ПРОБЛЕМНАЯ СТАТЬЯ

MINERALS AND TRACE ELEMENTS IN CYSTIC FIBROSIS

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ABSTRACT: Cystic fibrosis (CF) is a single gene disorder which affects multiple organs. Due to intestinal malabsorption, several micronutrients, such as minerals and trace elements (TE), are not adequately absorbed by CF patients. Most studies agree that CF patients have low blood selenium and iron. Copper was found elevated in nails of CF patients and zinc decreased while magnesium elevated in hair of affected. However, studies on the levels of these TE in blood of CF patients have reported controversial results. This is probably due to the fact that only few studies analysed large groups of affected and that there might be variation in TE levels depending on the age and ethnicity. Thus, a new, large scale study should be conducted in order to determine the levels of different TE in CF patients. This will allow supplementing the affected with the correct combination of minerals and thus increase their well-being.

KEYWORDS: cystic fibrosis, micronutrients, minerals, trace elements, imbalance, metabolic disorders.

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disorder that affects multiple organs and results in a median survival age of 35 years (Braga, Almgren, 2013). In the United States, approximately 30000 people suffer from CF (O'Brien, et al., 2013). In Russia it is estimated that about 12000 people are affected, however, only about 2600 patients are recordedin the national CF-register (Kashirskaya, 2008). 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 ΔF508, i.e. the deletion of the amino acid phenylalanine (F) at position 508 (Saleheen, Frossard, 2008). 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 analtered mucososmolarity. This leads to blocked bronchial airways by the mucous and results in impaired breathing and bacterial infections (Siwamogsatham, et al., 2014). 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 (Dodge, Turck, 2006). Although pancreatic enzyme replacement therapy is common in CF affected, fat malabsorption still continues at a certain degree (Siwamogsatham, et al., 2014). This results in the development of severe deficiency of fat-soluble vitamins (A, D, E, and K) (Carr, McBratney, 2000) and trace elements (Yadav, et al., 2014). It has been established that the nutrition status of CF patients correlates with their lung function and survival rate (Liou, et al., 2001; Gozdzik, et al., 2008). 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 trace element deficiencies or excesses present in CF patients is going to be summarised.

TRACE ELEMENTS

Similarly to vitamins, trace elements (TE) are absorbed mostly in the intestine. However, although much attention has been paid to vitamin deficiency in CF patients, much less consideration has been given to a balanced trace element level in the patients. Indeed, while 81% of pancreatic insufficient patients were reported to regularly use fat-soluble vitamin supplements, only few chose to supplement their diet with TE (Hollander, et al., 2010).

Selenium (Se) is a TE known for its antioxidant function, as part of the active site of glutathione peroxidase (GPX). This protein is found in the cytosol and membranes, which protects the cell from oxidative stress (Portal, et al., 1993). It was suggested that CF patients are at risk of Se deficits due to the element malabsorption. In addition, this deficit maycontribute to the pathogenesis in the form of higher oxidative damage resulting in lipid peroxidation (Dworkin, et al., 1987). Most authors agree on a decreased Se level and GPX activity in a fraction of the CF population (Dworkin, et al., 1987). Others state that Se deficiency is only significant in CF children below the age of 6 (Ward, et al., 1984). Se deficiencies were also reported in hair of children and teenagers (Savrasova, et al., 2009).

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Zinc (Zn) is a TE that has an essential role in many organs which are affected in CF (Damphousse, et al., 2014). For instance, Zn is involved in the ciliary function, wound healing and has antioxidant function in the airways epithelium (Rottner, et al., 2011). Zn is also profusely found in the pancreas, where it is involved in glucagon secretion and insulin signalling (Kelleher, et al., 2011). CF related diabetes is characterised by decreased insulin sensitivity and secretion which is associated with Zn deficit (Costa, et al., 2005). The reported authors do not agree whether Zn levels are high, low or do not change in CF patients. However, most state that Zn levels are low in hair of CF patients (Kopito, Shwachman, 1964; Jacob, et al., 1978; Varkonyi, et al., 1992). Zn levels of CF patientsin cerumen were 16 times higher than in controls (Brand-Auraban, et al., 1972).

Copper (Cu) is a TE involved in proper organ functioning and metabolic processes. Humans with Cu deficiency exhibit anaemia and neutropenia (Danks, 1988), while animal experiments have shown Cu deficiency to eventually lead to connective tissue impairment (Medeiros, et al., 1993), pancreatic atrophy (Weaver, et al., 1988) and an impaired immune system (Lukasewycz, Prohaska, 1990).Authors do not agree on Cu levels in blood. Some claim they are decreased, some elevated, while others detect no difference compared to control levels (Table). Cu levels were found elevated in nails of CF patients (van Stekelenburg, et al. 1975; Escobar, et al., 1980).

Table. ***Results of the investigations of macro- and trace elements levels in the blood, if not stated otherwise, of CF patients compared to controls***

Indication	Number of patients	Age, years	Summary of results	Source
Selenium (Se)				
Decreased levels	15	–	In 29% and 33% of CF patients in plasma and red blood cells (RBC) respectively	(Dworkin, et al., 1987)
	6	Children	Very low in plasma and RBC of not supplemented children	(Foucaud, et al., 1988)
	20	Children	Mild deficiency in plasma and RBC of children with pancreatic enzyme replacement	(Foucaud, et al., 1988)
	20	7–19	In plasma and RBC	(Neve, et al., 1983a)
	20	7–19	In plasma and RBC	(Neve, et al., 1983b)
	14	2–19	In plasma	(Richard, et al., 1990)
	13	6–15	In plasma	(van Caillie-Bertrand, et al., 1982)
	20	19–34	In serum	(Stead, et al., 1985)
	31	3–35	In serum	(Michalke, 2004)
	15	0–14	–	(Ward, et al., 1984)
No difference	27	7–20	In plasma	(Portal, et al., 1993)
Decreased GPX levels	14	2–19	In plasma and RBC	(Richard, et al., 1990)
	6	–	Very low levels in untreated children	(Foucaud, et al., 1988)
	20	–	Mild deficiency in children with pancreatic enzyme replacement	(Foucaud, et al., 1988)
	15	0–14	Significant decrease in children below the age of 6	(Ward, et al., 1984)
No difference	13	10–22	–	(Percival, et al., 1995)
Se levels in other analytes	–	1–18	Decreased Se levels in hair of CF patient from Stavropol region, Russia	(Dworkin, et al., 1987)
Zinc (Zn)				
Decreased levels	40	1–46	In plasma of 10% of CF patients	(Akanli, et al., 2003)
	15	Mean 1.8 months	In plasma of 30% of CF patients	(Krebs, et al., 2000)
	27	3 months–12 years	In 96% of North Indian CF children	(Yadav, et al., 2014)
	304	18–66	In plasma of 22% of patients with moderate lung disease	(Damphousse, et al., 2014)

	13	2–19	In plasma	(Safai-Kutti, et al., 1991)
	20	7–19	In plasma of patients with moderate-severe growth retardation and severe pulmonary disease	(Neve, et al., 1983b)
	14	2–19	In serum	(Richard, et al., 1990)
	51	1–46	In RBC of 31% of CF patients	(Akanli, et al., 2003)
Elevated levels	20	7–19	In RBC	(Neve, et al., 1983a)
	20	7–19	In RBC	(Neve, et al., 1983b)
No difference	18	6–17	In plasma, decreases with age	(Jacob, et al., 1978)
	20	7–19	In plasma of relatively healthy CF patients	(Neve, et al., 1983b)
	15	5–22	In plasma and RBC	(Vormann, et al., 1992)
	62	8–11	In plasma	(Maqbool, et al., 2006)
	13	10–22	–	(Percival, et al., 1995)
	13	6–15	In serum	(van Caillie-Bertrand, et al., 1982)
	101	Mean 16	In serum	(Van Biervliet, et al., 2007)
	117	–	In serum	(Kelleher, et al., 1986)
Zn levels in other analytes	18	6–17	Decreased Zn levels in hair	(Jacob, et al., 1978)
	9	–	Decreased Zn levels in hair	(Varkonyi, et al., 1992)
	30	–	Decreased Zn levels in hair and nails	(Kopito, Shwachman, 1964)
	–	–	Elevated Zn levels in nails	(Escobar, et al., 1980)
	23	–	Elevated Zn levels in sputum	(Gray, et al., 2010)
	52	Children	Elevated Zn levels in sputum	(Sirotkin, 1999)
	35	4–21	No difference in Zn levels in submandibular saliva	(Blomfield, et al., 1973)
	52	Children	Elevated Zn levels in urine of CF patients with pulmonary heart disease	(Sirotkin, 1999)
	20	7–30	Elevated Zn levels in the exhaled air condensate	(Griese, et al., 2003)
	7	11–17	Elevated (16 times higher) Zn levels in cerumen	(Brand-Auraban, et al., 1972)
Copper (Cu)				
Decreased levels	27	3 months–12 years	In 44% of North Indian CF children	(Yadav, et al., 2014)
Elevated levels	20	7–19	In RBC	(Neve, et al., 1983a)
	20	7–19	In RBC	(Neve, et al., 1983b)
	7	19–32	In plasma	(Percival, et al.,, 1999)
	18	6–18	In plasma	(Solomons, et al.,, 1981)
No difference	13	10–22	–	(Percival, et al., 1995)
	20	7–19	In plasma	(Neve, et al., 1983b)
	117	–	In serum	(Kelleher, et al., 1986)
	13	6–15	In serum	(van Caillie-Bertrand, et al., 1982)

Cu levels in other analytes	9	–	No difference in Cu levels in hair	(Varkonyi, et al., 1992)
	–	–	Elevated Cu levels in nails	(Escobar, et al., 1980)
	36	Children	Elevated Cu levels in nails	(van Stekelenburg, et al., 1975)
	23	–	Elevated Cu levels in sputum	(Gray, et al., 2010)
	35	4–21	No difference in Cu levels in submandibular saliva	(Blomfield, et al., 1973)
	13	6–15	Elevated Cu levels in urine	(van Caillie-Bertrand, et al., 1982)
	16	0–20	Decreased Cu levels in pancreas	(Kopito, Shwachman, 1976)
Iron (Fe)				
Decreased levels	27	3 months–12 years	In 48% of North Indian CF children	(Yadav, et al., 2014)
	14	2–19	–	(Richard, et al., 1990)
	18	6–18	In plasma	(Solomons, et al., 1981)
	15	5–22	In plasma	(Vormann, et al., 1992)
	117		In serum	(Kelleher, et al., 1986)
No difference	7	19–32	In plasma	(Percival, et al., 1999)
Fe levels in other analytes	9	–	No difference in Fe levels in hair	(Varkonyi, et al., 1992)
	–	1–3	Decreased Fe levels in hair	(Savrasova, 2009)
	52	Children	Elevated Fe levels in sputum	(Sirotkin, 1999)
Magnesium (Mg)				
No difference in Mg blood levels	15	5–22	In plasma and RBC	(Vormann, et al., 1992)
	117	–	In serum	(Kelleher, et al., 1986)
Mg levels in other analytes	30	–	Elevated Mg levels in hair and nails	(Kopito, Shwachman, 1964)
	–	4–6	Elevated Mg levels in hair of CF patient from Stavropol region, Russia	(Savrasova, 2009)
	35	4–21	No difference in Mg levels in submandibular saliva	(Blomfield, et al., 1973)
	7	11–17	Elevated Mg levels in cerumen	(Brand-Auraban, et al., 1972)
	16	0–20	Decreased Mg levels in pancreas	(Kopito, Shwachman, 1976)
Calcium (Ca)				
No difference in blood	117	–	No difference in Ca levels in serum	(Kelleher, et al., 1986)
Ca levels in other analytes	9	–	No difference in Ca levels in hair	(Varkonyi, et al., 1992)
	35	4–21	Elevated Ca levels in submandibular saliva	(Blomfield, et al., 1973)
	7	11–17	Elevated (6 times higher) Ca levels in cerumen	(Brand-Auraban, et al., 1972)
	16	0–20	Elevated Ca levels (10 times higher) in obstructed ductal structures in pancreas, with Ca deficit in adjacent regions	(Kopito, Shwachman, 1976)

Potassium (K)				
K levels in other analytes	9	–	No difference in K levels in hair	(Varkonyi, et al., 1992)
	22	2 months–9 years	No difference in K levels in nails	(Antonelli, et al., 1969)
	30	–	Elevated K levels in hair and nails	(Kopito, Shwachman, 1964)
	4	–	Elevated K levels (1-3 times) in eccrine sweat	(Kopito, Shwachman, 1964)
	35	4–21	No difference in K levels in submandibular saliva	(Blomfield, et al., 1973)
	7	11–17	Elevated K levels in cerumen	(Brand-Auraban, et al., 1972)
	16	0–20	Decreased K levels in pancreas	(Kopito, Shwachman, 1976)
Sodium (Na)				
Na levels in other analytes	4	–	Elevated Na levels (2-5 times) in eccrine sweat	(Kopito, Shwachman, 1964)
	30	–	Elevated Na levels in hair and nails	(Kopito, Shwachman, 1964)
	22	2 months–9 years	Elevated Na levels in nails	(Antonelli, et al., 1969)
	35	4–21	Elevated Na levels in submandibular saliva	(Blomfield, et al., 1973)
	20	7–30	No difference in Na levels in the exhaled air condensate	(Griese, et al., 2003)
	16	0–20	Decreased Na levels in pancreas	(Kopito, Shwachman, 1976)
Chlorine (Cl)				
Cl levels in other analytes	9	–	No difference in Cl levels in hair	(Varkonyi, et al., 1992)
	35	4–21	Elevated Cl levels in submandibular saliva	(Blomfield, et al., 1973)
	20	7–30	No difference in Cl levels in the exhaled air condensate	(Griese, et al., 2003)
Cobalt (Co)				
Co levels in other analytes	–	1–18	Decreased Co levels in hair of CF patient from Stavropol region, Russia	(Savrasova, 2009)
Strontium (Sr)				
Elevated levels in blood	52	Children	Elevated Sr levels in serum	(Sirotkin, 1999)
Srlevels in other analytes	52	Children	Elevated Sr levels in sputum	(Sirotkin, 1999)
	52	Children	Elevated Sr levels in urine of CF patients with pulmonary heart disease	(Sirotkin, 1999)
Manganese (Mn)				
Mnlevels in other analytes	30	–	Elevated Mn levels in hair and nails	(Kopito, Shwachman, 1964)
	–	1–18	Decreased Mn levels in hair of CF patient from Stavropol region, Russia	(Savrasova, 2009)
Chromium (Cr)				
Crlevels in other analytes	52	Children	Elevated Cr levels in urine of CF patients with pulmonary heart disease	(Sirotkin, 1999)

Most of the body iron (Fe) reserve (70%) is located in erythrocytes, while 25% of it is found in ferritin and haemosiderin in the liver, spleen and bone marrow (Sinaasappel, et al., 2002). The level of Fe is usually measured as the amount of ferritin in serum. However, as ferritin concentration might increase with infection, CF patients' Fe levels greatly vary (Sinaasappel, et al., 2002). Fe levels were found by most authors to be decreased in the blood of CF patients.

Magnesium (Mg) participates in various processes of the skeleton and muscular development (Sinaasappel, et al., 2002). In addition, Mg deficits increase oxidative damage (Spasov, et al., 2012), which is already at high levels in CF patients (Dworkin, et al., 1987). Although no decreased Mg levels were found in the summarised studies, cases with hypomagnesaemia due to excessive renal loss of Mg have been reported in children affected with CF (Akbar, et al., 1989). Mg levels have been found elevated in hair of CF patients (Kopito, Shwachman, 1964; Savrasova, et al., 2009).

Less knowledge has been accumulated on the levels of other TE in CF patients and thus their levels in patients will have to be confirmed in future investigations.

CONCLUSION

The abovementioned studies show that there is still no consensus on which TE CF patients are deficient of. Most studies agree on the deficiency of Se and Fe in blood of CF patients. Findings regarding Zn, Cu, Mg and other TE are more controversial. In this literature review only one work was found that comprehensively analysed all TE in different organs (Kopito, Shwachman, 1964). It is now time to repeat such work using more precise techniques and larger groups of patients in order to finally shed some light in what minerals CF patients have deficits and in what tissues.

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МАКРО- И МИКРОЭЛЕМЕНТЫ ПРИ МУКОВИСЦИДОЗЕ

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РЕЗЮМЕ: Муковисцидоз – заболевание, обусловленное мутацией одного гена, поражающее многие органы. Вследствие кишечной мальабсорбции у пациентов с муковисцидозом нарушается всасывание некоторых микронутриентов, таких как макро- и микроэлементы. Большинство исследований показывают сниженную концентрацию селена и железа в крови при заболевании; в ногтях отмечается повышенное содержание меди и пониженное цинка, а содержания магния повышено в волосах. Однако изучение концентраций этих элементов показывает противоречивые результаты. Возможно, это связано с тем фактом, что всего несколько исследований было проведено на больших группах пациентов, также показатели могут варьироваться из-за отсутствия учета возраста и этнической принадлежности. В связи с этим должно быть проведено крупномасштабное исследование по изучению обмена различных макро- и микроэлементов при муковисцидозе. Это позволит поддерживать обмен веществ пациентов путем коррекции комбинацией макро- и микроэлементов с целью улучшения их здоровья.

КЛЮЧЕВЫЕ СЛОВА: муковисцидоз, микронутриенты, макроэлементы, микроэлементы, дисбаланс, нарушение обмена веществ.