

Enzyme replacement therapy for maldigestion syndrome: clinical surveillances

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The syndrome of maldigestion develops in approximately 50% of patients with chronic pancreatitis (CP) after an average of 10 to 12 of onset of the disease, but in a small number of patients do not develop clinically significant exocrine pancreatic insufficiency (EPI) even at a later date [3]. Despite the fact that outcomes maldigestion, secondary relative to CP, insufficiently studied generally accepted that this difficulty has important prognostic value. Together with the well-known problems linked to the malnutrition, second in CP maldigestion associated with life-threatening complications, including cardiovascular events, which is related to the abnormally low levels of lipoprotein C of high density, apolipoprotein A-1 and lipoprotein A [1, 3]. So maldigestion adequate therapy is crucial in reducing morbidity and mortality linked to the CP.

Treatment maldigestion obviously indicated in symptomatic cases steatorrhea or steatorrhea exceeding 15 g/day [2, 11]. The therapy of choice in these cases is based on oral pancreatic enzymes. Mostly because of the problems is related to the inactivation of acid lipase, and the need for adequate gastric stirring and evacuation enzymes with nutrients, generally the best form of pancreatic enzymes is lined shell enteric soluble minimicrospheres [1, 6, 8, 11]. The only representative of this form of release is enzymesubmitted under the brand name Creon® (Abbott Laboratories GmbH). Minimicrospheres important advantage compared, for example, minitabket drugs are the number of particles with enzymes in one capsule. Obviously, the capsule containing 280 — 500 shares (minimicrospheres) with enzymes provide much more uniform mixing of chyme than a capsule containing 24 — 30 microtablets [1]. Such careful distribution achieves minimicrospheres contact area of the enzymes in the chyme 2 — 2.5 times more than her than with minitabket and 8 times more than her, than with tabletk. [12] This significantly speeds up the start splitting lipids and increases ist effective digestion using enzymes as minimicrospheres [9]. This was confirmed by his own studies [4].

In respect of about the lack of 'subjective method of selection of adequate doses of enzymes for each individual patient, the dose usually is calculated empirically to avoid diarrhea and weight loss [2].

But, 70% of patients with maldigestion associated with CP, are abnormally low nutritional indicators (usually it is the serum levels of fat-soluble vitamins), despite the subjective improvement of clinical symptoms by means of substitution enzyme therapy [10]. There is a concept that enzyme replacement therapy is given to normalize redigestion and absorption of fat and not only them, to obtain a clinical response. Quantitative determination of fecal fat is considered as the gold standard for assessing the digestion of fats in the context of CP [7]. This method, however, is too technically difficult and carries significant discomfort to be widely used in clinical practice to optimize enzyme replacement therapy. Therefore, in clinical practice, do not use methods against "subjective control intended dosage of enzyme preparation (EP) or taken into consideration usual scatological study. In the last decade in clinical practice implemented method of appointment of EP depending on the EPI defined research fecal elastase-1. As shown by our study, based only on the data, it is difficult to pick up once the optimal dose of EP.

With this in mind, this study had the following **aim is to** evaluate the effectiveness individually selected oral enzyme replacement therapy using enzymes to form minimikrosfer in patients with pancreatic and maldigestion enterogenous origin and determine the effect of treatment on the nutritional status **of patients.**

The work was performed at the Department of Internal Medicine number 1. The study included a control group of healthy volunteers (30 persons) and 135 patients with CP, and 30 patients who had celiac disease combined with CP. All patients were chosen enzyme therapy, based on data ^{13}C -triglyceride breath test and inspect the spare wires at 1 year and 2 years after treatment of EP. The survey involved a re-performance ultrasound of the abdomen, repeated execution General clinical tests (complete blood count, blood chemistry, coprogram, urinalysis), enzyme-linked immunosorbent research quantities of fecal elastase-1, ^{13}C -corn starch breath test (CBT) and ^{13}C -triglyceride breath test (TBT) under the standard procedure outside reception enzymes [2, 3, 4, 13, 14]. Controlled by one year left on camping 129 patients. Mortality was 2.2% (3 persons), three more persons (2.2%) were lost due to loss Communications with them for some reason. Poor (EP irregular intake and/or alcohol above safe doses) compliance was 19 people (14.7%). These patients were re-examined, stressed the need for adherence data relevant recommendations, but with experimental studies on long-term results were excluded. For further revised results comparing changes in the range of 1 year of treatment was revised distribution of patients according to the initial clinical groups, the results of which are shown in Table 1.

The reliability of the difference data with repeated measurements was evaluated using Wilcoxon method. The reliability of these differences when comparing different groups was evaluated using the method of Mann-Whitney.

Table 1

Exocrine function of the pancreas in patients with CP before treatment and in 1 year of observation

Group	The degree of severity EPI	Elastase-1 (faecal) mg/g M ± m		KD (360hv),% M ± m	
		Before treatment	After 1 year	Before treatment	After 1 year
Group 1, (n = 24) (-6)	Lightweight (no fecal elastase according to 1)	23 8,9 ± 11,2	261,3 ± 10,9	23,9 ± 4,3	27,3 ± 3,4 *
Group 2, (n = 28) (-2)	Easy	166.2 10.2 ±	226,9 ± 11,4 *	19.1 ± 3.0	29,6 ± 3,9 *
Group 3, (n = 40) (- 10)	The average	75.2 ± 7.6	131, 4 ± 10,7 *	1 0 9 2,2 ±	18,7 ± 2, 9 *
Group 4, (n = 18) (-7)	Weight	34.5 ± 3.9	46,2 ± 4,4	5.0 ± 1.2	8,1 ± 1,9 *
Control, (n = 30)	No	390.1 30.2 ±		42.0 ± 7.8	

Note: zme nshennya parentheses indicate the absolute number of patients compared with primary survey one year ago.

* — Figures statistically significant (p <0.05) as compared to before treatment.

It was found that long-term treatment of pancreatin patients with CP of EPI can restore (in whole or in part, depending on the initial level EPI) own exocrine function pancreas that may, due to a regeneration proper parenchyma pancreas and improvement pits receipt of enzymes in the lumen of the duodenum due to recovery reflex opening of the sphincter of pancreatic duct. The latter factor largely linked to the normalization of diet, its regularity, cessation of alcohol abuse. Thus, among patients first 2 groups (in fact, these patients with mild EPI) observed EPI to restore normal numbers, as according to the TBT and according fecal elastase-1. At the individual level is concerned mainly patients under 65 years.

In the third group, 22 of 41 patients (53,7% ± 7,8%) experienced a significant improvement in all indicators EPI. Overall, the results were significantly different from the initial (before treatment) data. Among patients of the fourth group also observed a tendency to self improvement pancreas function

according to a study of fecal elastase-1, the results of TBT significantly observed great improvements.

Correction dose FP, according to the TBT was performed in all patients that needed it. Patients who were found EPI normalization, it was recommended adherence to diet and intake of enzymes "on demand" with the appearance of bloating or unformed stool, a possible consequence of personal dietary errors.

After 2 years, examined a total 99 patients (Table 2). Lost of research we had 2 patients because of death (from causes not linked to the CP), 6 patients refused to participate in further investigation of personal circumstances, and 3 patients changed their residence.

Table 2

Exocrine function of the pancreas in patients with CP in comparison to the control treatment and observation after 2 years

Group	Initial severity EPI	Elastase-1 (faecal) mg/g M ± m		K D (360hv),% M ± m	
		After 1 year	After 2 years	After 1 year	After 2 years
Group 1, (n = 20) (-4)	Lightweight (no fecal elastase according to 1)	255,7 ± 11,1	2 48,3 ± 11,1	27,3 ± 3,4	25,9 ± 3,4
Group 2, (n = 27) (-1)	Easy	226,2 ± 11,4	209.2 11.2 ±	29,6 ± 3,9	23.1 ± 3.0 *
Group 3, (n = 36) (-5)	The average	127, 3 ± 10,7	134.2 ± 7.6	18,3 ± 3 0	19,0 ± 3 0
Group 4, (n = 17) (- 1)	Weight	46,1 ± 4,4	44,2 ± 4,4	8,0 ± 1,9	8,2 ± 1,9
Control, (n = 30)	No	390.1 30.2 ±		42.0 ± 7.8	

Note: The parentheses indicate a decrease in the absolute number of patients compared with primary survey one year ago.

* — Figures statistically significant (p <0.05) as compared to before treatment.

Results of follow generally showed that after 2 years of treatment EPI indicators remained generally comparable with those that received 1 year of observation, indicating only partial repayment reduction EPI. Significantly difference appeared only in terms of TTX in patients with mild EPI — in this group of indicators of fecal elastase-1 is not materially different from the data after 1 year of treatment. Such data can be explained, firstly, greater sensitivity to mild EPI, second, the permanent abolition of enzyme therapy in some patients adversely

affected the utility is subject NSO in terms of diet and drinking no more than 30 g/day.

The evolution of the body mass index (BMI) of patients are shown in Fig. 1 and Fig. 2.

Thus, to treat the average BMI among 110 patients was $16,7 \pm 1,1 \text{ kg/m}^2$. Observation 1 year — $20,9 \pm 1,3 \text{ kg/m}^2$, $p < 0.0001$. After 2 years of follow-up statistically significant increase in BMI was not, it was $21,0 \pm 1,3 \text{ kg/m}^2$, $p = 0,189$, but he remained in the normal range, which is 18.6 — 24.9, i.e. clinical task of eliminating malnutritional status was achieved.

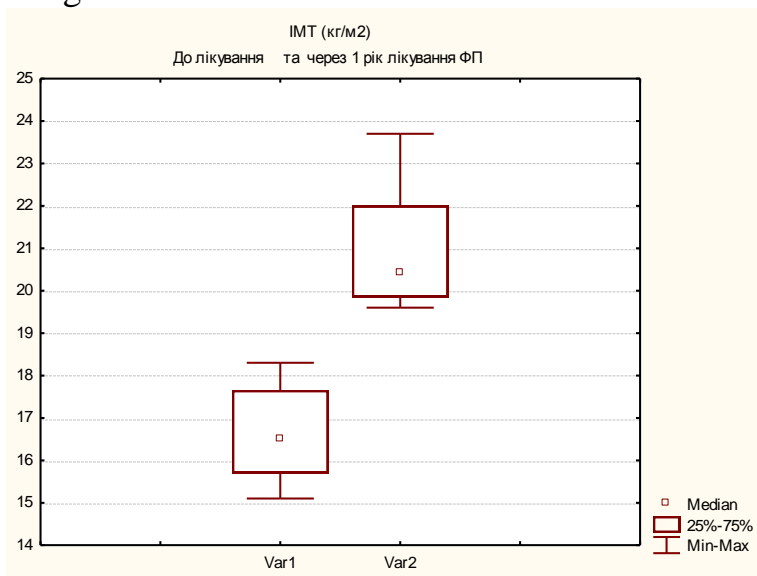


Fig. 1. BMI in the dynamics of treatment after 1 year.

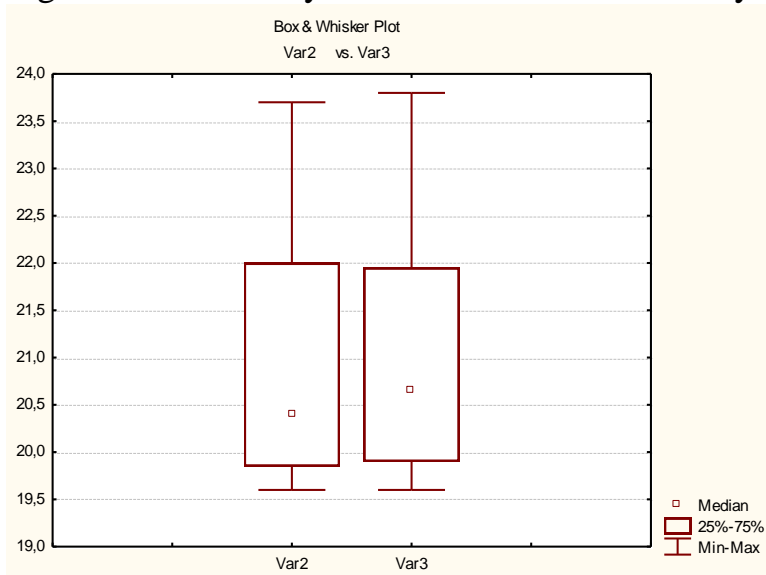


Fig. 2. BMI dynamics in the second year of treatment.

Given the relatively low specificity CBT on diagnosis function is pancreas, survey of patients with the help of the dynamics in terms of inappropriate

monitoring of patients with established pancreas function. Therefore, data analysis CBT in the long term among patients with CP was not carried out.

CBT was done after 1 year of therapy in patients who had United pathology — CP and celiac disease. Treatment of these patients has included compliance with a gluten-free you use enzymes, the dose of which was picked up by the results of TBT. Especially in attention to was paid utility is NSO patients in this group that carried out for monthly consultations with making dietary adjustments and giving me recommendations on the need to observe a gluten-free diet, and exclude alcohol pereyidan, fatty, fried foods, and -required 'compulsory admission designated EP — minimicrosphere pancreatin in the form of a soluble enteric capsule (Creon in individual dose). The results of the comparative evaluation of data fecal elastase-1 and CBT are given in the tTable 3.

Table 3

Indicators of CBT and fecal elastase-1 in patients with celiac disease combined with CP in the dynamics of treatment

The degree of severity EPI	Elastase-1 (faecal), M ± m, mg/g		CD to treatment M ± m,%	CD 1 year, M ± m,%
	Before treatment	After 1 year		
Easy (n = 9)	130 ± 11.2	139.3 11.2 ±	10.9 ± 1.7	18.9 ± 1.7 *
The average (n = 12)	63.1 ± 7.1	77.3 ± 7.1	5.1 ± 1.2	11.5 ± 1.3 *
Heavy (n = 9)	28.1 ± 3.4	36.4 ± 3.4	2.6 ± 1.1	8.7 ± 1.1 *
Control (n = 30)	390.1 30.2 ±		21.5 ± 3.6	

Note: * — p <0.05 compared to results before treatment.

Analyzing these data, we can note that none of the groups divided by the level of severity of faecal elastase-1 have been no significant changes in their own exocrine function Software patients studied. But in all groups was found significant reduction of amylase insufficiency. Assuming that the level amylase-forming pancreas tool, which, as was previously shown to correlate with data fecal elastase-1, also stayed Uneditable it can make the following assumptions. First, celiac disease is an aggravating factor XII flow and reduce enterogenous EPI stimulation, especially at the initial stage of combined treatment of the two diseases (gluten-free diet, PT) substantially prevents the regeneration of the parenchyma own pancreas. Secondly, reducing amylase insufficiency is linked primarily to the restoration of the function of the mucous membrane of the small intestine due to a gluten-free diet. Third, patients with celiac disease, accompanied EPI require the compulsory replacement enzyme therapy in the form of enzyme preparations minimicrospheres, without which normalization nutritional status of the patient is impossible, both theoretically and practically. Regarding the latter,

we have assessed body mass index of patients before treatment and after 1 year of therapy. In general, the group noted a significant improvement of this indicator: the beginning of the treatment he has averaged 16.7 kg/m^2 , standard deviation σ was 1.2, after 1 year of observation, this figure was $20.2 \pm 1.2 \text{ kg/m}^2$, $p < 0.0001$.

Conclusions:

1. Partial recovery of its own pancreatic function in patients with CP is possible within 1 year of treatment.
2. If the combination of CP and celiac disease reduction enterogenous stimulate pancreatic secretion substantially prevents the regeneration of the parenchyma own pancreas.
3. Continued therapy over 1 year is needed because improves the nutritional status of the patient, but the exocrine function of the pancreas no longer a trend towards improvement.
4. Selection and subsequent dose adjustment enzyme therapy designed according breath test can effectively monitor the nutritional status of patients with EPI.

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Maldigestion persists in most patients with chronic pancreatitis (CP) and celiac disease. The objective lipase and amylase insufficiency diagnosis is needed to achieve an adequate clinical response to oral pancreatic enzyme substitution therapy. The novel data are presented in the article on the role of ^{13}C -mixed triglyceride and ^{13}C -corn starch breath tests as tools for exocrine pancreatic insufficiency diagnostics, for evaluating fat and starch malabsorption in CP patients. 165 patients (135 with CP and 30 with CP + celiac disease) and 30 healthy volunteers were included in the investigation. Delayed results of enzyme replacement therapy for maldigestion were estimated in 1 and 2 year of surveillance. It has been shown that partial recovery of exocrine pancreatic function is possible, and replacement therapy leads to patients' nutritional status improving. It has been shown that ^{13}C -breath tests could be useful tools in clinical practice for CP diagnostics. They are well-correlated with fecal elastase-1 level, have high sensitivity and specificity for diagnostics of lipase and amylase deficiency. Tests make it possible to choose the initial pancreatic enzyme dosage and are beneficial during the treatment for pancreatic enzyme dose correction.