

Teresa Grzelak¹, Klaudia Mikołajczyk²

¹Poznan University of Medical Sciences, Poznan, Poland

²Nutrigenomics Student Research Group Poznan University of Medical Sciences, Poznan, Poland

Pleiotropic effect of vitamin D in cystic fibrosis

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Abstract

Cystic fibrosis (CF) is the most common recessively autosomally inherited disorder in the Caucasian population. It is incurable, multi-systemic disease with progressive course. CF is caused by *CFTR* gene mutation, the product of which is Cystic Fibrosis Transmembrane Conductance Regulator (CFTR). CF patients are exposed to fat-soluble vitamins deficiency, including vitamin D. It is related to fat malabsorption (caused by exacerbation exocrine pancreatic insufficiency), decreased sun exposure (caused by receiving antibiotics photophobia), reduction of adipose tissue and insufficient supply with food. The discovery of vitamin D receptor (VDR) presence outside the skeletal system allowed to conclude that vitamin D is responsible not only for mineral economy, but also for immunological processes, respiratory status, intestinal microflora and cystic fibrosis-related diabetes (CFRD) course.

Basing on literature data, it is suggested that vitamin D plays an important role in the prevention of diseases coexisting with CF. The right dosage of vitamin D allows to maintain a better lung function and prevent chronic pulmonary infections. It has also been shown that normal levels of vitamin D may be important in increasing the chances of successful lung transplant surgery. Taking the wide spectrum of vitamin D effects into account, it is recommended to maintain serum concentrations above the minimum in patients with CF. In summary, maintaining the proper vitamin D levels in patients with CF is important because of its pleiotropic effect. It can be achieved through regular monitoring of vitamin D levels and individual supplementary dose for each patient.

Key words: cystic fibrosis, vitamin D, supplementation

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Cystic fibrosis (CF) is the most common monogenic disease among the Caucasian population, inherited in an autosomal recessive manner [1–3]. This progressive disorder includes many organ systems and is characterized by high mortality at relatively young age. CF is caused by *CFTR* gene mutation, the product of which is the CFTR protein, located on the top surfaces of the epithelial organs' cells [2]. It is the ion channel protein, responsible for adjusting chloride and water flow through cell membranes [2, 3]. Each of over 2,000 known mutations of the *CFTR* gene impairs the CFTR protein functions, resulting in overproduction of viscous, thick mucus, which accumulates in the organs of the respiratory and digestive systems [2].

The ones suffering from CF, besides other irregularities related to nutrition, are exposed to a defi-

ciency in fat-soluble vitamins, including vitamin D. Its shortages (25(OH)D₃ below 20 ng/ml) are observed among 22% of infants and the suboptimal level (25(OH)D₃ 20-30 ng/ml) — even among 90% of older children and young adults [4, 5]. Due to a prevalence of insufficient concentration of vitamin D in serum, it is recommended by the Cystic Fibrosis Foundation to examine its body resources annually, preferably in the winter season. If vitamin D's saturation of the body during the reduced endogenous synthesis is appropriate, it leads to the conclusion that this condition will be maintained through the year while keeping an individual supplementation scheme [4].

The reasons for vitamin D shortages among patients with CF may include: fat absorption disorders (caused by coexisting pancreatic exocrine insufficiency), low level of specific vitamin D

Address for correspondence: Teresa Grzelak Poznan University of Medical Sciences, Poznan, e-mail: tgrzelak@ump.edu.pl

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binding protein (DBP) and impaired hydrolysis to bioactive compounds in the liver, reduced exposure to sunlight (the result of photosensitivity of used antibiotics), reduction of adipose tissue, as well as insufficient supply from food [4, 6–9].

Along with the life prolongation of patients suffering from CF, the co-occurrence of diseases characteristic of the adult population are observed more often. Available literature data indicate a positive correlation between age and severity of pulmonary disease and the level of advancement of skeletal changes and the vitamin D deficiency among these patients [9]. About 40% of children with CF also suffer from osteopenia, and 25% of adults — from osteoporosis [10]. This fat-soluble vitamin is necessary to maintain the proper condition of the skeletal system, because it stimulates calcium and phosphorus absorption from the gastrointestinal tract and renal tubules, additionally affecting the mineralization of the bone matrix [7, 11, 12]. It is also proved that the active form of vitamin D influences the activity of the calcium receptor gene (changing its expression), regulates the secretion of parathyroid hormone (PTH) (inhibiting the proliferation of parathyroid cells), and — what is associated with it — reduces bone resorption [11]. It is particularly important in the context of the fact that the suboptimal level of vitamin D in CF patients' serum may result in secondary hyperparathyroidism [7]. Maintaining their bone system in a proper condition is essential. Every injury within it, immobilization and persistent pain may impair lung functioning, effective expectoration and clearing the airways, which ultimately leads to the progression of lung failure. It should be remembered that the reduction of bone mass is associated with muscle weakness, ribs and vertebrae fractures, as well as the formation of chest deformities, which additionally promote the development of the disorders given above [9, 11].

The discovery of the presence of the vitamin D receptor (VDR) outside the bone cells leads to the conclusion that it is responsible not only for mineral metabolism, but also can affect other organs and their functions, including: respiratory system status, immunological processes, intestinal microflora condition and process of cystic fibrosis-related diabetes (CFRD) [6, 11, 13, 14]. What is more, the status of vitamin D management plays an important role in the prevention of disorders co-occurring with the basic disease. Supplying a proper supplementation dose (preferably a medicine) allows to protect structures and functions of the respiratory sys-

tem, especially by reducing the number of the sinuses, bronchi and lung infections. Therefore, it should be remembered that the most frequent reason for death among CF patients' are respiratory complications [15]. The Third National Health and Nutrition Examination Survey (NHANES III) researches revealed a positive correlation between a low vitamin D derivative (25-hydroxyvitamin D) concentration in serum and acute pulmonary disease among patients with CF. It was observed that patients with the highest concentration of this vitamin in serum had 126ml higher forced expiratory volume (FEV₁) and 173 ml higher forced vital capacity (FVC), in comparison with the group of patients with significant hypovitaminosis D. The protective effect of vitamin D in the course of chronic lung disease in CF is mainly discerned in its anti-inflammatory and immunomodulatory properties. The influence of vitamin D management in maintaining the proper level of proinflammatory cytokines, inhibition of oxidative stress development and homeostasis of protease — antiprotease system may result in collagen degradation and processes responsible for lung remodelling suppression [16]. The results of studies indicate that a single dose of 250,000 IU of cholecalciferol to adults with CF who were admitted to the hospital due to exacerbations from the respiratory system, significantly reduced the necessity of next hospitalization during following six months, in comparison to those who were given the placebo [8, 17]. Such a bolus of vitamin D instantly increased its concentration in serum, determining the patients' life extension for at least a year, and also decreased the tumor necrosis factor (TNF- α) in plasma and significantly improved lung functioning [17].

The presence of dense, residual mucus, increased bacterial adherence to epithelial cells and impaired mucociliary clearance makes CF patients' bronchi a perfect place for the development of bacterial infections [18]. It is confirmed by epidemiological studies, which indicate that 40-50% of CF infants undergo such an infection before the age of 6 months [19]. In response to the pathogen in the patient's body, an inflammatory reaction arises, having a destructive effect on the lungs structure, much worse than the infection itself [18]. This immunologic response contributes to the intensified proinflammatory cytokines production (e.g. IL-1 β , IL-6, IL-8) and reduction of anti-inflammatory interleukin (IL-10), which is a reason for increased neutrophil influx to the infected area and respiratory system cells damage [19]. Vitamin D, which inhibits the secretion of TN-

F- α (released under the influence of bacterial lipopolysaccharides) and the expression of pro-inflammatory cytokine genes, plays an essential role in this process. Considering immunological processes, there seems to be an important mechanism in which 1,25(OH)₂D₃ stimulates the expression of VDR, activating the secretion of cathelicidins — peptides with bactericidal effect on many microorganisms [6]. This form of vitamin D prevents, among others, colonization of *Pseudomonas aeruginosa* — a common phenomenon which leads to impaired lung functioning and increased CF patients' mortality [8].

Another potential point of vitamin D impact is the effect on carbohydrate metabolism disorders among these patients. Cystic fibrosis-related diabetes (CFRD) is one of the co-occurring diseases, which early diagnosed and adequately treated extends the patients' survival time. The frequency of its diagnosis increases with age — from 5–8% among 5–10-year-old children to 50% among adult patients [20]. The causes of CFRD are insulin shortages, caused by pancreatic β -cells dysfunction to allow the resistance of peripheral tissues to its action, severity of which is associated with glucocorticotherapy [13, 20, 21]. A specific phenomenon in this type of diabetes is the dynamic variability of glucose metabolism, depending on the presence of the infection, the functioning of respiratory and digestive systems and the nutritional status [22]. Although the vitamin D's influence on CFRD cannot be precisely defined, it is worth considering reports on other types of diabetes. Studies carried out among the populations of patients with type 1 diabetes have shown that the immunomodulatory effect of this vitamin helps to reduce the overactivity of the immune system against pancreatic β cells [23]. What is more, experiments conducted on the NOD mice have proved that long-term calcitriol supplementation results in a reduction of the pancreatic islet cells inflammation and diminishing the incidence of type 1 diabetes [24]. Adequate vitamin D intake in type 2 diabetes is also significant. A decrease of 1,25(OH)₂D₃ concentration in serum is associated with β cells sensitivity to glycemic changes reduction and the insulin resistance of peripheral tissues increase, which increases the risk of developing this disease and results in hindering treatment [23].

The lung transplantation surgery, which is the only chance for some CF patients to improve the quality and length of their lives, is the situation when the proper level of vitamin D can play a crucial role [2]. The effect of calciferol is impor-

tant even before the moment of qualifying patient for the transplantation because contraindications to its implementation include considerable chest distortion or *Pseudomonas aeruginosa* infection (the carrier of this bacterium is considered in some transplantation centers). Furthermore, vitamin D deficiency might be a disqualifying criterion because 20% of CF patients suffer from CFRD, osteopenia, and osteoporosis after transplantation [15]. On the other hand, its proper concentration in serum may determine transplantation success because this fat-soluble vitamin affects antigen presenting cells (including dendritic cells) maturation, which weakens the T lymphocytes effect [25]. At the same time, studies carried out on rats have shown that calcitriol suppresses the transplant rejection reaction more strongly than cyclosporine, simultaneously not increasing susceptibility to fungal and viral infections [26]. Lowry *et al.* [25] conducted experiments assessing the effect of 25(OH)D deficiency in serum of lung transplant recipients' clinical indicators. Their research revealed that such a condition during pre-transplantation period was associated with high risk of organ rejection and infection. What is important, this risk persisted if the level of hydroxyvitamin D did not improve in a year after surgery and had consequences in low patients survival. Moreover, similar results in the prognosis of patients with hypovitaminosis D were found after liver transplantations [27].

Retention of large amounts of sticky mucus impairs not only the lung, but also the intestines functioning, becoming the basis for excessive bacterial colonization, and consequently — intestinal microbiome disorders and the small intestinal bacterial overgrowth syndrome [28]. The proper functioning of the microflora in cystic fibrosis is additionally disturbed by constant exposure to antibiotics used in respiratory tract infections [14]. This type of disorder impairs the complex nutritional compounds metabolism, disrupts energy balance and immunological homeostasis, which leads to malnutrition and increases susceptibility to pathogens and inflammatory reactions [29]. Studies, comparing the composition of the intestinal microbiome among children with CF and healthy ones, revealed that in the first group, there was intestinal dysbiosis present from an early age which worsened over time. Besides, the loss of beneficial bacterial species was associated with the first lung exacerbation and *Pseudomonas aeruginosa* colonization [14]. The influence of vitamin D on the intestinal microflora is possible thanks to the VDR receptor, which plays an

Table 1. The standard and maximum dose of vitamin D3 depending on the cystic fibrosis patient's age and condition (own elaboration based on: [4, 5])

Groups of patients with cystic fibrosis (CF)	The standard supplement dose of vitamin D	The maximum supplement dose of vitamin D
Newborns and infants	400–500 IU/day	2,000 IU/Day
Children 1–10 yr of age	800–1,000 IU/day	4,000 IU/Day
Children > 10 yr of age and adults	800–2,000 IU/day	10,000 IU/day
Pregnant women	extra 600 IU/day	10,000 IU/day

important role in maintaining the integrity of the intestinal mucosa [13]. It is assumed that the role of calcitriol, in this case, is based on increasing of mucous membrane intercellular connections, which control its permeability and reduce the number of proinflammatory cytokines. Its deficiency may enlarge the risk of intestinal damages and inflammation [14]. What makes keeping the normal state of the intestinal microbiome more important, are researches indicating the relationship between the type of bacteria colonizing intestine and lungs. Namely, a large number of pathogens appear in the intestines before hitting the respiratory system [30].

And last but not least, hypovitaminosis D promotes depression. Research indicated a negative correlation between depressive symptoms and serum 25-hydroxyvitamin D concentration. Its deficiency may result in an 8–14% increase in the incidence of depression and 50% higher risk of committing a suicide [31]. Groups of patients suffering from an incurable disease (such as cystic fibrosis) and requiring constant supportive therapy, are particularly vulnerable to mood swings [32]. Recurrent states of symptoms' exacerbation, fears associated with uncertain future, frequent hospitalizations and separation from family, as well as medication reluctance and associated with them side effects, make the effective antidepressant therapy difficult. Vitamin D supplementation, which is a primary prevention and supportive psychological treatment, could be a significant element of multidisciplinary support of CF patients [31, 32]. Especially, that findings from a recent meta-analysis showed that subjects with clinically significant depression had a depressive symptoms reduction after adequate vitamin D supplementation [33].

Considering the wide spectrum of this vitamin activity, it is recommended to keep the concentration of hydroxyvitamin D in serum at the level higher than minimum among patients suffering from CF. The ESPEN-ESPGHAN-ECFS

guidelines indicate that it should exceed 20 ng/ml (50 nmol/l) [5], while the Cystic Fibrosis Foundation sets a concentration of 30 ng/mL (75 nmol/l) as the minimum level [4]. Currently, European organizations recommend an individual vitamin D3 supplementation scheme, with initial and maximum dose depending on the patient's age and condition (table 1) [4, 5]. The initial dose should be modified according to current hydroxyvitamin D concentration in serum, its dietary intake and the level of endogenous synthesis related to sunlight exposure [5].

In conclusion, it can be certainly said that vitamin D plays a significant role in the course of cystic fibrosis. It exerts positive therapeutic effects not only on complications resulting from the basic disease but also on comorbidities. Maintaining its proper concentration in serum can be achieved by its regular monitoring, implementation of an individual supplementation scheme and — if there are no contraindications — sunbathing.

Conflict of interest

The authors declare no conflict of interest.

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