

## VITAMINS AND AMINO ACIDS IN CYSTIC FIBROSIS

Parakhonsky A.P.

Kuban medical institute, Krasnodar, Russia

**Abstract.** Considered the etiology is mucoviscidose. Characteristically, this pathology leads to the airway to breathing problems and bacterial infections. Documented the development of a severe deficiency of fat-soluble vitamins (A, D, E and K), trace elements and amino acids in such patients. Concluded that vitamin supplements make it easier for mucoviscidose, however, the amount of additives is not sufficient for a significant proportion of patients with this disease.

**Keywords:** cystic fibrosis, micronutrients, vitamins, amino acids, imbalance, metabolic disorders.

Cystic fibrosis (CF) is an autosomal recessive disorder that affects multiple organs and results in a median survival age of 35 years. In the United States, approximately 30000 people suffer from CF. In Russia it is estimated that about 12000 people are affected, however, only about 2600 patients are recorded in the national CF-register [3]. The low number of recognised patients is probably due to inadequate screening and diagnosis.

Cystic fibrosis is caused by one of about 2000 possible mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The most predominant mutation, found in about 66% of patients is AF508, i.e. the deletion of the amino acid phenylalanine (F) at position 508 [2]. The protein encoded by the CFTR gene is responsible for the transport of chloride and sodium ions through the plasma membrane. Changes due to mutations in the influx and efflux of the ions result in an altered mucous osmolarity. This leads to blocked bronchial airways by the mucous and results in impaired breathing and bacterial infections.

The pancreas is another organ greatly affected by CF. In pancreatic insufficiency, present in 85-90% of CF patients, the pancreatic ducts are blocked by thick mucus which hinders food digestion, especially of fat and absorption of nutrients. Although pancreatic enzyme replacement therapy is common in CF affected, fat malabsorption still continues at a certain degree. This results in the development of severe deficiency of fat-soluble vitamins (A, D, E, and K) and trace elements. It has been established that the nutrition status of CF patients correlates with their lung function and survival rate. Thus it is important to understand to what deficiencies CF patients are prone to, in order to compensate for them and hence increase their life quality. In this review, the present knowledge of vitamins and amino acids deficiencies or excesses present in CF patients is going to be summarised.

Vitamins are molecules with different functions which are essential for proper development and functioning of the human body. Although CF was not found to be directly correlated with the lack of any specific vitamin, their deficit may significantly aggravate the patient's well-being. Deficiencies in one or more vitamins were found in 46% of CF infants at 4 to 8 weeks of age, with more than one third having multiple vitamin deficiencies. These patients were supplemented with vitamins, and their status checked each year for a period of 10 years. However, despite supplementation, between 4 and 45% of patients showed some vitamin deficit each year. It was also reported that fat-soluble vitamin deficiencies are present in 10-35% of children with pancreatic insufficiency, but in very few pancreatic-

sufficient

patients

[3].

A-tocopherol, is a fat soluble molecule, commonly known as vitamin E. It is present in the plasma membrane of cells and reduces the effects of free radicals. It acts as a powerful antioxidant by decreasing lipid peroxidation, a process in which vitamin E is consumed. Due to the fact that lipid peroxidation is usually increased in CF patients, prophylactic supplementation of vitamin E is recommended [4]. However, most studies agree that there is a portion of CF patients (10-57%) that have vitamin E deficiency. Some reports also suggest that a-tocopherol levels decrease with age [5].

Retinol, is a fat soluble vitamin also known as vitamin A. Among its functions is to maintain the mucus secreting epithelia. Studies on vitamin A deficient rats show that the depletion of the molecule causes changes in the structure of the respiratory epithelium by replacing mucous secreting ciliated cells with squamous epithelium [6]. Although vitamin A supplementation is recommended to CF patients [4], studies mostly agree on the deficiency of this vitamin in a portion of patients (5-29%).

Vitamin D is a fat soluble molecule, the deficiency of which is involved in a wide range of diseases. Vitamin D levels affect bacterial flora, immunity and bone mineralisation. Indeed, the lack of vitamin D leads to reduced calcification of the bone and results in rickets and osteoporosis with associated osteomalacia, CF patients have an increased incidence of bone mineralisation associated diseases, thus they are regularly supplemented with this vitamin [4].

Vitamin K acts as cofactor for the carboxylation of many proteins. Although the exact mechanism still remains to be better understood, the carboxylation of vitamin K-dependent proteins occurs in several tissues and is involved in soft tissue calcification and insulin resistance. A fraction of CF patients has been found to develop CF related diabetes due to insulin resistance and vitamin K deficiency has been reported in CF probably due to malabsorption or the destruction of the intestine microflora by antibiotics. The few studies conducted on vitamin K deficiencies within the CF population show that the molecule levels are decreased in 30-70% of patients [3].

Ascorbic acid, or vitamin C, is the only water soluble vitamin usually included in CF studies. Other water soluble vitamins are thought to be well absorbed by CF patients. However, due to the high lipid peroxidation in CF patients, an increased intake of the antioxidant vitamin C could be beneficial. It has been shown that a higher intake of vitamin C leads to better pulmonary function and is inversely proportional to cough occurrence. CF patients with low vitamin C levels were found to have more incidences of inflammation and oxidative stress. However, consensus has not yet been reached whether CF patients have lower vitamin C levels than health controls. Some authors report that vitamin C levels decrease with age [5].

The study of protein and amino acid levels and their turnover in cystic fibrosis is still in its infancy. Nevertheless, CF patients have been noticed to often suffer from unbalanced protein synthesis and breakdown due to anorexia, inflammation, hypoxia, inactivity, and impaired glucose tolerance.

L-Arginine (Arg) is synthesised in the human cells from glutamine, glutamate and proline. Arg is degraded by arginase and other enzymes into nitric oxide, polyamines, proline, glutamate, creatine, and agmatine. Although being produced by the human body.

Arg is a nutritionally essential amino acid for several human developmental stages. CF patients were reported to have a different Arg metabolism compared to controls. Arg levels were found reduced in CF patients, thus leading to decreased NO levels and impaired pulmonary function [8].

However, plasma arginine and whole-body NO production rate did not differ from controls in all CF patients. Nevertheless, patients with nutritional failure had higher Arg synthesis, but lower plasma Arg concentrations. Arginase was found elevated in lungs tissue of CF patients. This results in Arg deficiency and leads to low levels of nitric oxide in airways and thus impaired pulmonary function [8]. Additionally, the concentration of the Arg product L-ornithine and its derived polyamines was tested in sputum of CF patients and controls. Putrescine and spermidine levels were similar in sputum of both groups. Spermine levels, on the other hand, were increased in CF patients and correlated with disease severity. Spermine contributes to airways obstruction and decreased NO-mediated muscle relaxation [7].

The abovementioned studies show that with in the CF affected population, there is a significant deficit of vitamin E, A and D. the levels of which might depend upon age or ethnicity. More knowledge has to be gained on the levels of vitamin K and C in CF patients. Vitamin supplementation has been shown to alleviate the CF pathology, however, the amount of supplementation is not adequate for a significant part of CF patients. Thus, instead of having general recommendations on vitamin consumption, more personalised approaches have to be implemented in order to supplement each CF patient with an adequate vitamin amount. The impact of cystic fibrosis on amino acids levels still remains to be elucidated. The available data indicate that the amino acid metabolism in CF patients differs from healthy individuals and has to be thoroughly studied.

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