News of European pancreatology (by materials of the 48th Meeting of the European Pancreatic Club, July 6–9, 2016, Liverpool, Great Britain)

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Key words: European Pancreatic Club, Ukrainian Pancreatic Club, diagnostics and treatment of chronic pancreatitis, pancreatic insufficiency, Creon

On July 6-9, 2016 in Liverpool (United Kingdom) the 48th meeting of the European Pancreatic Club took place. At the meeting were presented more than 400 oral and poster presentations [1].

Our attention was drawn to a number of reports. Let's start with the anatomy: M. A. Suarez-Munoz et al. (Spain), volumetry (measuring volume) of the pancreas. The method consists in a special data processing computer tomography (CT) in the axial, coronal and sagittal projections, while avoiding the volume of blood and lymphatic vessels pancreas. A study conducted in 50 patients, which CT was performed about the disease not related to the pancreas and other digestive organs. The average pancreas volume was 86,82±24,13 ml. There was no difference in pancreas volume, depending on the gender of surveyed found. In patients younger than 70 years, pancreas volume was 80 ml, and older patients — usually less than 70 ml.

Several reports were devoted to the pathogenesis of chronic pancreatitis (CP). Particular attention was paid to the genetic predisposition to CP. Thus, in the report of J. Rosendahl (Germany) analyzed in detail the different mutations that lead to activation of intraorgan trypsinogen: trypsinogen cationic mutation (PRSS1), Casale inhibitor (SPINK1), chymotrypsin C (CTRC), carboxypeptidase A1 and others. In some cases, these mutations are the main mechanism of the disease, and in other cases — contributing background. In any case, the mutations play a role of "match", to which you want to bring "fire", i.e. a permissive factor (alcohol, smoking, and others.). Then, start the activation of trypsinogen, which is due to a genetic defect inhibiting trypsin is not stopped in due measure, and developed pancreatitis. This is the principle of the pathogenesis of most genetically caused pancreatitis. For detailed lecture on the pathophysiology of pain in CP and its treatment have read A. Drewes (Denmark). The basic mechanisms of pain include the following:

– local causes: inflammatory focus (mass) in the pancreas, pseudocyst, etc .;
– duct obstruction;
– extrapancreatic complications (peptic ulcer and other.);
– inflammation (inflammatory cytokines);
– interstitial hypertension;
– complications of surgical or endoscopic intervention;
– drug-induced bowel dysfunction (paresis when using opioids);
– increased production of cholecystokinin;
– deficit gastrointestinal hormones, gut motility disorders, bacterial overgrowth

syndrome in the small intestine;

– peripheral sensitization, Psychosomatics, neuropathy;

– other reasons (changes in the enteric nervous system, increased sympathetic tone, mesenteric ischemia, comorbidities, opioid-induced hyperalgesia).

A. Drewes brought evidence-based studies on the relief of pain in CP (Table. 1 and 2). The Rapporteur also relied on a review article S. S. Olesen et al. the pathogenesis and treatment of abdominal pain in CP. The full text of this article can be found on the website link Pancreapedia: http://www.pancreapedia.org/sites/www.pancreapedia.org/files/DOI%20Pathogenis%20and%20Treatment%20of%20Pain%20in%20CP.pdf [23].

Table 1

Recommendations to address the (treatment) risk factors and etiologic factors of pancreatic pain in CP (S. S. Olesen et al., 2013 [24])

Risk Factors/etiological factors	Treatment	Comments
Alcohol	Avoiding alcohol	Reduction of disease progression, reduction in pain intensity
Smoking	To give up smoking	Reduction of disease progression, reduction in pain intensity
Food	Specific recommendations are missing	No evidence
Heredity	Control of the state of the ducts in the dynamics pancreatectomy	No evidence At high risk of malignancy
Pancreas divisum	Endoscopic surgery or	The results are contradictory
Autoimmune CP	Glucocorticosteroids	Convincing treatment results [8]
Metabolic disorders	Lipid-lowering therapy, hyperparathyroidism, and others.	Consultation endocrinologist
Peptic ulcer	PPIs +/- Helicobacter pylori eradication	Avoid NSAIDs
pseudocyst	Endoscopic, percutaneous drainage, surgical treatment	The method of treatment depends on the location, size of the pseudocyst, Histology
obstruction of duodenum	Endoscopic dilatation or surgical treatment	Endoscopic dilatation — the treatment of first choice
Obstruction of the common bile duct	Stenting	Data communication obstruction of the bile duct

		with pain contradictory

Table 2

Analgesics and adjuvant analgesics for the treatment of pain in CP (S. S. Olesen et al., 2013 [24])

Group products and the direction of action	Preparations	Comments	Литературная ссылка
Central sensitization	Antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin reuptake inhibitors/norepinephrine	According to experts, research evidence is not carried out	[16]
	Gabapentinoids (gabapentin/pregabalin)	A moderate effect on pain was proved in randomized, placebo-controlled study (pregabalin)	[13]
	Ketamine	Eliminates hyperalgesia in a pilot study	[10]
Analgesics	Tramadol in comparison with morphine	There is no difference in pain relief, fewer side effects in the treatment of tramadol (randomized controlled trial)	[7]
	Fentanyl versus morphine	There is no difference in pain relief (randomized controlled trial)	[24]
	Oxycodone in comparison with morphine	Oxycodone effective morphine (experimental study)	[24]
	ADL 10-0101: agonist of κ-opioid receptors	ADL 10-0101: κ-agonist opioid receptors more potent than morphine (experimental and clinical data, a limited number of patients — n = 6)	[21]

Prof. D. Whitcomb (USA) delivered a keynote lecture on preparing international recommendations on the diagnosis and treatment of CP. According to experts, CP should be considered in accordance with the following definition: "CP is a pathological fibro-inflammatory syndrome in individuals with genetic, external and/or other risk factors that lead to the development of persistent pathological response to stress or damage to the parenchyma". Common symptoms at diagnosis of CP and its later stages include atrophy and fibrosis of the parenchyma of the pancreas, abdominal pain, irregularity of ducts and stenosis, calcification, violation of foreign and endocrine pancreatic function, dysplasia. The recommendations are in the process of development and have not been published yet.

A number of papers were devoted to the diagnosis of pancreatic diseases and, in particular, CP. A. R. G. Sheel (UK) described the role of endosonography in the diagnosis of early stages of CP. Endosonography is a revolutionary innovation in pancreatology, it is increasingly being used for imaging of the pancreas. Endosonography more informative than CT for the detection of structures less than 2 cm, and allows you to visualize the parenchyma, and the ducts of the pancreas, as well as perform a biopsy and therapeutic manipulation.
The lecturer cited results of a survey 805 patients diagnosed with "chronic pancreatitis" from 2003 to 2016 in the pancreatologic center of Liverpool. In 116 (14.4%) patients, with careful examination of the diagnosis of CP was rejected. Of these, 31% were diagnosed with chronic abdominal pain syndrome. In these patients, with careful examination of the tool change is detected by the pancreas. In 24% of patients minor changes of the pancreas have been found, which could not qualify as CP. In 8% of cases the diagnosis of CP changed to the diagnosis of recurrent acute pancreatitis (AP). In 20% of cases of pancreatic changes were associated with a history of AP. In 4% of the erroneous diagnosis of CP revealed intraductal mucinous neoplasia. In 13% the diagnosis of CP was rejected for other reasons (diagnosed with cancer of the pancreas, pancreatic steatosis, and so on. D.). Interestingly, for establishing the correct diagnosis for patients was carried out on the whole 252 radiological studies, 170 CT, 61 endosonography, 20 magnetic resonance cholangiopancreatography, 2 with the introduction of secretin and 1 endoscopic retrograde cholangiopancreatography.

J. Iglesias-Garcia (Spain) reported on the results of a prospective study of cross-correlation. 43 patients underwent endosonography pancreas with endoscopic elastography and sekretinovy test assessment bicarbonate products. We obtain a strong correlation between the results of elastography, to assess the extent of fibrosis of the pancreas, and the production of bicarbonate. This indicates the informativeness elastography to determine the severity of pancreatic fibrosis.

A series of reports was devoted to various aspects of trophological failure in CP with exocrine pancreatic insufficiency (EPI). In particular, the report S. Stigliano (Italy) discussed about osteopathy in CP. Osteopathy leads to increased fracture risk, reduced quality of life, even in the absence of fractures. It is very important that osteopathy applies to CP complications that can be prevented.
Reduced bone mineral density occurs in a number of digestive diseases:

– celiac — risk of fracture increased by 40%;

– gastrectomy — Osteopathy in 37-42%;

– Crohn's disease — osteopenia in 22-55%, osteoporosis in 3-6%;

– ulcerative colitis — in 32-67% osteopenia and osteoporosis in 4-50%;

– orthotopic liver transplantation/primary biliary cirrhosis — in 46% (17% in the first year);

– CP — 23% in osteoporosis, any osteopathy 65%.

According to the results of a multicenter cross-European study, which included 135 patients with CP who underwent dual energy X-ray absorptiometry, osteopenia was diagnosed in 40.7%, osteoporosis — in 23.7% of cases. Normal bone mineral density occurred in 35.6% of cases. Pathological changes were localized at the femoral neck at 37% in the lumbar spine — in 22%, both localization — 41% of cases. According to the results of statistical analysis, independent risk factors of osteopathy are older age and female gender. Reduce risk of osteopathy increased body mass index and diabetes mellitus (?!). No correlation was found between bone mineral density, fecal elastase and the level of vitamin D in the blood. Particular attention was drawn to the report of N. Vallejo-Senra (Icpaniya) on cardiovascular risk at EPI in patients with CP. The speaker of the national retrospective cohort study in Denmark, showing a significant increase in the mortality of patients with CP compared with the general population (Fig. 1). Contribution to mortality in CP introduces and cardiovascular disease.

The pathophysiology of cardiovascular events in CP:

– alcohol and smoking;

– diabetes;

– trophological failure (EPI):

- shortage of high-density lipoprotein, apolipoprotein A-1, A lipoprotein;
- deficiency of vitamin D;
- micronutrient deficiencies;
- inflammatory syndrome associated with malnutrition.

According to study by N. Vallejo-Senra, the life expectancy of patients with CP without EPI significantly more than EPI (Fig. 2) .In a prospective cohort study, the author examined 430 patients. CP diagnosis was made based on endosonography data when necessary to perform magnetic resonance tomography, magnetic resonance cholangiopancreatography with secretin. The diagnosis was based on the results of EPI triglyceride breath test. Nutritional status was evaluated (hemoglobin, magnesium, albumin, prealbumin, retinol-binding protein, glycosylated hemoglobin). For great cardiovascular events included myocardial infarction, stroke, and peripheral to the cardiovascular events . Arterial thrombosis, intermittent claudication and other results of the study are presented in Table 3. The risk of cardiovascular events was 2.46 at EPI without EPI 0.67 ($p < 0.001$). Conclusions: More than 10% of CP patients over 8 years of observation were cardiovascular events; cardiovascular events associated with EPI, hypertension and alcohol abuse, smoking; in the future it is necessary to study the effect of enzyme replacement therapy on the incidence of cardiovascular events in CP.

Table 3

The frequency of cardiovascular events in CP (N. Vallejo-Senra et al., 2016 [2])

	EPI	Without EPI	p
All cardiovascular events	23,00%	5,26%	<0,001
Big cardiovascular events	10,31%	2,63%	0,739
Peripheral cardiovascular events	12,69%	2,63%	0,309

L. K. Frandsen et al. (Denmark) studied 166 patients with CP and showed that when EPI reduced strength of skeletal muscle. Thus, they found a correlation between the fat mass in a patient according bioimpedance and skeletal muscle strength, such as a handshake force (measured with a dynamometer) (Fig. 3). Consequently, when EPI appears and gradually increases fatigue. M. Moneo (Spain) examined 42 patients with CP during the first visit to the doctor. Patients with the following frequency EPI deficiency was detected:

– Vit. A — 34.6%;

– Vit. E — 15.4%;

– Vit. D — 80,7%;

– Retinol binding protein — 38.5%;

– Magnesium — 7.7%;

– Prealbumin — 42.3%.

Interestingly, in the absence of EPI vitamin D deficiency was defined in 75.1%, i.e. This does not depend on vitamin deficiencies EPI. When EPI overweight occurred in 46.2%, obesity — in 3.8% of cases, only 3.8% of patients had a decrease in body weight.

Prof. M. Lerch (Germany) delivered a lecture "Chronic pancreatitis: indications and optimization of enzyme replacement therapy".

The main symptoms of CP — pain, steatorrhea, weight loss:

– pain — recurrent girdle, is often associated with low back pain;

– steatorrhea — excretion of more than 7 grams of fat per day as a result of malabsorption;

– weight loss — loss of more than 20% of body weight.

Incidence EPI in CP is shown in Fig. 4.

Features of EPI:

– maldigestion of fat, protein and carbohydrates;

– steatorrhea, flatulentsiya, intestinal pain;

– weight loss;

– growth retardation in children;

– deficiency of fat-soluble vitamins;

– decrease in bone mineral density;
– deficit minerals (zinc, magnesium, etc.);
– increased morbidity and mortality.

Secretin-pancreozymin test, which is the "gold standard" direct test probe for diagnosing EPI currently in practice because as the complexity of the procedure, and because of the high cost of stimulants. EPI informative method of diagnosis, but also rarely used in practice, is the quantitative determination of fat in the feces. The ability of the test is determined by the need to collect feces for 72 hours. Furthermore, steatorrhea develops only when stored below 10% parenchyma functioning pancreatic lipase with a corresponding reduction of production (Fig. 5, 6). By Fig. 6 should be added that the triglyceride breath test to diagnose EPI while retaining more than 60% of the parenchyma of the pancreas, i.e. on the informativeness of approaching secretin-pancreozymin test.

To diagnose EPI widely used fecal elastase test. Indicators of fecal elastase-1 correlated with steatorrhea, t. E., These rates are lower when steatorrhoea (Fig. 7). In addition, a correlation was found with the level of vitamin D in the blood (Fig. 8). This shows the reflection of indicators of fecal elastase-1 reduction of exocrine pancreatic function and severity of malabsorption.

Advantages of fecal elastase test:
– a non-invasive method of tubeless;
– elastase-1 — pancreatospecific enzyme;
– minimal changes of elastase activity in the intestinal transit;
– stability of the enzyme;
– simple measurement technically;
– there is no need to abolish enzyme preparations;
– relatively low cost.

EPI develops not only in CP, but also in other diseases of the pancreas, for example after suffering AP (Fig. 9). Especially often develops EPI in Vol. H. EPI with severe steatorrhea in patients undergoing severe AP, which required the implementation necrectomy. Thus, after developing necrectomy steatorrhea in 25%, without EPI steatorrhea in 33% of cases, while the outer pancreatic secretion remained normal in 42% of cases. In patients undergoing AP, but without performing necrectomy, RV function is preserved in 87% EPI formed in 13% of cases, and no steatorrhea recorded [22].

EPI develops in a significant proportion of patients with pancreatic cancer (Fig. 10), is often diagnosed with diabetes, especially type I [11]. EPI formed and is the basis for the appointment of enzyme preparations after surgery for CP (pancreatectomy, and others) (Fig. 11).

To avoid steatorrhea is necessary to have 30 thousand. Units FIP lipase duodenal lumen in the postprandial period (10% of normal), but taking into account risks to lipase, received per os (effect of acid and pepsin in the stomach, possible asynchrony passage pancreatin and chyme in the case receiving a tablet formulation), it is necessary to appoint more — 40-50 thousand units FIP on the main meal, and 20-25 thousand units in the FIP snack [15]...

Indications for enzyme replacement therapy:

– pancreatin preparations are indicated for proven or suspected steatorrhoea;

– as quantitative determination of fat in the stool is rare, enzyme preparations are shown in pathological results of functional tests and the clinical manifestations of malabsorption (weight loss, abdominal pain, flatulence pronounced, dyspepsia, diarrhea);

– enzyme preparations shown ex juvantibus with fuzzy symptoms.

In preparing for the publication of harmonized European recommendations on diagnostic and CP treatment (HaPanEu) contains the following provisions concerning the replacement of the enzyme.

- What are indications to the replacement enzyme therapy in chronic pancreatitis?

• Substitution therapy is indicated for CP EPI with the presence of clinical symptoms or laboratory evidence of malabsorption of. It recommended that a study of nutritional status for signs of malabsorption (1A level, strong agreement).

- What are the enzymatic drugs of choice?

• Enteric coated microspheres or minimicrospheres smaller than 2 mm are the drugs of choice for EPI. Micro or minitablets size 2.2-2.5 mm can also be effective, but the scientific evidence of their effectiveness is limited in CP. Comparative clinical study of different enzyme preparations are absent (1B level of strong agreement).

Comment. The efficacy of pancreatic enzyme preparations depends on several factors: 1) mixing with food; 2) the evacuation of the stomach with food, 3) mixing with duodenal chyme and bile acids; 4) rapid release of the enzymes in the duodenum.

- How should enzyme preparations be prescribed?

• Oral enzyme preparations should be distributed between the main meals and snacks (1A level, strong agreement).

- What is the optimal dose of enzyme preparations with EPI due to CP?

• Minimum dose of lipase from 40 000 to 50 000 units in the FIP main meal and half dose snack (1A level, strong agreement).

Prof. M. Lerch presented algorithm of enzyme replacement therapy (Fig. 12). Innovation of substitution enzyme therapy is the creation of drugs based on microbial lipases, for example Liprotamaza drug. Prof. M. Lerch talked about research and evidence-based perspectives of these drugs (the results of one such study are presented below). Microbial enzymes have a number of positive qualities: a broad substrate specificity, the preservation of activity in the broader framework of pH.

Lecture emphasized that the lack of effectiveness of enzyme preparations need to be combined with proton pump inhibitors for adjusting pH in the duodenal lumen. Enzyme preparations it is important to designate at the beginning of the meal, which creates the best conditions for the realization of their effect. Prof. M. Lerch presented results of a double blind, randomized, placebo-controlled study of the efficacy and safety of a new enzyme preparation based on the microbial lipases in cystic fibrosis (J. E. Heubi, Germany) (Fig. 13). It is interesting and it is important that this medication is available in liquid form (for drinking) that allows you to assign it to

young children and need to enter through probe. Monitoring EPI effectiveness of treatment:

– positive dynamics of clinical symptoms (weight gain, normalization of vitamin status, the disappearance of abdominal symptoms);

– in the absence of positive dynamics of clinical manifestations it is necessary to conduct functional tests (triglyceride breath test) to evaluate the fat excretion in feces.

Interesting results were obtained in a pilot study by A. Mosseler (Germany) "Taurine upon EPI to improve the assimilation of fat". Taurine is a sulfonic acid, its main feature is the formation of conjugates with bile acids. Upon EPI taurine increased loss due to the breach of the enterohepatic circulation of bile acids. And has a value that bacterial overgrowth in the small intestine syndrome results in deconjugation of bile acids. In the study, two groups were examined animals EPI (pancreatic duct ligation) — or just treated with an enzyme preparation or the enzyme preparation in combination with taurine. It is shown that taurine has a positive effect on fat absorption in experimental animals. Several reports were dedicated to CP, pancreatic steatosis and their combination with hepatic steatosis. S. Beer et al. (Germany) examined 35 patients after resection of the pancreas over the CP, 54 patients with CP, are not subjected to surgical treatment. Steatosis and liver fibrosis was assessed by FibroTest and Fibroscan. Fecal elastase test was conducted. The results are shown in Fig. 14 and 15. The authors concluded that in patients with CP high incidence of steatosis (particularly after resection of the pancreas) and fibrosis of the liver, but these changes in the liver had no association with alcohol abuse, the degree of reduction of foreign and endocrine functions of the pancreas. In all cases, liver fibrosis associated with its steatosis.

P. O. Coe (United Kingdom) used magnetic resonance imaging with spectroscopy to detect fat in the pancreas. We studied the tissue of the pancreas in 12 patients who underwent resection of the pancreas, and the results of imaging 15 volunteers were analyzed. The author was able to develop a quantitative method for non-invasive evaluation of the content of fat in the pancreas. This is important, t. K. Experimentally shown that the accumulation of fat in pancreatic adenocarcinoma predisposes to [20] .

G. Zsori et al. (Hungary) conducted treatment of non-alcoholic fatty liver disease and pancreatic metformin. The study included 14 patients. Degree of fat accumulation in the liver and the pancreas was evaluated by Hounsfield scale (CT). Metformin in high therapeutic doses for 4 months was presvribed. If the degree of fat accumulation in the liver during the period of treatment was significantly decreased, the significant reduction in the severity of pancreatic steatosis did not happen. E., No this, no earlier studies did not give a clear result with regard to the treatment of pancreatic steatosis. Prof. H. Friess gave a lecture on surgical treatment CP.

Indications for CP surgical treatment:

– intractable pain;

– duodenal stenosis;

– stenosis of the common bile duct;

– stenosis of the pancreatic duct;
– compression of the portal vein;
– suspected pancreatic cancer.

Main conclusion of lectures: early surgery (less than 3 years from the start of abdominal pain) leads to significantly better indices.

Results of interesting retrospective study "on weekends and holidays, patients with more severe acute pancreatitis admitted to hospital" introduced S. Fernandes (Portugal). Indeed, a retrospective analysis of case histories of 524 patients it was found that on weekends and public holidays the heavy AP (Atlanta classification) was diagnosed in 68.9% of all hospital admissions, and on weekdays — at 56,0% ($p = 0.02$). No significant difference in mortality was found out.

S. Beer (Germany) studied the question of the pancreas cancer due to increased intake of cadmium in cigarette smoke into the body of patients. We studied 16 cancer tissue samples of the pancreas and the surrounding non-tumor tissue (surgical material). Cadmium in tissue was determined by atomic absorption graphite. In tumor tissue cadmium content was 13,58±3,99 g/g, and in the surrounding tissue swelling — 5,60±1,36 g/g ($p < 0,05$). Author conjectured that perhaps smoking causes cancer of the pancreas due to the high concentration of cadmium in cigarette smoke.

The results of a number of more interesting and promising research were presented in Liverpool, but all of them can’t be set as part of article. Participators of the meeting in Liverpool returned home with new information and positive experience.

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Article represents the results of main scientific researches in pancreatology conducted in 2015–2016. There are stated achievements of leading pancreatologists of Europe regarding study of etiology, pathogenesis, diagnostics and treatment of pancreatitis and tumors of the pancreas.

Figures

Fig. 1. Mortality in chronic pancreatitis (U. C. Bang et al., 2014 [19]).

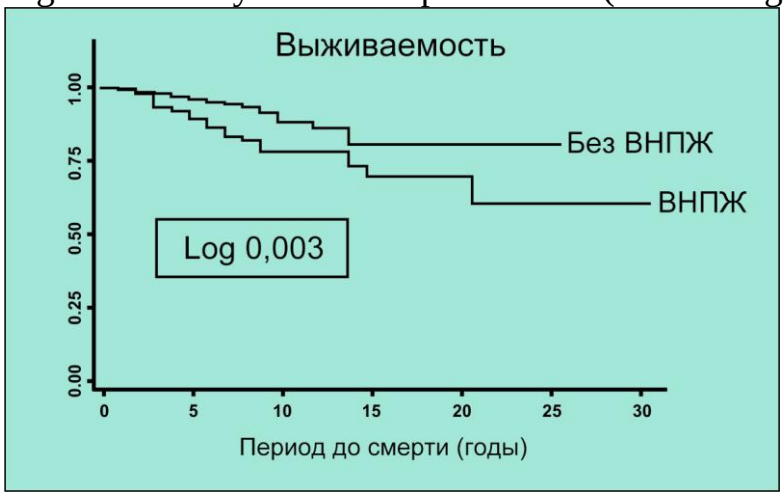

Fig. 2. Life expectancy of patients with CP are subject to availability of EPI (N. Vallejo-Senra et al., 2016 [2]).

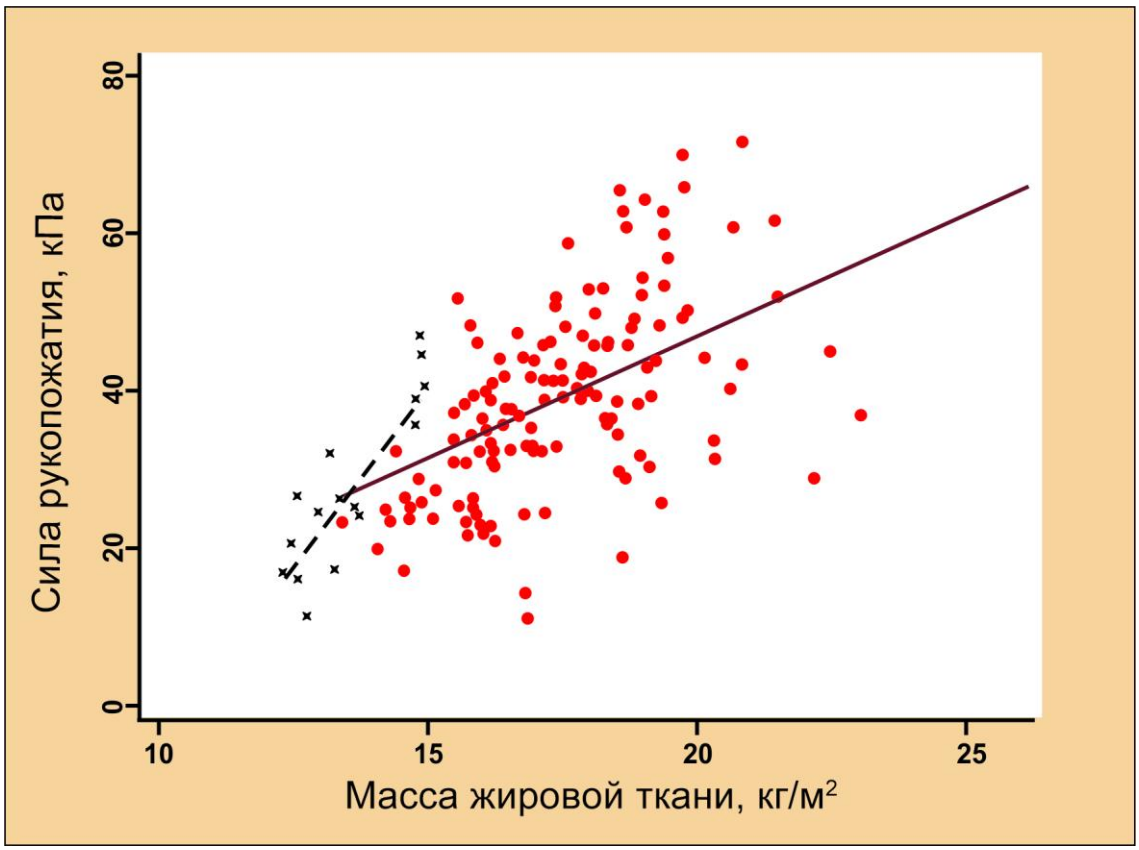

Fig. 3. Correlation between the mass of adipose tissue in the body of patients with CP (according to the bioimpedance) and the strength of a handshake (measuring dynamometer) (L. K. Frandsen et al., 2016 [17]).

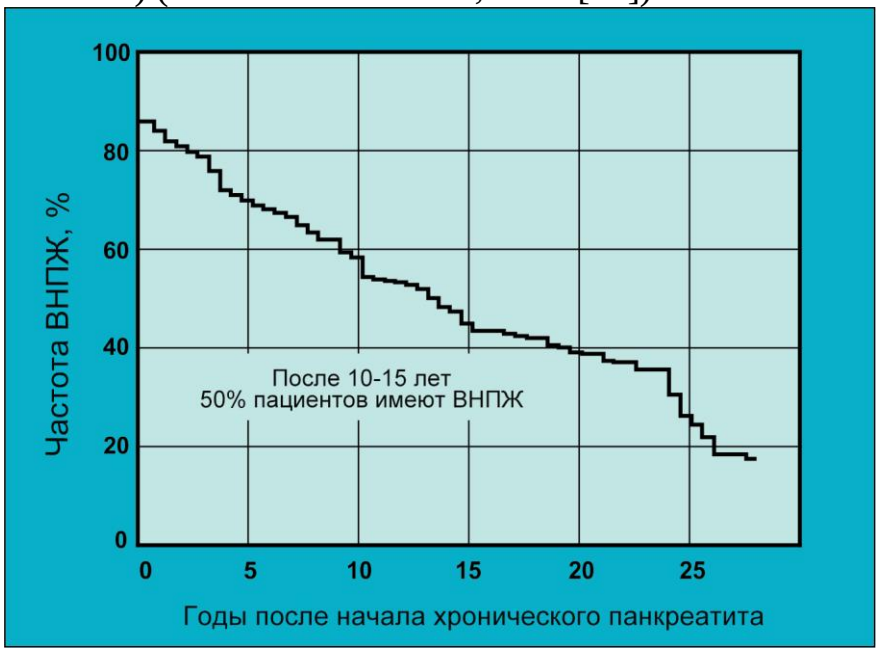

Fig. 4. Frequency of EPI development in CP (P. Layer et al., 1994 [4]).

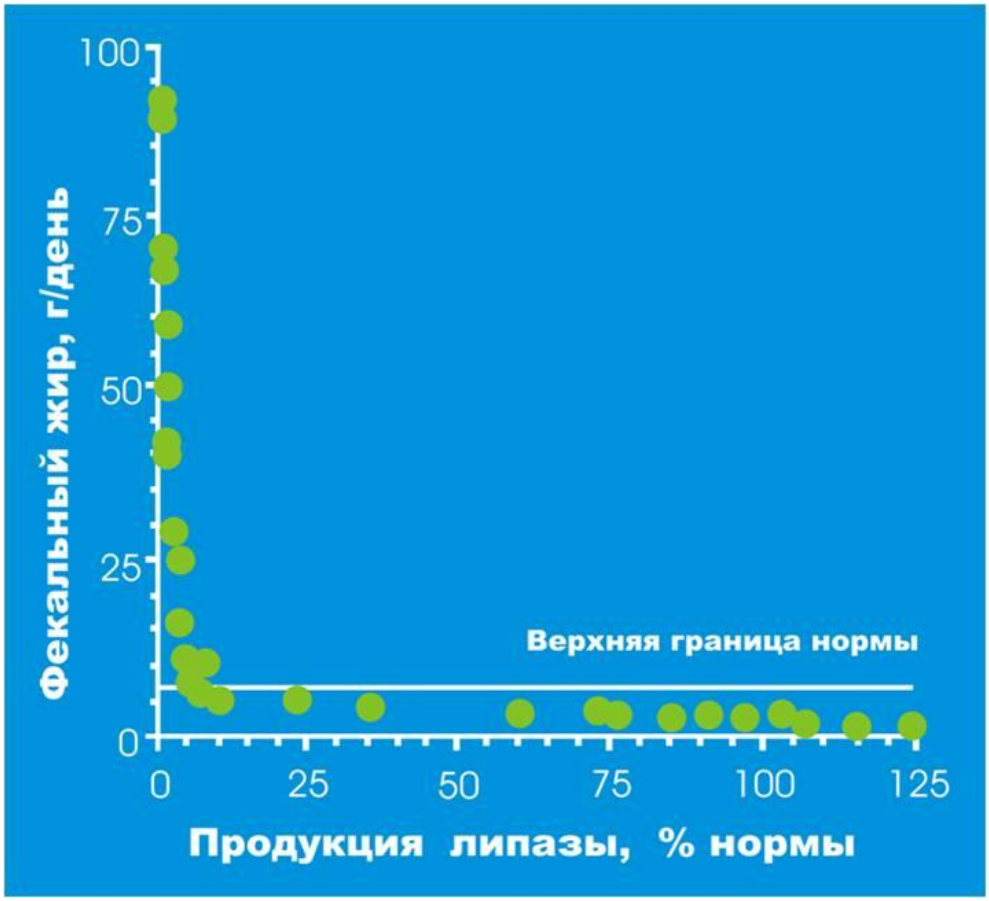

Fig. 5. Relationship between the degree of reduction of pancreatic lipase production and development of steatorrhea (E. P. DiMagno et al., 1973 [6]).

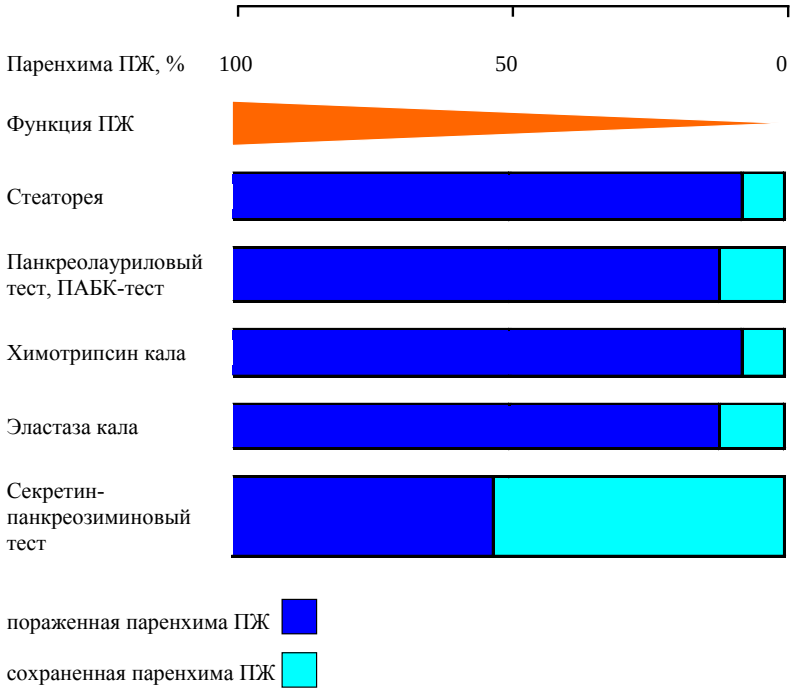

Fig. 6. Sensitivity of functional tests for pancreatic pathology (M. W. Buchler et al., 2002 [3]).

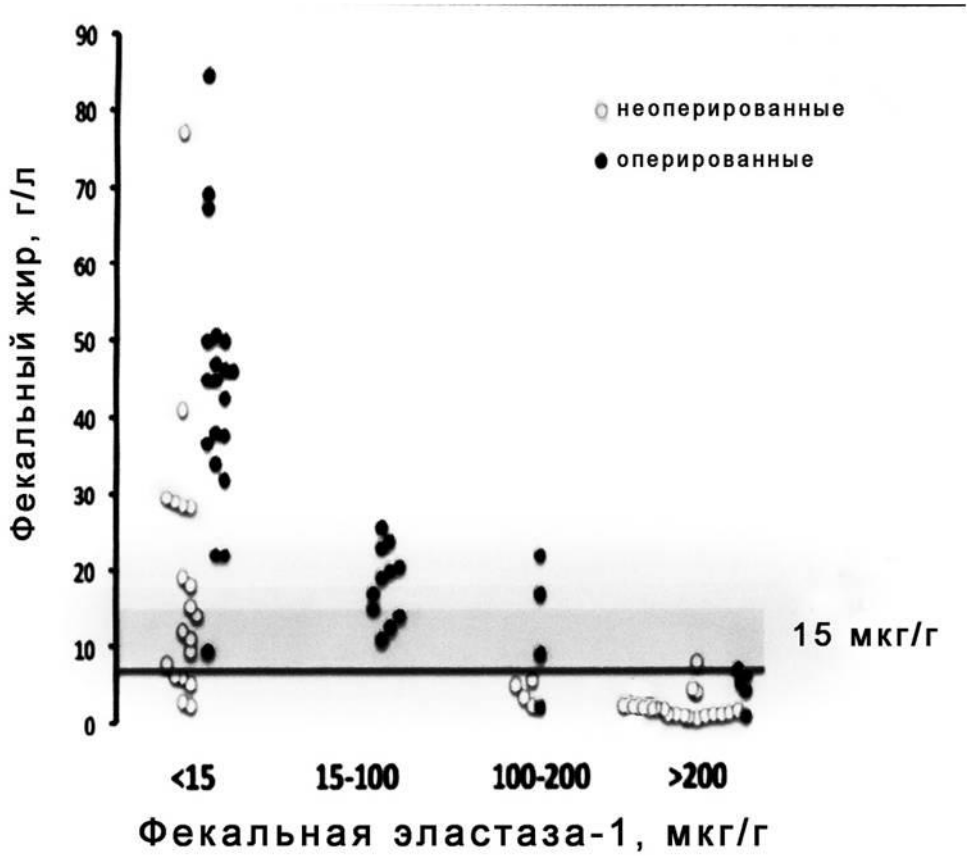

Fig. 7. Ratio of fecal elastase-1 and steatorrhea (L. Benini et al., 2013 [9]).

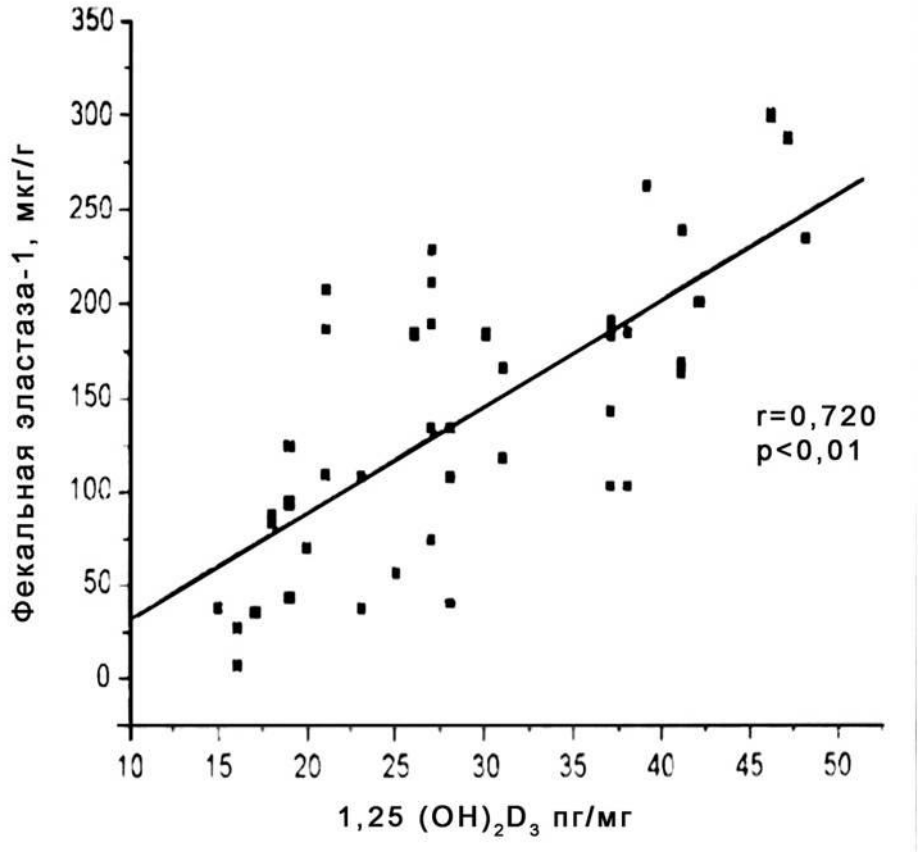

Fig. 8. Correlation between indicators of fecal elastase-1 and level of vitamin D metabolite in the blood (S. T. Mann et al., 2003 [26]).

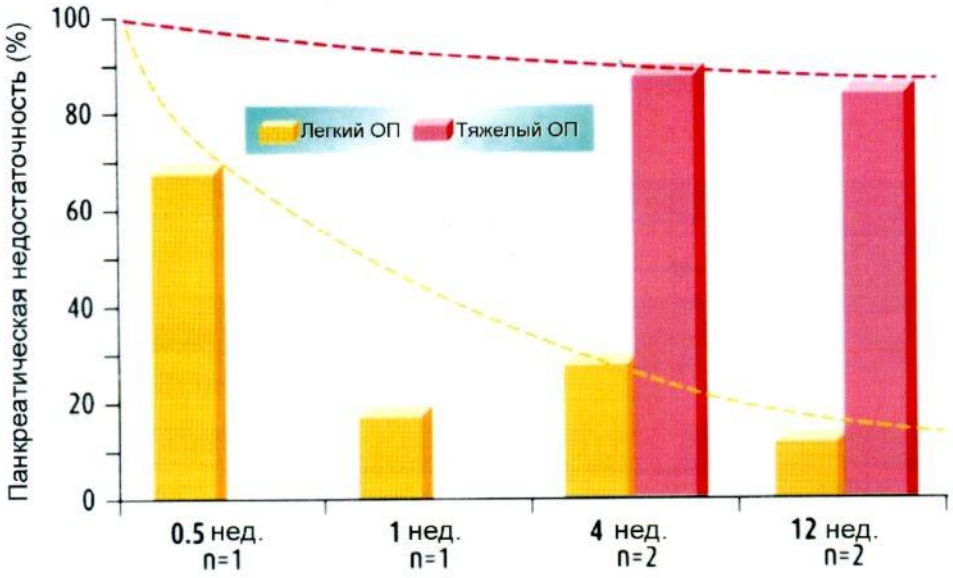

Fig. 9. Frequency of exocrine pancreatic function decline during convalescence after AP depending on the severity of AP (A. M. Masclee Ad et al., 2005 [18]).

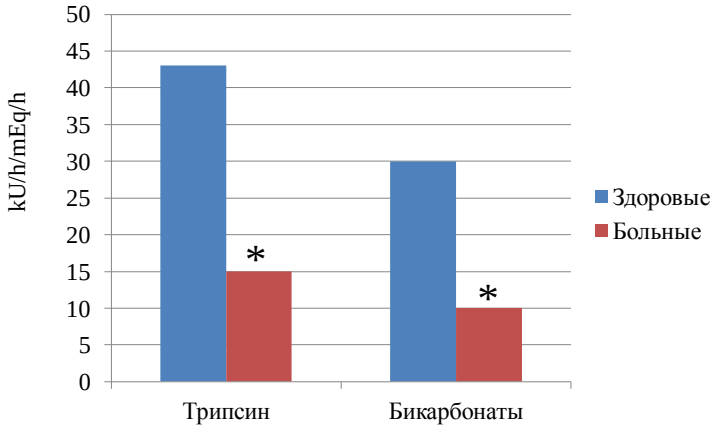

Fig. 10. Trypsin and bicarbonate products in patients with pancreatic cancer as compared to healthy (E. P. DiMagno, 1979 [5]).

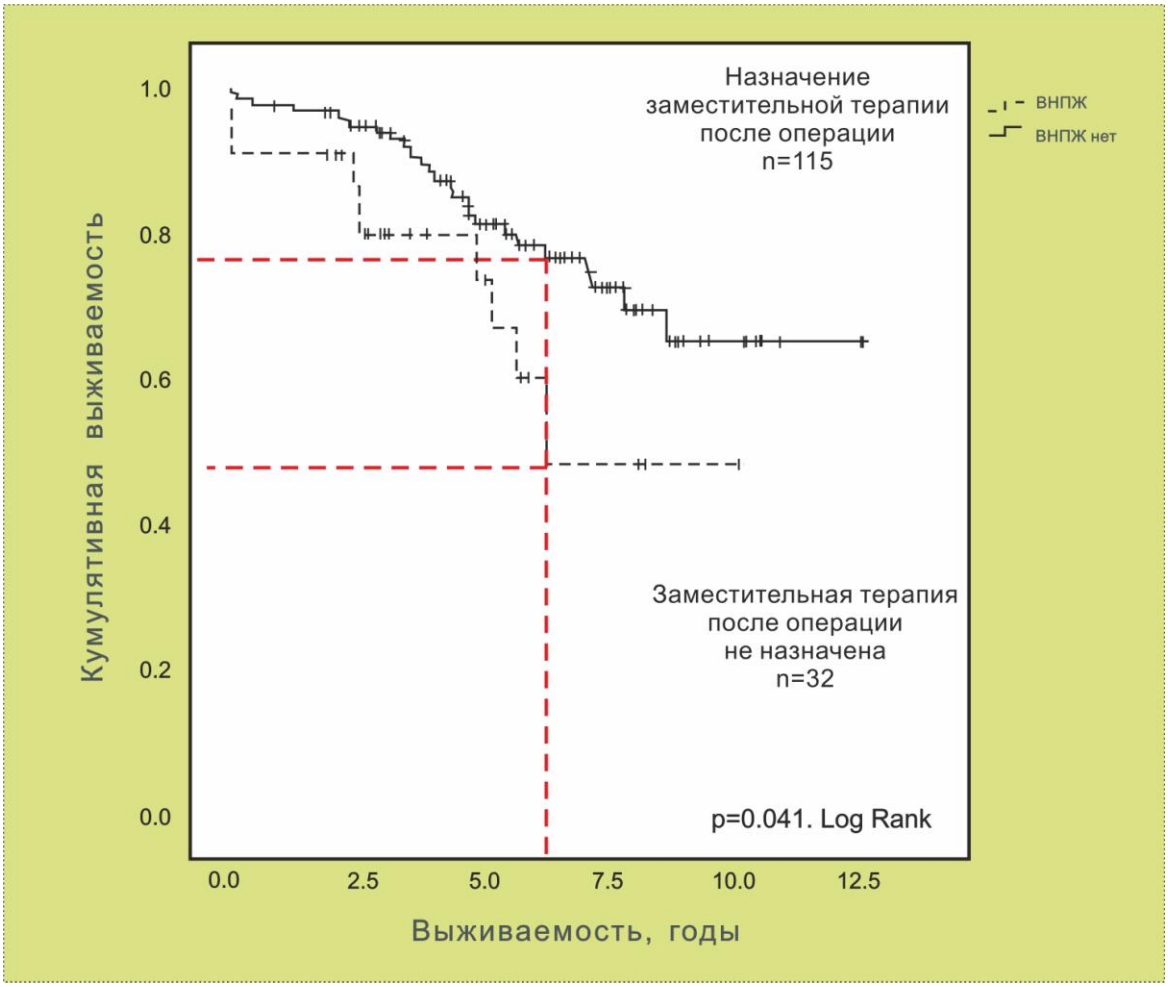

Fig. 11. Life expectancy of patients with CP after surgical intervention, depending on the purpose of enzyme replacement therapy (M. Winny et al., 2014 [14]).

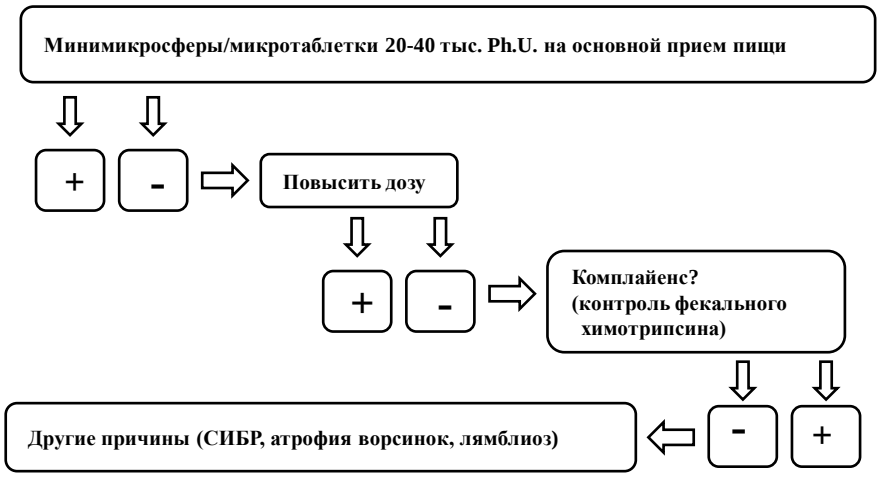

Fig. 12. Algorithm of enzyme therapy, presented in a lecture by Prof. M. Lerch.

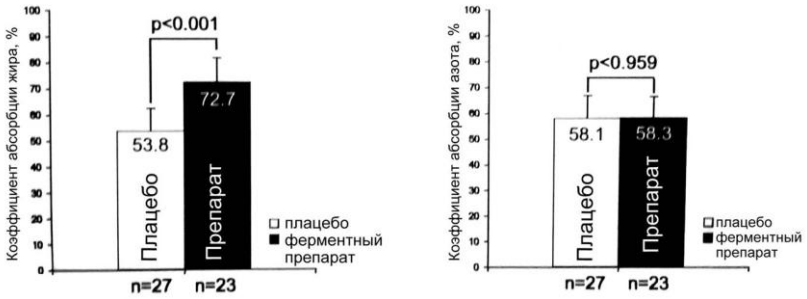

Fig. 13. Results of investigation of the influence of the enzyme preparation on the basis of a microbial lipase in cystic fibrosis patients in the absorption of fat and nitrogen ratios (J. E. Heubi et al., 2016 [25]).

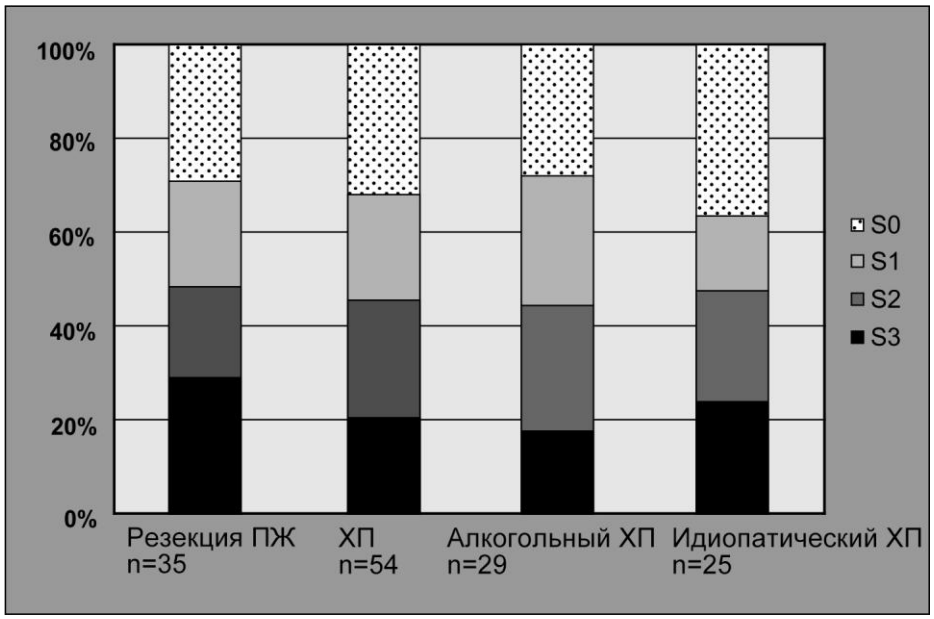

Fig. 14. Severity of hepatic steatosis in patients with CP (S. Beer et al., 2016 [12]).

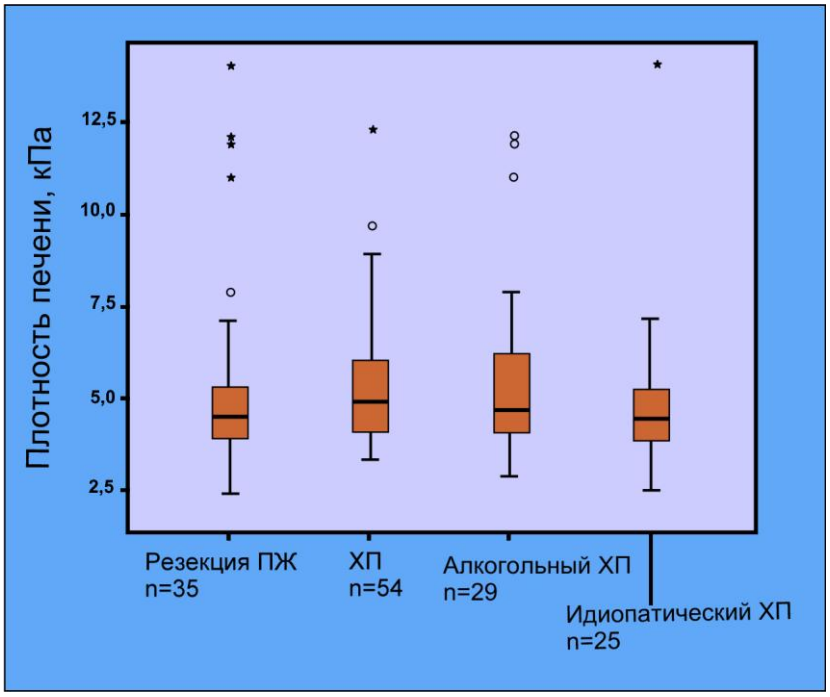

Fig. 15. Severity of liver fibrosis in patients with CP (S. Beer et al., 2016 [12]).