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## Case Report

# Up-To-Date Approach To Monitor Pancreatic Exocrine Insufficiency In Adult Patients With Cystic Fibrosis.

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**Abstract:** Cystic fibrosis (CF) is a rare multi-system autosomal-recessive genetic disease. Pancreatic exocrine deficiency (PEI) develops in 85-90% of patients. Proper monitoring of ongoing PEI treatment prevents the development of complications - cardiovascular events, osteoporosis, poor quality of life. In this case of a 32-year-old patient with advanced PEI, we demonstrate the modern approach to monitor patients in adulthood.

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**Keywords:** Cystic fibrosis, pancreatic exocrine failure, malnutrition, monitoring.

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## Introduction:

Cystic fibrosis (CF) is a multi-system autosomal-recessive genetic disease. The most common congenital metabolic disorder among the white population of Europe (20000) and the United States (30000 patients). Historically, it was described for the first time by Fanconi et al. in children in 1936. There are over 1500 mutations in the gene on the 7q31.2 chromosome, a gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein.  $\Delta F508$  is the most common cause of the disease. CFTR is an epithelial cell chloride channel that is expressed in many tissues including the respiratory tract epithelium, sweat glands, pancreatic ducts, liver, colon, parotid gland, kidney and seminiferous tubules. Phenotypic (clinical) manifestations of cystic fibrosis are very different, even in siblings with the same genotype. In the homozygous form, the pancreas is most severely affected, while in the heterozygous form dominates the lungs pathology. In Bulgaria, about 200 patients have cystic fibrosis and fewer than half are adults. About 1/3600 children will be affected by cystic fibrosis. Pancreas exocrine deficiency (PEI) develops in 85-90% of patients due to viscous pancreatic secretions causing luminal ducts obstruction with acinar cell destruction and fibrosis. PEI represents a functional restriction of pancreatic enzyme (amylase, proteases, lipase, colipase and phospholipases) and bicarbonate secretion. Pancreatic enzyme replacement therapy (PERT) is considered to be a golden standard and a fundamental part of PEI treatment including cessation of smoking and alcohol consumption. Optimal PERT allows normalization of nutritional status by preventing potential complications of PEI - increased risk of osteoporosis and fractures, life-threatening cardiovascular events, cachexia. Malnutrition undoubtedly has an adverse impact on the quality

of life. [1, 2, 3]

## Case report

We present a 32-year-old white woman diagnosed with CF in her childhood with pulmonary and pancreatic involvement. At the age of 18 she manifested pancreatogenic insulin-dependent type 3c diabetes mellitus. After a normal pregnancy in 2014 she gave birth to a healthy child. She received as a daily treatment Pulmozyme, Simbocort, Spiriva, Insulin, PERT 125,000 U lipase/daily. By the time of hospitalization, she did not perform any laboratory evaluation and follow-up of the nutritional status, relying solely on the symptoms themselves. She was admitted at the gastroenterology department of University Hospital Tsaritsa Ioanna-ISUL because of malabsorption clinical signs – weight loss of 2 kg during the last month with twice appeared steatorrhea-like stools. On exam, there were no pathological abnormalities in the respiratory and cardiovascular status with mild abdominal pain with punctuate maximus the right hypochondrium. Her habitus was considered as asthenic with estimated BMI of 16.5 kg/m<sup>2</sup> (underweight) and muscle mass of 7.7 kg.

An indirect functional test was performed to assess the residual pancreatic function, indicating severe PEI - faecal elastase-1 = 4.54 mcg/g feces. For better understanding and evaluating of the pancreatic structure and function, a secreted-enhanced MRCP was performed. Intra- and extrahepatic bile ducts were not dilatated. The body and tail of the pancreas were with reduced size. The pre-secretin images visualized an unregularly dilated main pancreatic duct (up to 4.3 mm) with at least 7 small-sized cystic formations (diameter 4 to 8 mm) in between. After secretin administration, the pancreatic exocrine secretion was inadequate, with a poor filling of the

duodenal bulb at 13th minute. The visible part of the pancreatic duct was inadequately dilated (less than 1 mm). As a further finding of the post-secretin images, a duct of Santorini was established. The morphological changes were assessed as severe - grade IV by the Cambridge classification for CT/MRCP (figure 1). We demonstrated a significant reduction of the exocrine function - grade I by Matos (figure 2, 3). According to the chronic pancreatitis severity M-ANNHEIM classification, the patient was assessed with an advanced chronic pancreatitis- grade C.



Figure 1



Figure 2



Figure 3

Hemoglobin A1c and nutritional status were examined for monitoring of endocrine and exocrine pancreatic function. We observed a good glycemic control based on HbA1c - 6.9%. We demonstrated protein malnutrition via low levels of prealbumin (0.129 g/L) and retinol-binding protein (0.016 g/L). In addition, we found a severe vitamin D deficiency (13.8 nmol/L), which is increasing the risk of osteoporosis, vitamin A (187 µmol/L) and vitamin E deficiency (1.9 mg/L) in the presence of a normal lipid profile: HDL cholesterol: 1.57 mmol/L; LDL-cholesterol: 3.49 mmol/L, triglycerides: 0.71 mmol/L; VLDL-cholesterol: 0.55 mmol/L; Cholesterol: 5.61 mmol/L. Magnesium levels of 0.8 mmol/L were within the normal range.

Because of the elevated cardiovascular risk in patients with PEI and diabetes mellitus, we further investigated the protective apolipoproteins (apo) - Apo A-I: 163.63 mg/dL and Apo A-II: 0.158 g/L as well as the pro-atherogenic ApoB-100: 107.95 mg/dL and Apo C-III: 64 mcg/ml. Except for Apo A-II, which was below normal ranges, all other apolipoproteins were in reference values. However, when calculating the Apo B/ Apo A-I ratio, used for myocardial infarction risk assessment (AMORIS, INTERHEART studies), we demonstrated a moderate risk of 0.66 in our patient. A periodical monitoring of cardiovascular risk factors shall be performed.

The suboptimal dose of PERT was increased to 250000IU lipase / daily. In the second follow-up 3 months later, there was no weight loss with an increase in BMI (19.5 kg / m<sup>2</sup>). Although there was no significant improvement in protein status (prealbumin 0.133 g/L and retinol-binding protein 0.014 g/L), we observed elevated levels of vitamin A (250 µmol/L) and D (57.3 nmol/L), normalization of vitamin E (7.3 mg/L) with a normal lipid profile. The daily dose of PERT was further increased to 350000IU lipase daily without reaching the maximum daily dose of 500000 IU. Oral vitamin D supplementation was included.

### Discussion:

Severe malabsorption and malnutrition in CF are mainly connected to pancreatic dysfunction, although other possible causes - dysfunction of the small intestine and bacterial overgrowth. Providing pancreatic enzymes improves malabsorption, but does not return the absorption function of the gastrointestinal tract to normal. The dosage should be individualized. When monitoring the nutritional status of patients with CF, the BMI aims at more than 20 kg/m<sup>2</sup>, which correlates with better pulmonary function. The optimal effect of pancreatic enzyme replacement therapy (PERT) is determined clinically by signs of malabsorption and by monitoring nutritional status. The symptoms absence does not guarantee the normalization of nutritional status. CF patients should start treatment with the lowest recommended dose and increase it on the basis of weight gain and gastrointestinal symptoms to the lowest effective dose. Excessive doses are associated with the development of a fibrotic colon. Therefore, 10000 IU lipase / kg / day or 6000 IU / kg / meal should not be exceeded. Enteral nutrition is indicated if the nutritional status gets worse or does not improve. Supplementing with fat soluble vitamins should be indicated by laboratory testing [3, 4, 5].

Common pancreatic morphological changes in adults are pancreatic small-sized 1-3 mm cysts (pancreatic cystosis), fat replacement being the most common pancreatic finding 56-93% of patients - lipomatous pseudohypertrophy. Pancreatic calcifications occur in about 7%, varying in size, shape and position in the main pancreatic duct. Pancreatic ducts disorders include strictures, dilations, obstructions [6, 7].

Good prognosis requires an early diagnosis and effective treatment. Average survival rate in Europe is 37 years. It is expected to reach over 40-50 years. Patients with type 3c diabetes have a 6-fold higher mortality. The disease could progress to lung and heart failure, severe PEI. There is an increased risk of developing pancreatic adenocarcinoma (OR 1.82, 95% CI, 1.14-2.94, p = 0.011) [8].

### Conclusion:

The treatment and monitoring of malnutrition in people with CF is a difficult and inexact science. The reported clinical case demonstrates the necessity to apply modern standards for evaluation and monitoring of nutritional status in patients with cystic fibrosis with subsequent onset of enzyme replacement therapy and / or correction of suboptimal dose. PERT overcomes some, but not all, signs and symptoms of malabsorption and clinical parameters commonly used to adjust PERT dosing are shown not to be good discriminators. The right approach would improve the quality of life and average survival of CF patients.

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