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The practical application of modern guidelines for the diagnosis and treatment of exocrine pancreatic insufficiency in patients with chronic pancreatitis

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Abstract
The article presents an overview of current European and Russian guidelines of the diagnosis and management of exocrine pancreatic insufficiency in patients with chronic pancreatitis. The results of our own comparative studies on the treatment of pancreatic enzyme insufficiency in 55 patients treated with enzyme replacement therapy with adequate and low doses confirm the advisability of using the recommended doses of enzyme replacement therapy (ERT) (micronized polyenzyme drugs), since not only the reduction of the clinical signs are observed, but also the normalization of the nutritional status. The results of the study indicate that the optimal way to assess the effectiveness of the ERT is to normalize the anthropometric and biochemical parameters of the nutritional status.
Key words: chronic pancreatitis; exocrine pancreatic insufficiency; nutritional status; treatment.

In February 2017, terms of the Russian consensus on the diagnosis and treatment of chronic pancreatitis were presented. Purposes of this consensus document, prepared on initiative of the Russian " Pancreatic Club " were the identification and consolidation of leading domestic specialists' views (gastroenterologists, surgeons, pediatricians) on current diagnosis and treatment issues of chronic pancreatitis (CP) [1].

In March 2017 Paneuropean clinical guidelines for the diagnosis and treatment of chronic pancreatitis, based on the principles of evidence-based medicine, were published. Twelve interdisciplinary groups presented systematic reviews of the scientific literature describing etiology of CP, instrumental diagnostics using visualization methods, diagnostics of exocrine pancreatic insufficiency (EPI), surgical, medical and endoscopic treatment; treatment of pancreatic pseudocysts, pancreatic pain, mallutrition and nutrition, pancreatogenic diabetes, the natural course of the disease and quality of life [2].

It should be noted that all the recommendations, built on the basis of modern scientific data, are close to the framework. Following recommendations are given in the Russian consensus section on the diagnosis of the EPI:

1. In clinical practice, estimation of pancreatic elastase in feces should be used to identify exocrine pancreatic insufficiency, because this test is the most accessible.

2. After CP diagnosis, an examination of pancreas exocrine function should be conducted.

3. Progression or emergence of new symptoms that may be associated with EPI, are grounds for re-examination of its exocrine function, if previous data did not differ from the normal range.

4. Patients with diabetes mellitus have an increased risk of developing exocrine pancreatic insufficiency, therefore, if there are clinical signs, functional tests should be performed.

European recommendations, in response to the question "What analysis / research is indicated for the diagnosis of exocrine pancreatic insufficiency in clinical practice?", Indicate the following:

"In a clinical setting, it is necessary to conduct a non-invasive functional study of the pancreas. Fecal elastase-1 (FE-1) analysis is widely available, and a breath test using 13C-mixed triglycerides seems to be an alternative examination. The use of MRCP with secretin can also be used as a diagnostic method for exocrine pancreatic insufficiency, but this technique provides only "semi-quantitative data". Thus, estimation of pancreatic elastase in feces comes first concerning EPI diagnosis in everyday practice.

Approaches to the medical correction of exocrine pancreatic insufficiency are almost identical: the indications for replacement enzyme therapy are clinical symptoms or laboratory signs of malabsorption. To identify signs of mallutrition, it is recommended to conduct an appropriate nutritional assessment. The classic indication for enzyme replacement therapy is steatorrhea with the excretion of fat with feces at a level of> 15 g / day. However, the quantitative determination of fat in feces is often not carried out. Therefore, the indications for enzyme replacement therapy are also the pathological results of a functional study of the pancreas in conjunction with clinical signs of malabsorption or anthropometric and (or) biochemical signs of malnutrition. These signs include: weight loss, diarrhea, marked flatulence, and abdominal pain. Low values of the most common markers of nutritional deficiency (fat-soluble vitamins, prealbumin, retinol-binding protein and magnesium) are also an indication for the appointment of enzyme replacement therapy. Body weight, body mass

index, shoulder circumference, cholesterol, lymphocyte level, muscular strength of the hand (compression into a fist), symptoms of specific nutritional deficiency (hair loss, glossitis, dermatitis, parasthesia) can be used as other parameters of the clinical assessment of nutritional status.

The drugs of choice for the treatment of exocrine pancreatic insufficiency include microencapsulated pancreatine preparations in the enteric coating, the size is up to 2 mm. Micro- or mini-tablets of 2.2–2.5 mm in size can also be effective, although there is much less scientific evidence about this. Small differences are observed in relation to the recommended dose of lipase: according to the European recommendations, 40-50 thousand units with main meals should be used for initial therapy and half of this dose should be used for intermediate meals. Domestic recommendations offer 25 -40 thousand units for the main meal, and 10-20 thousand units for snacks with remark that we are talking about the minimum doses.

To assess the effectiveness of enzyme replacement therapy, it is proposed to determine the dynamics of symptoms associated with maldigestion (steatorrhea, weight loss, flatulence), and the parameters of the nutritional status of patients (anthropometric and biochemical). In the domestic recommendations, clinical indicators are suggested for evaluating effectiveness: weight gain, normalization of vitamin status, cessation of abdominal symptoms. The analysis of the data suggests that Russian and European approaches are identical in both diagnosis and treatment of exocrine pancreatic insufficiency in patients with CP.

However, a review of real practical recommendations given to patients with CP with exocrine pancreatic insufficiency in clinics or hospitals, doctors of various specialties (general practitioners, surgeons, less often - gastroenterologists) suggests that the above provisions on the required doses of multienzyme preparations are not always followed. Often you can find recommendations with an indication of the daily dose of the multienzyme medication 30 - 60 thousand units for lipase activity. There is an opinion among both patients and, unfortunately, individual doctors about the deterioration of the pancreas during the treatment with adequate (100-150 thousand units) doses of modern multienzyme medications. Another reason for non-compliance with the latest recommendations may be the high cost of microencapsulated pancreatin drugs.

The purpose of this study was to compare the effectiveness of enzyme replacement therapy with microencapsulated multienzyme preparations in patients with chronic pancreatitis with exocrine pancreatic insufficiency using adequate and low doses. The first group consisted of 40 patients with CP and exocrine pancreatic insufficiency, proved by the fecal elastase test results, and treated with enzyme replacement therapy at a dose of 100-150 thousand units for lipase activity, depending on the degree of exocrine pancreatic insufficiency. The second group consisted of 15 patients with CP with exocrine pancreatic insufficiency, who for various reasons (impossibility or reluctance, the existing recommendations of other doctors) received enzyme replacement therapy in a random dose, from 10 to 25 thousand units for lipase activity for food intake, the average dose amounted to 12.5 thousand units for a meal. The follow-up period was 3 months. General data is presented in table 1.

Table 1

Group	1 st	2 nd
Number of patients	40	15
Average age	54,9±13,8	54.7±14,0
Number of men	24 (60%)	9 (60%)
Number of women	16 (40%)	6 (40%)

Investigation of patients was the collection of complaints and anamnesis, physical examination, registration of anthropometric indicators (height, weight). Evaluation of clinical symptoms was carried out on a 5-point scale: 1 point - a symptom is absent, 2 points - symptom severity is weak (you cannot notice if you do not think), 3 points -

Table 2

Clinical and anamnestic data of patients of the studied groups

Group		1 st	2 nd
Number of patients		40	15
Duration of illness, years		4,1±7,2	2,9±3,9
Alcohol		24 (60%)	8 (53%)
Smoking		18 (45%)	7 (47%)
Complications of CP	Ectasia of Wirsung's duct	7 (17,5%)	8 (53%)
	Pancreatic Pseudocyst	11 (27,5%)	7 (47%)
	Lithiasis of Wirsung's duct	2 (5%)	2 (13%)
	Infiltrates	2 (5%)	2 (13%)
	Pancreas Fibrosis	7 (17,5%)	1 (7%)
	Pancreatic calcifications	5 (12,5%)	3 (20%)
Etiology of the disease	Alcoholic	25 (62,5%)	7 (47%)
	Biliary	5 (12,5%)	4 (27%)
	Idiopathic	8 (20%)	4 (27%)
	Pancreatectomy	2 (5%)	0 (0%)
Concomitant pathology	Duodenal ulcer	4 (10%)	0 (0%)
	Stomach ulcer	2 (5%)	0 (0%)
	Chronic alimentary hepatitis	6 (15%)	2 (13%)
	A history of cholecystectomy	7 (17,5%)	0 (0%)
	Cholelithiasis	2 (5%)	3 (20%)
	Chronic cholecystitis	1 (2,5%)	2 (13%)
	Diabetes	8 (20%)	3 (20%)

moderate symptom severity (you cannot ignore, but does not violate daily activity or sleep), 4 points - the severity of the symptom is strong (disrupts daytime activity or sleep), 5 points - the severity of the symptom is very strong (significantly disrupts daytime activity or sleep, rest is required); studied clinical and biochemical blood tests, conducted an ultrasound examination of the abdominal cavity organs. Determination of fecal elastase-1 was carried out by enzyme immunoassay (once at the beginning of the study). The results of the study with values above 200 μg / g of feces were considered normal, with values from 100 to 200 μg / g of feces, a moderate degree of exocrine pancreatic insufficiency was recorded, with values below 100 μg / g of feces - a pronounced degree of exocrine pancreatic insufficiency.

Statistical processing of the results was carried out using StatSoft STATISTICA 10 software. Student's t-test was used to analyze the parametric data, and Wilcoxon signed-rank test for non-parametric data. Differences with $p \leq 0.05$ were considered statistically significant.

Characteristics of the studied patients are presented in table 2.

Evaluation of parameters number of nutritional status is presented in table 3.

Table 3

Initial parameters of patients` nutritional status

Parameters	1 st group	2 nd group
BMI (kg / m^2)	22,2±3,5	20,4±2,8
Hemoglobin (g / l)	130,8±19,9	128,5±18,2
LYM	2,14±1,3	2,0±0,7
Cholesterol (mmol / l)	4,7±1,43	4,75±1,7
HDL (mmol / l)	1,25±0,36	1,2±0,5
Triglycerides (mmol / L)	1,34±0,73	1,4±0,6
Total protein (g / l)	70,5±8,9	63,6±16,4
Albumin (g / l)	36,1±6,7	29,8±10,3
Prothrombin index (%)	91,7±18,6	90,5±19,0

As demonstrated in the table, no significant differences in the studied parameters of the nutritional status were observed before treatment.

Comparison of clinical efficacy is presented in Tables 4 and 5.

The table shows that group 2 is characterized by a less pronounced dynamic in almost all symptoms.

Table 4

The frequency of symptoms before and after treatment

Parameters	1 st group		2 nd group	
	Before treatment	After treatment	Before treatment	After treatment
Pain	20 (50%)	12 (30%)	8 (53%)	5 (33%)
Heartburn	6 (15%)	0 (0%)	1 (7%)	1 (7%)
Nausea	4 (10%)	0 (0%)	1 (7%)	1 (7%)
Belching	2 (5%)	1 (2,5%)	10 (67%)	8 (53%)
Abdomen heaviness	22 (55%)	12 (30%)	3 (20%)	2 (13%)
Early satiety	19 (47,5%)	10 (25%)	4 (27%)	2 (13%)
Flatulence	29 (72,5%)	13 (32,5%)	5 (33%)	3 (20%)
Frequent bowel movements	20 (50%)	9 (22,5%)	0	0

Table 5

Symptom intensity before and after treatment

Parameters	1 st group		2 nd group	
	Before treatment	After treatment	Before treatment	After treatment
Pain	1,8±0,8	1,2±0,4*	1,73±0,8	1,3±0,5*
Heartburn	1,3±0,6	1*	1,1±0,3	1,1±0,3
Nausea	1,1±0,2	1	1,1±0,3	1,1±0,3
Belching	1,1±0,2	1,0±0,1	1,7±0,5	1,5±0,5
Abdomen heaviness	1,9±0,9	1,3±0,6*	1,26±0,6	1,15±0,4
Early satiety	1,7±0,8	1,3±0,4*	1,26±0,5	1,15±0,4
Flatulence	2,4±1,1	1,4±0,6*	1,33±0,5	1,23±0,4
Frequent bowel movements	2,1±1,2	1,3±0,6*	0,77±0,4	0,85±0,4

* differences are statistically reliable (t-test for paired samples, P≤0.05).

Table 6

Dynamics of clinical blood analysis

Indicator	1st group		2nd group	
	Before treatment	After treatment	Before treatment	After treatment
Erythrocytes (10^{12} / l)	4,4±0,7	4,5±0,7	4,2±0,5	3,9±0,6*
Hemoglobin (g / l)	130,85±21,7	135,0±14,9*	128,5±18,2	111,1±11,8
Platelets (10^9 / L)	275,9±115,1	253,8±72,2	301,6±77,5	441,5±280,4
Leukocytes (10^9 / l)	7,1±3,6	6,95±2,1	9,98±3,6	6,8±2,3*
Lymphocytes (%)	29,2±8,7	33,4±7,6*	21,2±11,8	22,3±16,8
LYM (10^9 / L)	2,14±1,3	2,6±1,1*	1,75±0,9	1,65±0,5
ESR (mm / hour)	12,4±7,5	11,0±6,1	15,2±7,6	26,8±12,9

* differences are statistically reliable (t-test for paired samples, P≤0.05).

Table 7

Dynamics of biochemical blood analysis

Indicator	1st group		2nd group	
	Before treatment	After treatment	Before treatment	After treatment
Cholesterol (mmol / l)	4,7±1,43	5,1±1,2*	4,75±1,7	4,8±1,6
HDL (mmol / l)	1,25±0,36	1,4±0,4*	1,2±0,5	1,1±0,5
Triglycerides (mmol / L)	1,34±0,73	1,47±0,7*	1,46±0,6	1,4±0,7
Total protein (g / l)	70,5±8,9	72,9±6,8*	63,6±16,4	65,1±7,7
Albumin (g / l)	36,1±6,7	40,9±5,8*	29,7±10,3	34,6±6,3
Prothrombin index (%)	91,7±18,6	97,4±15,4*	72,6±15,9	70,0±17,1

* differences are statistically reliable (t-test for paired samples, P≤0.05).

The intensity of the symptoms before and after treatment are presented in table 5

The table shows that in 1 group there was a significant positive dynamics of pain, heartburn, abdomen heaviness, early satiety, flatulence and bowel movements frequency, whereas group 2 showed a significant positive dynamic only of pain severity.

Comparison of laboratory studies presented in tables 6 and 7.

From the data presented in the table we can see that in group 1 there was a significant positive change in hemoglobin level, relative and absolute number of lymphocytes, whereas in group 2 there was a decrease in the level of erythrocytes and leukocytes, with an increase in ESR.

Dynamics of biochemical blood analysis is shown in Table 7.

Thus, in group 1, there was a significant positive trend in all the studied parameters, while in group 2, no reliable positive dynamics were found for any of them, moreover, there was a tendency to decrease in such parameters as total protein, albumin and prothrombin index.

Comparison of the dynamics of BMI. In the first group, there was a significant positive dynamics of BMI: from 22.2 ± 3.5 kg / m^2 to 23.0 ± 3.2 kg / m^2 (p = 0.000004), whereas in the second group there was no dynamics - from 20,4 ± 2,8 kg / m^2 to 20,2 ± 3,3 kg / m^2

Conclusion

The results of the study suggest that the use of multienzyme drugs for the treatment of exocrine pancreatic insufficiency in patients with chronic pancreatitis should be carried out in doses prescribed by modern guidelines. At the same time, there is significant positive dynamics of symptoms and improvement of anthropometric and biochemical markers of nutritional insufficiency. In case of treatment with insufficient doses, there is a positive dynamics of the clinical picture, however, there are no changes in the indicators characterizing the nutritional status, which indicates a low efficacy of therapy with insufficient doses of enzyme drugs. Despite the fact that the disappearance of clinical signs of malabsorption is generally considered the most important criterion for the success of enzyme replacement therapy, it has been shown that relief of symptoms is not always combined with normalization of nutritional status. A recent review showed that the best way to assess the effectiveness of enzyme replacement therapy is normalization of the nutritional status parameters, both anthropometric and biochemical [3].

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