CLINICAL AND PATHOGENETIC SIGNIFICANCE OF ULTRASONIC HISTOGRAPHY IN THE DIAGNOSIS OF PANCREATIC FIBROSIS AND EXACERBATION OF CHRONIC PANCREATITIS

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Key words: chronic pancreatitis, clinical manifestations, fibrosis of the pancreas, ultrasonic histography, functional state of the pancreas

Chronic pancreatitis (CP) is one of the most common gastrointestinal diseases accounting for about 8-10% of all the digestive diseases [1, 12]. Prevalence and incidence of chronic pancreatic diseases in Ukraine have increased significantly for the last years, and much of this pathology (in 2010 — 12.3%) determines the clinical and social significance in the general structure of the digestive system diseases. Health indicators of population concerning pancreatic diseases were as follows in 2006-2010: prevalence increased by 21.3% to 2311.3 in 2010 per 100,000 adults [11].

Tissue fibrosis is defined as the excessive accumulation of extracellular matrix, fibrillar collagen in particular, due to the loss of balance between its accumulation and degradation. Pancreatic fibrosis is a leading pathological mechanism in the CP development [3, 9, 15, 21]. The molecular mechanisms leading to pancreatic fibrosis weren't studied sufficiently before. Cells in the pancreatic tissue which play an important role in fibrogenesis have been isolated and characterized recently [13, 17], named as pancreatic stellate cells (PSC) — stellate cells, the activation of which leads to fibrosis of the tissue. These cells are described as myofibroblasts producing extracellular matrix with the release of smooth muscle actin, collagen and fibronectin synthesis. There are lots of arguments for the primary role of stellate cells in collagen-formation in the pancreatic tissue (this is confirmed by the presence of smooth muscle actin in the areas of pancreatic fibrosis, which is characteristic of the activated stellate cells) [13]. It is believed that pancreatic fibrosis, particularly in the early stages, can be reversed [3, 20, 21].

The aim of study is to evaluate the clinical and pathogenetic significance and diagnostic capabilities of ultrasound histography in the diagnosing the pancreatic fibrosis and CP exacerbation.

Materials and methods. We examined 186 patients with CP exacerbation aged from 23 to 74. Among the patients were 80 (43.0%) men and 106 (57.0%) women. 30 almost healthy were examined.

All the patients were asked about their complaints and anamnesis, an objective investigation was conducted, laboratory and instrumental examination were carried out.

The intensity of pain and other CP clinical manifestations were evaluated semiquantitatively according to the special scale [10]: 0 points — no complaints; 1 point — minimal complaints; 2 points — moderate complaints; 3 points — evident or highly evident complaints. In accordance with the assessment of this scale, we counted average severity rate (ASR) of various clinical manifestations as follows [10]:

$$\text{ASR} = \frac{a + 2b + 3c}{a + b + c + d}$$

ASR — average severity rate of clinical manifestations;

a —number of patients with symptoms at 1 point;

b — number of patients with symptoms at 2 points;

c — number of patients with symptoms at 3 points;

d — number of patients with no symptoms.

Upon laboratory examination, we conducted total blood count, urinalysis, biochemical tests of blood, urine, duodenal contents; coproscopy; enzymatic and radioimmunoassay study.

To determine the severity of the CP exacerbation, the state of the exocrine pancreatic function, and the degree of the phenomenon of "deviation" of enzymes in the blood, we studied the activity of blood and urine α-amylase, blood and urine P-isoamylase, blood lipase, immunoreactive trypsin content (IRT) in blood [14].

We performed tube (direct) examination of the state of exocrine pancreatic function with a determination of the types of pancreatic secretion. With this aim, we applied test aminophylline-calcium test and two-channel gastroduodenal tube of original design developed in our clinic [4]. Basal and 4 portions of stimulated pancreatic secretion were analyzed: we took into account the volume of received duodenal contents, debit-hour of bicarbonates, α-amylase, P-isoamylase, lipase, trypsin. Three days before the tube examination patients stopped the intake of the enzymatic preparations, antisecretory drugs.

Biochemical methods were performed on the analyzer Vitalab Flexor-2000 (Netherlands). The activity of α-amylase, P-isoamylase in blood, urine, duodenal contents were studied on the same analyzer (kits Lachema, Czech Republic). The activity of lipase in the blood and duodenal contents was measured on the same analyzer with the use of kits Sentinell (Italy). IRT content was investigated with the use of kits CIS (France) and gamma-pulses counter "Gamma-800" (Medequipment, Ukraine) [6]. Bicarbonates and trypsin debit-hour in the duodenal contents was evaluated by the manual methods. Bicarbonate indices were determined by reverse titration, and rates of trypsin — by Gross method [2].

The level of pancreatic elastase-1 in feces was studied with the use of fecal elastase test on the immunoenzymatic analyzer Sanofi (France) (kits Schebo, Germany) [16].

Ultrasonography of the pancreas and liver was performed before and after treatment (device ALOKA SSD-630, Japan). We evaluated the size of the pancreas and its parts (head, body, tail), clearness of circuits, homogeneity of structure, echogenicity, Wirsung's duct diameter, presence of pseudocysts, calcifications. Ultrasound histography was additionally performed in the area of pancreatic head with the evaluation of L, N, K_{gst} indices [7]. Ultrasound histography of the liver in the area of right lobe was conducted considering L index. Splenic sonography, diameter of portal and splenic veins were also assessed, attention was paid to the presence of free fluid in the abdominal cavity. Patients were not included in the study upon the presence of such a fluid, splenomegaly, enlargement of portal and/or splenic vein.

Dopplerography was performed on the device "PhilipsEnVisor" (Netherlands). We determined peak systolic flow velocity (V_{ps}), end diastolic flow velocity (V_{ed}), resistance index (IR) and pulsation index (PI) in the abdominal aorta (AA), celiac trunk (CT) and superior mesenteric artery (SMA). Patients were examined before and after treatment. Each examination included dopplerography on an empty stomach and 30-45 minutes after intake of 50 g of glucose solution in 200 ml of warm boiled water [8].

As a direct marker of fibrosis, we assessed the levels of transforming growth factor β1 (TGFβ1). We used kits DRG TGF-β1 ELISA ("DRG International, Inc", Germany).

Results. L index in the pancreatic head of the examined patients increased to 23.6±0.8; in healthy — 17.5±0.4 (compared to the norm $p<0.05$) and homogeneity index N was reduced to 13,82±0,15%, in healthy — 15,36±0,07% ($p<0.05$), K_{gst} — reduced to 73.4±12.5, in healthy — 125.2±11.6 ($p<0.05$).

When analyzing the correlation of the interrelations between indices of ultrasound histography and other clinical and laboratory data, we obtained the following results (Fig. 1).

K_{gst} of the ultrasonic pancreatic histogram was associated with other histographic indices: negatively with L index and positively with N index. This is due to the fact that K_{gst} was calculated considering L and N, N being included in the numerator, and L — in denominator of the formula for calculating K_{gst} [7]. K_{gst} negatively correlated with TGFβ1 and V_{ps} in CT, as well as with IR in the CT. This shows, on the one hand, the greater CP severity upon the disturbance of its blood supply, as V_{ps} and IR increase with a decreasing flow in the AA odd branches. It is logical to assume that the decrease in blood flow in the pancreas, especially after the food load, organ’s functioning will be worse, and more favorable conditions will be created for inflammation and structural changes. On the other hand, it seems that the negative correlation between K_{gst} and TGFβ1 reflects greater evidence of the pancreatic fibrosis on the background of CP. This is confirmed by a positive correlation between L index ultrasound pancreatic histography and TGFβ1. Thus, we

can assume that both L index and TGFβ1 levels in the blood may be used for indirect assessment of the degree of pancreatic fibrosis upon CP. This assumption is based on the data on L increasing upon increasing pancreatic fibrosis [7]. Results of studies on the growth of TGFβ1 levels in the blood upon liver and pancreatic fibrosis have been published [5, 18, 19]. Positive correlation between IR and V_{ps} in CT is of big importance. We explain it by the fact that both indicators increased upon the disturbance of blood flow in the odd AA branches [8]. We consider it important to draw attention to the positive correlation between L and IR in CT. This correlation seems to be a result of increased pancreatic fibrosis upon reducing blood supply of the organ. Positive correlation between L in the pancreas and V_{ps} in CT points out the correlation between the degree of pancreatic fibrosis and blood flow disturbance in the organ.

We determined correlations that characterize the fact that upon decreasing K_{gst} CP exacerbation is growing. This is evidenced by the negative correlation between K_{gst} and IRT levels in the blood, P-isoamylase in the urine and positive correlation between K_{gst} and lipase debit-hour, levels of fecal elastase-1. Both upon decreasing N and decreasing K_{gst}, degree of phenomenon of enzymatic "deviation" in the blood is increasing, as well as exocrine pancreatic insufficiency (Fig. 1).

Considering the positive correlation between N and K_{gst}, it’s logical that N also had the similar correlations (as K_{gst}) with lipase debit-hour and fecal elastase test results, as well as with IRT, P-isoamylase in the urine, V_{ps}. Thus, both upon decreasing N and decreasing K_{gst}, degree of phenomenon of enzymatic "deviation" in the blood is increasing, as well as exocrine pancreatic insufficiency (Fig. 1).

It’s important that L of the pancreas is associated by the evident direct positive correlation with L of the liver, reflecting the high frequency of combined lesions and fibrosis of both organs. Indeed, chronic diffuse liver and pancreatic diseases in many cases have a common etiology and pathogenesis, therefore, developing together [22].

Along with increasing the degree of pancreatic fibrosis in the CP examined patients, exocrine pancreatic function clearly worsened, which was reflected in the negative correlation between L of the pancreas and results of fecal elastase test, lipase

debit-hour. Fibrosing pancreas was also reflected by the severity of CP clinical manifestations. We found a positive relationship between L and ASR dyspepsia, mainly with the severity of intestinal dyspepsia, which is more characteristic of pancreatic insufficiency [22]. It's important that the correlation between L of the pancreas and SST of pain syndrome wasn't found, i.e. fibrosing pancreas affects the clinical manifestations of exocrine insufficiency and isn't associated with severity of CP exacerbation.

Conclusions:

1. Correlation "mirror" of the ultrasonic pancreatic histography indices upon CP demonstrates the possibility of using these indices as indirect markers of pancreatic fibrosis and assessing the severity of CP exacerbation.

2. Considering that the ultrasonic pancreatic histography indices are automatically determined during sonography, as well as during the calculation of the data, i.e. there is no need for additional invasive studies and material costs, we suppose the histography conducting to be reasonable and informative.

Perspectives of research consist in development of treatment aimed at the inhibition of pancreatic fibrosis upon CP.

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Clinical and pathogenetic significance of ultrasonic histography in the diagnosis of pancreatic fibrosis and exacerbation of chronic pancreatitis

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Key words: chronic pancreatitis, clinical manifestations, fibrosis of the pancreas, ultrasonic histography, functional state of the pancreas

Materials and methods. Article presents the data of 186 examined patients with chronic pancreatitis (CP). We investigated clinical blood count, urine analysis, biochemical blood test, duodenal intubation test, coproscopy, immunofermental and radioimmune study, assessed blood level of TGFβ1, fecal elastase-1, performed the sonography and ultrasonic histography of the liver and pancreas, dopplerography of the abdominal aorta (AA), celiac trunk (CT) and superior mesenteric artery (SMA).

Results and discussion. Upon the examination of patients, the following correlations were found: K_{gst} of ultrasonic histography had negative correlation with L and positive one with N, K_{gst} was negatively correlated with TGFβ1 and V_{ps} in CT, as well as with IR in CT, we found a positive correlation between IR and V_{ps} in CT, a positive correlation between L and IR in CT, a positive correlation between V_{ps} in CT and L, negative correlation between K_{gst} and immunoreactive trypsin in blood, P-isoamylase in urine, and positive correlation between K_{gst} and debit-hour lipase, fecal elastase-1. L of the pancreas was expressed by the evident positive correlation with liver, L of the pancreas was associated with negative correraltion between L of the liver and negative correlation between L of the pancreas and fecal elastase-1, debit-hour of lipase, we revealed a positive correlation between L and average severity of manifestations of dyspepsia, but correlation between L of the pancreas and average severity of manifestations of pain wasn’t found.

Conclusions: study of ultrasonic histography correlations of the pancreas let us draw a conclusion on the possibility of using this method in diagnosing of pancreatic fibrosis and evaluation of CP exacerbation.

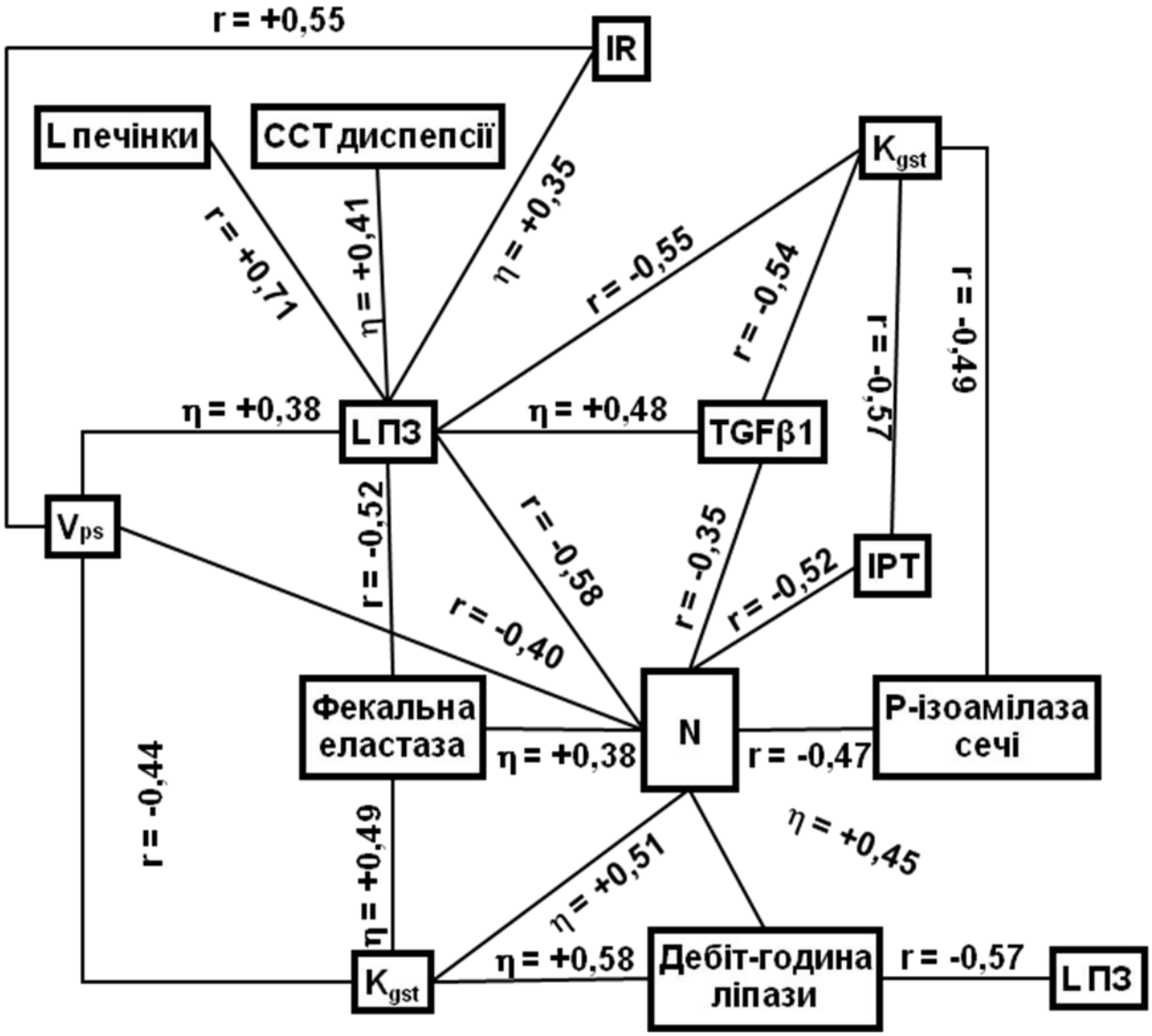

Fig. 1. Correlation between ultrasonic pancreatic histography indices, functional state of the pancreas and clinical, instrumental data.