$-vitamin D3 by granuloma-associated immune cells [126]. According to the above-presented data, the frequency of hypercalcaemia was different depending on the investigated population, and the strategy of vitamin D3 supplementation, however, the highest recorded incidence was 7.7% [116, 117, 119, 126, 127]. Nevertheless, due to the ambiguous effect of vitamin D3 supplementation on the course and development of pulmonary sarcoidosis, further clinical studies involving larger cohorts of patients are required.

THE POSSIBILITY OF VITAMIN D3 IN THE PREVENTION AND TREATMENT OF HYPERSENSITIVITY PNEUMONITIES

Hypersensitivity pneumonitis (HP) belongs to interstitial lung diseases in which the chronic inhalation of a diverse range of antigens may trigger in susceptible individuals a hypersensitivity immune reaction in the respiratory tract, which in extreme cases leads to pulmonary fibrosis [88, 128]. This disease may be induced by a wide variety of antigens, including fungi, bacteria, plant and animal proteins, metals and chemicals [128]. Dependent on the type of antigens and their source, several varieties of HP were distinguished e.g. farmer's lung, grain fever, bird fancier's lung, mushroom growers' lung and humidifier lung. Independently of the HP variants, the clinical course of the disease is similar [128, 129]. Due to prevalence and great variety antigens provoking HP, millions of people are exposed to them at home, work or rest-places; thus, HP is an important cause of pulmonary fibrosis worldwide [130]. Unfortunately, there is no effective therapeutic strategy for pulmonary fibrosis in the progression of HP; thus, the survival rate is dramatically low (3–5 years) [131, 132].

Since the key mechanisms of pulmonary fibrosis development in HP are alterations in the repair of injured pulmonary epithelium due to chronic inflammation, it was assumed in the current study that effective therapy should combine restoration of immune balance, as well as inhibition of the epithelial to mesenchymal transition (EMT) underlying fibrosis [133, 134]. These criteria are perfectly met by calcitriol.

As mentioned previously, vitamin D3 impacts on cells involved in lung immune responses to antigens provoking HP at all levels, including airway epithelium, alveolar macrophages, dendritic cells, T-cells, B-cells, and therefore, in the opinion of the authors, may modulate the progression of fibrosis in the course of HP.

One of the most important features of vitamin D3, which could be directly involved in the prevention and treatment of lung fibrosis observed during HP, is its impact on the production of cathelicidin. The current study demonstrated a significant cathelicidin deficiency in advanced lung fibrosis [135, 136, 137]. Moreover, earlier studies conducted in the murine model of HP, revealed that exogenous cathelicidin (CRAMP – cathelicidin-related antimicrobial peptide) supressed both immune responses and fibrosis development.

The favourable effect of cathelicidin discovered was based on maintaining the balance in the number of immune cells (macrophages, lymphocytes: B, Tc, Th, Treg, NK) and cytokines production (IFN-γ, TNF-α, TGF-β1, IL-1β, IL-4, IL-5, IL-10, IL-12α, IL-13). Nevertheless, CRAMP treatment did not completely prevent the development of fibrosis, probably due to the fact that inhalations with exogenous peptide were unable to restore the physiological level of cathelicidin [134].

The last, but not least argument for using vitamin D3 in the therapy of HP is based on its ability to EMT modulation, the importance of which for pulmonary fibrosis has been well documented [133, 138, 139]. Several studies revealed that calcitriol inhibits EMT via the induction of expression of genes which encode cell adhesion and polarity molecules (e.g. occludins, claudins, E-cadherin, keratin) which are essential for maintenance of the epithelial phenotype. Moreover, the calcitriol impacts on the expression of several transcription factors (Snai1, Snai2, ZEB1, ZEB2) that induce EMT [140]. Studies specifically dedicated to the pulmonary region have

demonstrated that calcitriol silences the stimulating impact of TGF-β1 on cell motility, and on the expression of Snai1, N-cadherin and vimentin in human bronchial epithelial cells [94, 95], and inhibits the TGFβ1-induced EMT in human primary alveolar type II cells [141].

The latest study by the authors of the current study is directly focused on the prevention and treatment of HP, and has indicated the above-mentioned beneficial effect of cathelicidin inhalations on fibrosis development [134], and was also associated with restoring the physiological level of myofibroblast markers (fibronectin, N-cadherin, α-smooth muscle actin, vimentin), epithelial markers (E-cadherin, occludin), as well as transcription factors associated with EMT (β-catenin, NF-κB, Snail, TGF-β1 ZEB1, ZEB2). Nevertheless, the endogenous cathelicidin was not able to silence the EMT process completely which, as mentioned before, could be caused by the inability to obtain and maintain a physiological concentration of the tested peptide [133].

Despite scientific data hypothesising the possibility of using vitamin D3 in the treatment of HP, so far no one has made any effort to verify this hypothesis. Thus, the current study focused on the possibility of using calcidiol and calcitriol in the prevention and treatment of lung fibrosis occurring in the progression of HP is unique. The study was performed on the internationally-recognized HP mice model, wherein lung fibrosis is provoked by an extract of *Pantoea agglomerans* (a well-known etiological factor of HP) administered for 28 days to a mice strain prone to fibrosis [142, 143]. The study was conducted in mice on diet with vitamin D3 deficiency, as well as diet with a recommended amount of vitamin D3. To reduce the danger of systemic toxicity, vitamin D3 was administered directly to the respiratory tract via inhalations; this is a unique approach as well as the intended route of its administration in individuals at risk of developing pulmonary fibrosis.

The project should verify the following:

1) utility of vitamin D3 in the prevention and/or treatment of pulmonary fibrosis;
2) describe the influence of vitamin D3 delivered with food and inhalations on lung tissue under physiological and pathological conditions;
3) increase knowledge about the molecular mechanism of vitamin D3 action during the development of HP, with particular emphasis on its impact on epithelial to mesenchymal transition and immune responses, including the endogenous cathelicidin level.

CONCLUSIONS

In this review, some important clinical data on the role of vitamin D3 in the pathogenesis of selected respiratory diseases are examined. Most of the results revealed that vitamin D3 deficiency increases the risk and worsens the course of asthma, cystic fibrosis, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, COVID-19, as well as sarcoidosis. Despite the pivotal role of vitamin D3 deficiencies in the development as well as exacerbation of the reviewed pulmonary diseases, vitamin D supplementation has not always proved to be an effective therapeutic strategy, mostly because of the fact that obtaining and maintaining physiological calcitriol levels in complex pathological conditions (patients with the discussed lung diseases have many comorbidities as well as metabolic defects disrupting the calcitriol synthesis), requires more than simply increasing the vitamin D intake with food, supplements or drugs.

The task is not facilitated by the danger of vitamin D overdose which, although it occurs quite rarely, can lead to hypercalcaemia, hypercalcuria and hyperphosphataemia, and if untreated causes kidney stones, calcification of blood vessels and organ parenchyma [7]. This danger could be decreased by the direct delivery of vitamin D3 into the respiratory tract by nebulization. Nevertheless, with the exception of this study focused on HP, there are no clinical trials which would consider such a solution, despite the fact that it seems to be obvious in the case of respiratory diseases. This simple example shows how much should be done in the area of research into the role of vitamin D3 in the prevention and treatment of lung diseases.

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Conflicts of interest

There are no conflicts of interest that might be relevant to the contents of this manuscript.

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