Functional state of pancreas in patients with chronic pancreatitis

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Key words: chronic pancreatitis, pancreatic juice, functional state, duodenal intubation, fecal elastase-1

Chronic pancreatitis (CP) is a severe pancreatic disease, in which repeated inflammatory episodes result in substitution of pancreatic parenchyma by fibrous connective tissue. This fibrotic reorganization of pancreas leads to progressive exocrine and endocrine insufficiency of pancreas. In addition, there are characteristic complications such as pseudocysts, obstruction of the main pancreatic duct (MPD), obstruction of the duodenum or biliary tract, vascular complications, malnutrition and pain syndrome. Pain is a major symptom in patients with chronic hepatitis, due to which the disease significantly reduces the quality and life expectancy of patients. In addition, CP is a risk factor for carcinoma of pancreas [6, 7].

In the recommendations of the Joint European Gastroenterology Association for the diagnosis and treatment of evidence-based hepatitis (HaPanEU), it is indicated that a diagnostic test for a CP must be performed to determine the functional state of the pancreas [7]. S. Albashir et al. It is proved that either morphological or functional disorders can be the only sign of histologically confirmed CP [1]. Thus, the diagnosis of CP depends on a combination of clinical, histological, visualization and functional criteria. Functional tests are especially needed for the diagnosis of CP in patients who remain suspected of being ill with negative data from instrumental studies [1].

Aim of research is to study the functional state of pancreas in patients with various forms of CP.

Materials. Complex examination of 210 patients with CP was conducted. Patients were divided into groups: the I group consisted of 26 patients (12.4%) on the obstructive form of CP, II — 56 patients (26.7%) with calcifying form, III — 78 patients (34.1%) with fibrous parenchymal form, IV — 50 patients (23.8%) with CP, complicated by pseudocyst. Among men surveyed, men (169 men and 41 women),

the average age of patients (47.3±0.7) years, prevailed. The largest number of patients (60.5%) belonged to the age group of 41-60, who make up an able-bodied population. Control group — 20 practically healthy persons.

The work is part of the author's dissertation research and was performed at the Institute of Gastroenterology of the National Academy of Medical Sciences of Ukraine in the framework of research works “To study the mechanisms of the development of complications of chronic pancreatitis and to develop methods of diagnosis and surgical treatment using non-invasive technologies”, 2008-2010 (VH code.25.01.001.08, state registration number 0107U012136) and “To study the mechanisms of development of fibrotic processes in chronic pancreatitis and to improve the technologies of their surgical correction”, 2011-2013 (VH code 25.01.001.11, number of state registration № 0111U001065).

Research methods. The activity of enzymes (amylase, lipase, trypsin, phospholipase A) in blood serum (n = 73), duodenal (n = 12) and duct (n = 13) content of the enzymes generally accepted in clinic methods [4]. Additionally, the content of bicarbonates was determined in duodenal and ductal contents. To obtain duodenal content in 12 patients, the technique of duodenal sensing was used [3]. The evaluation of the studied indicators was given in accordance with their changes from the minimum and maximum limits of the physiological norm and the rate-of-time. In addition, the external secretion function of the pancreas was evaluated for the level of fecal elastase-1 (n = 95) [3]. The state of the endocrine function of the gland was assessed by the level of glycosylated hemoglobin and blood glucose.

Results of reaserch. Increased intake of enzymes in blood ("deviation of enzymes") is due to violation of the integrity of its parenchyma or acute stagnation of secretion in one or another section of the strain of pancreas. It should be noted that at CP, the concentration of pancreatic enzymes can be not only increased, but even reduced. The data shown in the tables 1 and 2 indicate quite high activity of enzymes of pancreas.

Table 1

Biochemical indices of blood serum, which characterize the functional state of the pancreas in patients with chronic pancreatitis

Biochemical index	Group I (n=10)	Group II (n=19)	Group III (n=24)	Group IV (n=20)	Total (n=73)	Control (n=20)
	M±m	M±m	M±m	M±m	M±m	M±m
α-amilase, mg/s·L	18.59±4.16*	19.94±4.0*	17.29±3.50*	16.92±2.81*	18.3±1.82*	6.10±0.37
Tripsin, μmol/ml·min	6.58±1.87	8.09±0.62*	7.77±0.64*	7.68±0.88*	7.94±0.46*	2.50±0.35
Lipase, nmol/s·L	1.37±0.15	$1.31\pm0.10^{+}$	$1.41\pm0.10^{+}$	1.41±0.19	$1.38\pm0.07^{+}$	1.07±0.05
FLA, U/ml	1.10 ± 0.10^{1}	$1.82\pm0.41^{+}$	$2.32\pm0.20^{+}$	$2.07\pm0.16^{+}$	$2.06\pm0.14^{+}$	0.98+0.07
GHb, μmol fru/gHb	$7.84\pm1.05^{+}$	6.04±0.92	5.51±1.10	6.95±1.24	6.20±0.62	5.25±0.28

Notes:

1. * — statistically significant (p<0,002) difference between the indices in patients and healthy people;
2. $^{+}$ — statistically significant (p<0,05) difference between the indices in patients and healthy people;
3. ^{1} — statistically significant (p<0,02) difference between the indices in patients of groups I and III, I and IV.

Table 2

The frequency of deviations of the biochemical parameters of blood serum, which characterize the functional state of the pancreas in patients with chronic pancreatitis

Index, units	Зміни рівня	Group I (n=10)		Group II (n=19)		Group III (n=24)		Group IV (n=20)		Total (n=73)		Control (n=20)
		M±m	%	M±m	%	M±m	%	M±m	%	M±m	%	M±m
1	2	3	4	5	6	7	8	9	10	11	12	13
α-amilase, mg/s·L	high	24.67± 4.04*	70.0	28.13± 4.96*	63.2	29.26± 4.97*	50.0	21.98± 3.13*	70.0	25.98± 2.18*	61.6	6.10± 0.37
	normal	4.39± 0.83	30.0	6.59± 0.60	31.6	6.01± 0.56	41.7	6.06± 0.97	20.0	5.96± 0.36	31.5	
	low	–		1.86±0	5.2	1.91± 0.60	8.3	3.23± 0.06	10.0	2.43± 0.38	6.8	
Lipase, nmol/s·L	high	1.78± 0.18 *	33.3	1.80± 0.08*	20.0	1.80± 0.12*	35.7	1.97± 0.33*	33.4	1.84± 0.09*	30.8	1.07± 0.05
	normal	1.17± 0.11	66.7	1.19± 0.07	80.0	1.19± 0.08	64.3	1.14± 0.14	66.6	1.17± 0.05	69.2	
Tripsin, μmol/ml·min	high	8.91± 1.74*	66.6	8.85± 0.52*	87.0	8.41± 0.52*	91.0	8.78± 0.76*	85.0	8.69± 0.33*	85.9	2.50± 0.35
	normal	3.0± 0.01	16.7	3.02± 0.91	13.0	2.13± 0.01	4.5	2.05± 0.35	10.0	2.61± 0.40	9.9	
	low	0.80± 0.01*	16.7	–	0	0.67± 0.01*	4.5	0.40± 0.01*	5.0	0.62± 0.12*	4.2	
FLA, U/ml	high	–	0	2.49± 0.05*	60.0	2.32± 0.20*	100.0	2.07± 0.16*	100.0	2.27± 0.12*	84.6	0.98+ 0.07

GHb, μmol fru/gHb	high	8.88± 0.01*	50.0	8.12± 0.65*	42.9	12.77± 4.42*	15.4	9.63± 2.05*	44.4	9.73± 1.15*	32.3	5.25± 0.28
	normal	6.79± 0.01	50.0	5.25± 0.80	42.9	4.93± 0.41	61.5	5.14± 0.68	44.4	5.16± 0.30	51.6	
	low	–	0	2.21± 0.01*	14.2	2.21± 0.45*	23.1	3.44± 0.01*	11.2	2.46± 0.35*	16.1	

Thus, the activity of amylase was significantly increased in 61.6% of patients with CP in 4,3 times compared to control (p <0,001). The analysis of the frequency of increase of this indicator in groups found that most often α-amylase activity increased in patients with I and IV groups (with the same frequency of 70.0%), somewhat less frequently in II and III groups of patients (63.2% and 50.0%, respectively, p> 0.05). A sufficiently significant increase in the activity of this enzyme in the bloodstream during CP can occur during the period of exacerbation of the process and when there are obstacles to the outflow of pancreatic juice (inflammation, swelling of the head of the SO and compression of ducts, cicatricial stenosis, etc.). In the intergroup analysis, there is no reliable difference in the activity of α-amylase in serum and its frequency increase in groups (Table 2). In a small number of patients (6.8%) the activity of this enzyme was reduced, which may indicate a loss of functional capacity of the PO due to the replacement of acinar cells of the gland with the connective tissue.

The activity of lipase in most patients (69.7%) was within the normal limits, only in one third of patients it was noted increase (30.3% of cases).

The appearance of active trypsin in the tissue of PO is one of the main pathogenetic factors of development of acute and chronic obstructive pulmonary disease. In this pathology, as a result of the delay in the secretion of the secretion of pancreas occurs intraorganic activation of pancreatic enzymes, primarily trypsin, which then activates other proenzymes, which ultimately results in autosomal parenchyma gland. In most patients (85.9%) the activity of trypsin was increased by 3.5 times compared with the control group (p<0.001). Increased activity of this enzyme was noted more frequently in patients of the III group (91.0% of cases), in the severity of this indicator, no significant differences were observed in the patients' groups.

Phospholipase A is very specific to the pancreas, is widely studied in connection with its participation in the pathogenesis of pancreatitis and it is an ideal marker for lesions of acinar cells in pancreas for pancreatitis. The activity of this enzyme was increased by 2.3 times in 84.6% of patients, no reliable differences in frequency and severity of this indicator in groups were established.

Increased activity of trypsin and amylase in patients with CP, complicated by pseudocyst (r = 0.84; p = 0.02 and r = 0.74; p = 0.02, respectively), showed that the external secretion function is retained, that is, most of the parenchyma of the pancreas is not damaged by fibrotic changes, which is explained by the less prolonged course of the disease in these patients and coincides with the literature on the development of pseudocyst in patients with chronic diseases soon after the onset of the disease [3, 9]. A reliable but not high level of association of α-amylase activity (r = -0,42; p = 0,03) with the severity of fibrotic changes in the pancreas according to ultrasonographic data confirmed the evidence that, with pronounced parenchymal fibrosis, decreased enzyme production through reduction of the number of acinar cells.

Thus, an increase in the activity of pancreatic enzymes in the blood serum of patients showed a violation of the integrity of the parenchyma of pancreas or the stagnation of its secretion on one or another section of the strain of pancreas.

For a more accurate evaluation of the functional state of the pancreas, its secretion by probe method was studied. In this case, the activity of pancreatic enzymes was studied: amylase, lipase, trypsin, determined bicarbonate alkalinity. Results of the study of pancreatic secretion obtained in patients on an empty stomach (basal fraction) are presented in Table 3.

Table 3

Indices of enzyme activity and bicarbonate content in duodenal contents of patients

Index	Norm, M±m	Patients with CP (n=12), M±m
α-amilase, mg/s·L	11.00±1.77	7.47±2.49
Lipase, ml 0,1n NaOH	7.05±0.73	7.60±1.43
Tripsin, μmol/ml/min	275.00±30.28	224.80±52.63
Bicarbonates, mekv./L	55.85±5.24	54.69±18.53

In the analysis of the data, it was found that the activity of α-amylase was 1.5 times lower than the control values, while the activity of trypsin tended to decrease. The activity of lipase and the concentration of bicarbonates remained practically within the limits of the physiological norm.

After eufillin-calcium stimulation of pancreatic secretion, four doses of duodenal contents (pancreatic juice) were administered at identical intervals. It is known that the basis of the change in the level of enzymes in the pancreas, blood and duodenal content in the CP is the phenomenon of “deviation of enzymes” in the blood, that is, the concentration of enzymes in the blood increases. To evaluate the functional state of the pancreas, the mortality of the enzymes of the SO in the basal portion and in all portions of the duodenal content (pancreatic juice) was determined (Table 4).

Table 4

Debit of amylase, lipase, trypsin of duodenal contents in patients

Index	Enzymes debit-hour in duodenal contents (basal fraction) (n=9)	Enzymes debit-hour in duodenal contents (fractions after stimulation) (n=9)
	M±m	M±m
Amylase debit-hour, A_d	127.03±59.11	179.83±72.12
Lipase debit-hour, L_d	56.57±5.29	76.36±7.81*
Trypsin debit-hour, T_d	1591.52±271.58	2251.66±301.14

Note: * — p<0,05 (significant difference of indices before and after stimulation).

As can be seen from Table 4, the debit-hour of pancreatic enzymes of duodenal contents after stimulation was characterized by elevated values of these indices from a similar rate for basal portion fractions. Thus, the break-time of the stimulated fraction of amylase and trypsin was 1.4 times higher, and lipase was 1.3 times (p <0.05).

In addition, for evaluating the external-secretory function of the pancreas, an evaluation of the content of the proximal contents of the pancreas received intraoperatively, in patients with CP. The obtained indicators are presented in the table. 5. According to the data presented, the activity of α-amylase and pancreatic juice lipase from the strains of PF was 1.4 times higher than normal (p <0.05) and (p <0.001) respectively. In norm, only the epithelium of the duct system secretes bicarbonates. When the epithelium is damaged, the secretion of bicarbonates is carried out by acinar cells. It was determined that the concentration of bicarbonates in duodenal and duct contents in the studied patients was 2.9 times higher in comparison

with the norm (p <0.001). The data are derived intraoperatively, consistent with the indexes of the debit-time enzymes of duodenal content.

Table 5

Indices of enzyme activity and bicarbonate content in the contents of the main pancreatic duct of patients

Index	Norm (for pancreatic juice)	Patients with CP, (n=13)
	M±m	M±m
α-amylase, g/h·L	10980.00±958.65	15303.45±1601.25*
Lipase, ml 0,1n NaOH	7.05±0.73	9.81±0.77*
Bicarbonates, mekv./L	55.85±5.24	161.38±11.41*

Note: * — p<0,05 (significant difference between indices and norm).

Thus, after stimulation of the pancreas, an increase in the debit time of pancreatic enzymes in the duodenal contents is found, which is consistent with the data obtained in the intraoperative, indicating the functional capacity of the organ and the presence of areas of intact parenchyma, the gland producing the enzymes.

The gold standard for the non-invasive diagnosis of exocrine function of the PO is to determine the level of pancreatic fecal elastase-1, which is characterized by high stability and does not decompose when passing through the intestinal tract. Such a study was conducted in 95 patients (Table 6).

Table 6

State of exocrine pancreatic function according to fecal elastase-1 data

Group of patients	Fecal elastase, mcg/g	Norm, mcg/g
I (n=9)	169.89±16.02*+	200
II (n=37)	170.32±8.16*+	
III (n=32)	200.31±9.43	
IV (n=17)	223.82±15.45	
Total (n=95)	189.96±5.81	

Notes:

1. * — statistically significant difference between the indices in patients compared with healthy people (p<0,05);

2. + — statistically significant difference between the indices of patients of Groups I and II as compared with Group IV (p<0,01).

As it is evident from the data presented, a significant reduction in the external-secretion function of a moderate severity of prophylaxis was observed in patients of

groups I and II (p <0.05), which can be explained by a more significant fibrobing of parenchymal POs and loss of its ability to produce enzymes. It has been established that the level of fecal elastase is significantly higher in patients of the IV group, which coincides with the shorter duration of the disease. We analyzed the severity of external-secretion insufficiency of PO on the level of fecal elastase in patients with CP, depending on the form of the disease (Table 7).

Table 7

Expression of exocrine pancreatic insufficiency in patients with CP

Fecal elastase, mcg/g	Group 1 (n=9)		Group 2 (n=37)		Group 3 (n=32)		Group 4 (n=17)		Total (n=95)	
	abs.n.	%	abs.n.	%	abs.n.	%	abs.n.	%	abs.n.	%
<100	1	11.1	7	18.9	1	3.1	–	–	9	9.5
100–200	5	55.6	19	51.4	22	68.8	7	41.2	53	55.8
>200	3	33.3	11	29.7	9	28.1	10	58.8	33	34.7

Changes in the level of faecal elastase, which corresponded to moderately pronounced and pronounced external-secretion insufficiency of the highest-frequency pancreas, were found in patients with II and III groups (70.3% and 71.9%, respectively).

However, the expressed foreign-secretion deficiency was most often detected in patients with II group compared with I ($\chi 2 = 2.78$, $p = 0.096$) and III ($\chi 2 = 0.036$, $p = 0.85$) groups. Patients with IV of such level of elastase-1 were not found.

The moderate external contraceptive failure of the program indicated a decrease in the level of fecal elastase of less than 200 μg/g but more than 100 μg/g. Such a degree of external-secretory deficiency of the pancreas is most commonly established in patients with the third group of 68.8%, whereas in I it was 55.6% ($\chi 2 = 0.12$, $p = 0.73$), in II — 51.4% ($\chi 2 = 1.49$, $p = 0.22$), while in the IV the lowest is 41.2% ($\chi 2 = 2.45$, $p = 0.12$). These data indicate the most pronounced defeat of parenchyma in patients with II and III groups (according to fecal elastase test).

In the study of the inhibitory function of PO on the level of blood glucose, different-directional changes in this index were found in patients with chronic

obstructive pulmonary disease. In general, in patients with CP, the level of glucose was within the normal range (5.52 ± 0.25) mmol/l, assuming a norm (4.44-6.66) mmol/liter. However, in 12.5% of patients with a complaint of thirst, dry mouth, polyuria, nicturias, itching of the skin, weight loss, an increase in blood glucose levels was noted, indicating a violation of the inoculant function of the pancreas, and this figure was significantly higher in I and II groups of patients and the frequency of its increase was 20.0%, 20.7%, 10.5% and 3.7% of patients, respectively ($p < 0.05$). The duration of the disease affects the state of decompensation of the exchange of carbohydrates. Thus, analysis of the dependence of hyperglycemia on the duration of the disease showed that in almost half of patients with elevated blood glucose (46.9%) the disease was prolonged, of which 53.3% — exceeded the term of 6 years.

Among patients with elevated glucose levels, there were 9 people with body weight excess (19.1% of patients with excess body weight), and they were characterized by hypercholesterolemia and concomitant cardiovascular disease, indicating the presence of metabolic syndrome [1]. At the same time, 3.1% of patients with CP had deficiency of body weight (BMI <18.5).

In other 9 patients (8.7%), glucose levels were lower than 4.0 mmol/L, that is, the level of apparent hypoglycemia, which can be interpreted as a manifestation of hyperinsulinemia, which is a violation of the inhibitory function of the pancreas and is considered to be a risk factor for the development of the second type of diabetes [1]. In the group of patients with established diabetes mellitus, the average glucose level for three-fold definition was (6.49 ± 0.45) mmol/l.

Indicator endocrine function of the pancreas is GHb. Determination of the concentration of GHb allowed to establish that its content was more indicative than the content of glucose, its level varied ambiguously: elevated in one third of patients (32.3%) pointed to the compensatory nature of diabetes, and decreased in 16.1% — about decompensation of diabetes patients with complicated forms of CP, indicating an intracellular digestion of glucose. Reliable increase of GHb level is defined only in the I group of patients. Lower GHb levels were more commonly seen in patients with long-term CV (group III — 23.1%, in comparison with I — not detected, II —

14.2%, IV — 11.2%, p> 0,05), that coincides with the literature data on the development of diabetes with a long history of the disease.

Thus, one of the leading mechanisms for the development of chronic inflammatory process in the pancreas is the delayed selection and intraorganic activation of pancreatic enzymes, primarily trypsin and lipase, which gradually cause autolysis of the parenchyma of the gland. This was confirmed by an increase in the activity of blood serum enzymes in patients of all groups — the activity of amylase (in 61.6% of cases), trypsin (85.9%) — in 3.5 times and phospholipase A (84.6%) in 2, 3 times compared with the control group (p <0.001). Often, the activity of α-amylase increased in patients with I and IV groups (with the same frequency of 70.0%), which was due to an aggravation of the process or an obstacle to the outflow of pancreatic juice, and increased activity of trypsin was more commonly observed in patients of the III group (91.0%). According to the fecal elastase test, the highest degree of defeat of parenchyma was defined in patients with II and III groups.

Basal pancreatic secretion was suppressed, and after stimulation of the pancreas, an increase in the morphology of pancreatic enzymes in duodenal contents was found to be consistent with the intraoperative data, indicating the preserved functional capacity of the organ and the presence of areas of intact parenchyma, producing enzymes.

It was determined that according to the obtained data, the functional activity of the pancreas was maintained in 83.3% of patients, which coincides with the literature data on the change in the parameters of functional activity of the gland in case of damage to 90.0% of its parenchyma [2, 3, 8].

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Aim of research is to study the functional state of the pancreas in patients with various forms of chronic pancreatitis.

Materials and methods. Complex examination of 210 patients with various forms of chronic pancreatitis (I, n=26 — obstructive, II, n=56 — calcifying, III, n=78 — fibrous-parenchymal, IV, n=50 — chronic pancreatitis complicated by pseudocyst) was carried out. Activity of enzymes (amylase, lipase, trypsin, phospholipase A) in serum, duodenal and ductal pancreatic contents was determined by common clinical techniques. In addition, content of bicarbonates was determined in duodenal and ductal contents. Exocrine pancreatic function was assessed by fecal elastase-1 level, endocrine function — by glycosylated hemoglobin level.

Results of study. Increased activity of enzymes was determined (amylase, lipase, trypsin, phospholipase A) in the serum of patients of all groups: amylase activity (61.6%), trypsin (85.9%) by 3.5 times and phospholipase A (84, 6%) — by 2.3 times in comparison with the control group ($p < 0{,}001$). Most often, α-amylase activity increased in patients of I and IV groups (with the same frequency of 70.0%) due to the process exacerbation or obstacle for the pancreatic juice outflow; increased trypsin activity was more frequent in III group of patients (91,0%). According to the fecal elastase test, the highest degree of pancreatic parenchymal involvement was detected in II and III groups of patients.

Fecal elastase test showed increased level of enzymes in the duodenal and ductal pancreatic contents, increased level of bicarbonates, and decrease in the exocrine pancreatic function. Inhibition of basal pancreatic secretion and increase of debit-hour of pancreatic enzymes in duodenal contents after stimulation of the pancreas was states, which corresponds to the intraoperatively obtained data.

Conclusions. It was found out that functional activity of the pancreas was preserved in 83.3% of patients, which coincides with literature data on changes in the indices of pancreatic functional activity upon 90.0% lesion of its parenchyma.