UDC 616-008.9-085:616.37-002.2

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CORRECTION OF MALNUTRITION IN PATIENTS WITH CHRONIC PANCREATITIS

Abstract

The objective of the study was to assess malnutrition incidence and effectiveness of various correction methods in patients with CP. **Materials and methods:** 148 patients were examined. Group I included 71 people with chronic alcoholic pancreatitis (CAP); group II — 77 patients with chronic obstructive pancreatitis (COP). Nutritional status (NS) was assessed by criteria of V. M. Luft. Lymphocytes, pancreatic amylase, lipase, total protein, albumin, urine diastase and fecal elastase-1 levels were estimated before and after treatment. We made a comparative assessment of the efficacy of two therapy regimens: combination therapy (CT) with enzyme products (Mezym 10,500 U/day) and sip feeding (Ensure 2 — 200 ml/day), or high-dose enzyme replacement therapy (HD ERT) (Creon 120,000 U/day), for 10 weeks. 62 patients received HD ERT (24 patients with CAP and 38 patients with COP); and 86 patients received CT, 47 and 39, respectively. **Results:** The prevalence of malnutrition in patients with CP was 92 % (n=136). Lymphopenia was determined in 44 %, hypoproteinemia — in 11,5 %, hypoalbuminemia — in 54 %. 12 (8 %) patients did not have malnutrition. Malnutrition was more significant in patients with CAP (16 points and 18 points; p=0.0007). In the CAP group: mild malnutrition was diagnosed in 44 patients, moderate in 20, severe — in 2, and eutrophia — in 6 patients; in the COP group: mild malnutrition was diagnosed in 33 petients, moderate — in 37, severe — 0, and eutrophia — in 6 patients. After treatment in the CAP group: moderate malnutrition — in 7, mild — 58, eutrophia — in 7 patients, in the COP group: moderate malnutrition — in 37, mind — in 31, and eutrophia — in 8 patients. **Conclusion:** Malnutrition is a frequent syndrome in patients with CP. Malnutrition is more severe in patients with CAP. Combined therapy regimen turned out to the most effective in patients with CAP. HD ERT is indicated in exocrine pancreatic insufficiency.

Key words: *chronic pancreatitis, malnutrition , lymphocytes, albumin, fecal elastase-1*

For citation: Gavrilina N. S., Ilchenko L. Yu., Sedova G. A. et al. CORRECTION OF MALNUTRITION IN PATIENTS WITH CHRONIC PANCREATITIS. The Russian Archives of Internal Medicine. 2019; 9(1): 70-80. [In Russian]. DOI: 10.20514/2226-6704-2019-9-1-70-80

DOI: 10.20514/2226-6704-2019-9-1-70-80

CAP — chronic alcoholic pancreatitis, COP — chronic obstructive pancreatitis, ESPEN — European Society for Clinical Nutrition and Metabolism, HD ERT — high-dose enzyme replacement therapy, MPD — major pancreatic duct, GB — gallbladder, BMI — body mass index, TSFT — triceps skinfold thickness, CT — computer tomography, FFBM — fat-free body mass, MAMC — mid-arm muscle circumference, UAC — upper arm circumference, NS — nutritional status, FE1 — fecal elastase 1, CP — chronic pancreatitis, EPI — exocrine pancreatic insufficiency

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Introduction

In recent years, more emphasis in the management of chronic pancreatitis (CP) has been placed on the assessment of the nutritional status (NS) of a patient and its correction. Malnutrition is a complex of symptoms, the development of which is associated with insufficient intake or absorption of nutrients, and leads to the altering of the component composition of a body (reduced fat-free body mass (FFBM)), which results in deteriorated body functioning and aggravated disease progression [1]. The primary factor for malnutrition development in patients with CP is exocrine pancreatic insufficiency (EPI).

According to the authors, the proportion of underweight patients with CP is 8 to 39 % [2–5], and body weight loss is reported in 20–49 % of patients with CP [3, 6].

Only in 2015, the European Society for Clinical Nutrition and Metabolism (ESPEN) proposed criteria for diagnosing malnutrition [1]. Furthermore, lately there have been discussions about secondary sarcopenia and related conditions, as well as deficiency of certain substances which can be decreased without weight loss and normal body mass index (BMI).

For diagnosing malnutrition, anthropometric and laboratory methods are used together with specific questionnaires (The Nutrition Risk Screening 2002 (NRS 2002) [7], Malnutrition Universal Screening Tool (MUST)) [8]. These tests are also recommended by ESPEN [9].

With the introduction of new concepts such as "sarcopenia" and "sarcopenic obesity" into clinical practice, greater attention is being paid to instrumental methods: bioimpedansometry, computer tomography (CT), dual-energy X-ray absorptiometry, magnetic resonance imaging.

Results of assessing the sensitivity of anthropometric measures and biochemical blood parameters (macro- and microelements) are mutually contradictory. First of all, this is due to the lack of a single diagnostic standard. It is now clear that NS assessment should be comprehensive and should include not only BMI but also parameters of laboratory and instrumental tests.

The objective of the study was to assess malnutrition incidence, intensity and effectiveness of various correction methods in patients with CP of different etiology.

Materials and Methods

The study was carried out in the Gastroenterology Unit of State-Funded Health Institution "Municipal Clinical Hospital named after V. M. Buyanov" of the Moscow Public Health Department (head physician — A. V. Salikov, Candidate of Medical Science) on the clinical basis of the Department of Internal Medicine, Advanced Course, No. 2 of the Department of General Medicine under State Federal-Funded Educational Institution of Higher Professional Training "Russian National Research Medical University named after N. I. Pirogov" of the Russian Ministry of Health (head of the department — Prof. I. G. Nikitin, Doctor of Medical Science).

The study protocol and questionnaires were approved by the local Ethics Committee of the N. I. Pirogov Russian National Research Medical University. All the patients signed a written informed consent to their participation in the study and analysis of the data obtained.

The open-label, prospective, comparative, randomized study was conducted in two phases: phase 1 — examination and treatment of patients with CP in the Gastroenterology Unit of V. M. Buyanov Municipal Clinical Hospital, and phase 2 — outpatient follow-up in the Diagnostic Unit of the hospital.

Chronic pancreatitis was diagnosed on the basis of patients' complaints, clinical findings and medical history, laboratory examination data (presence of amylasemia, lipasemia, diastasuria, EPI, ultrasonic and computer tomography data).

Two classifications of CP were applied: etiologic TIGAR-O and by CP stages ABC.

Criteria for the inclusion of patients in the study were: males and females aged 18 to 83 with chronic obstructive / alcoholic pancreatitis, who signed an informed consent for participation in the study and publication of its findings.

Exclusion criteria for the study were: acute surgical conditions; cancer; operative interventions in the colon; bowel diseases with malabsorption syndrome; diseases at the decompensation stage which require intensive measures and special treatment; drug abuse; HIV infection; lactation, pregnancy

or no adequate use of contraception by women of childbearing potential; no written informed consent.

148 (64.9 %) patients were examined, among them 68 (46 %) females and 80 (54 %) males with chronic pancreatitis. The age of the patients varied from 22 to 82 years, with mean age of 51.8±13.2 years.

Based on the etiology of CP, the patients were divided into two groups during examination. Group I included 71 patients with chronic alcoholic pancreatitis (CAP) who systematically consumed alcohol in toxic doses, with a history of habitual drunkenness or chronic alcoholism. The toxic dose is usually understood as consumption of over 30 g of ethanol per day for men, and over 20 g of ethanol per day for women [10]. The group of patients with CAP included 57 (80.3 %) males and 14 females (19.7 %), with mean age of 46.3±11.2 years.

Group II consisted of 77 patients with chronic obstructive pancreatitis (COP). Among them, 29 (37.6 %) males and 48 (62.4 %) females; mean age — 56.81±3 years.

The clinical study design is provided in Figure 1.

We made a comparative assessment of the efficacy of two therapy regimens. One regimen included combination therapy with enzyme products (Mezym 10,500 U/day) and sip feeding (Ensure 2 — 200 ml/day). The second regimen included high-dose enzyme replacement therapy (HD ERT) (Creon 120,000 U/day), while maintaining a fat-balanced diet.

In addition, the patients received an antispasmodic (Papaverine 40 mg TID) and antisecretory treatment (Omez 20 mg BID).

We used malnutrition classification proposed by V. M. Luft (Table 1) [19].

Complete blood count was performed on automatic Celltac MEK-6318K (Japan); biochemical serum analysis — on Metrolab 2300 (USA) multifunctional biochemical analyzer using appropriate reagents. The following serum parameters were determined for all patients: alanine transaminase, aspartate transaminase, amylase, total protein, protein fractions and absolute count.

Activity of hemolipase and fecal elastase 1 (FE1) was determined in ArkhiMed and NAKFF laboratories. FE1 was analyzed using the ELISA kit (ScheBo Biotech, Germany).

To assess EPI, FE1 levels recommended by the manufacturer were applied:

- 200 to over 500 μg/g of stool — normal exocrine pancreatic function;
- 100 to 200 μg/g of stool — mild and moderate exocrine pancreatic insufficiency;
- below 100 μg/g of stool — severe EPI.

Instrumental test included abdominal ultrasound and CT (if medically required).

Statistical data analysis was performed using Excel 10.0 and Statistica 13.0 software. Arithmetic mean (M) and standard deviation (SD) were calculated for each series of results, and median (ME), 25 % and 75 % quartiles (H and L) — for maldistributed parameters. Normality of parameter distribution was assessed by the Kolmogorov-Smirnov and Shapiro-Wilk tests.

Mean values were compared using Student's t-test (for normally distributed values). Mann-Whitney test was used to compare unrelated groups

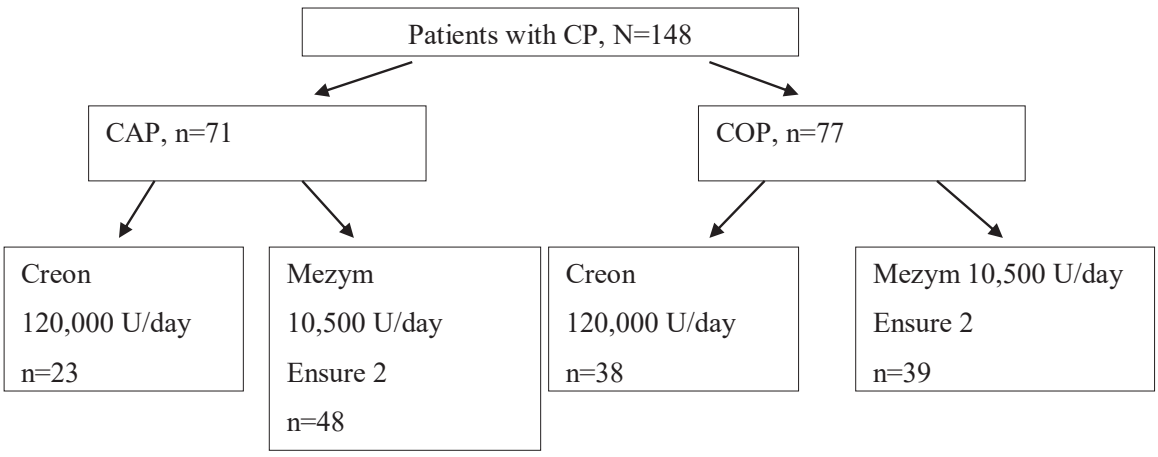

Figure 1. *The design of clinical study*

Table 1. *Criteria for diagnosis of malnutrition (ad. to V. M. Luft) [11]*

Criteria	Reference Ranges	Malnutrition		
		Mild	Moderate	Severe
Point	**3**	**2**	**1**	**0**
BMI, kg/m^2				
– 18–25 years	23–18.5	18.5–17	16.9–15	<15
– > 25 years	26–19	19–17.5	17.5–15.5	<15.5
Mid-arm circumference, cm				
– women	29–26	26–23	23–20	<20
– men	28–25	25–22.5	22.5–19.5	<19.5
Triceps skinfold thickness, mm				
– men	10.5–9.5	9.5–8.4	8.4–7.4	<7.4
– women	14.5–13	13–11.6	11.6–10.1	<10.1
Mid-arm muscle circumference, cm				
– men	25.7–23	23–20.4	20.4–17.5	<17.5
– women	23–21	21–18.5	18.5–16.5	<16.5
Total protein, g/L	≤65	64.9–55	54.9–45	≤44
Albumin, g/L	>35	34.9–30	29.9–25	≤24
Lymphocytes, 10^3/uL	>1.8	1.8–1.5	1.4–0.9	<0.9
Total points	**21**	**20–15**	**14–9**	**<9**

Notes: Mid-arm muscle circumference = Mid-arm circumference – (0.314 x Triceps skinfold thickness)

according to quantitative and ordinal signs, and non-parametric test of multiple comparisons (Kruskal-Wallis test) — to compare 4 groups.

Based on qualitative signs, unrelated groups were compared using Pearson χ^2 test.

To identify differences in dependent samples, Wilcoxon parametric test was used for quantitative parameters, and Cochran Q-test — for qualitative parameters.

Correlation was assessed by Spearman correlation analysis.

The critical value of statistical significance when testing null hypotheses was taken to be 0.05.

Results and Discussion

Based on the complete examination of 148 patients, primary clinical manifestations of CP of different etiology were analyzed.

Analysis of gender characteristics showed that patients with CAP were younger than those with COP (46.3±11.2 years vs. 56.8±13 years) and differed in gender (p=0.000000). Males prevailed in the CAP group, and females — in the COP group. This observation is consistent with the results obtained by other researchers [12].

When analyzing complaints of the patients, the following syndromes were identified: pain syndrome, dyspeptic syndrome and asthenic syndrome (Table 2).

Pain syndrome was the most common in patients with CP [13]. In our study, 106 (71.6 %) patients complained of abdominal pain; in COP, abdominal pain occurred considerably more often. However, according to I. E. Demir et al., pain syndrome is more pronounced in individuals with CAP [14]. According to other authors, patients report intense abdominal pain in 50 % of cases, and 15 % of patients have painless CP [13]. This difference can be due to the late stage of CP with developed atrophy of pancreatic parenchyma and complications, as well as the presence of toxic encephalopathy, underestimation of severity of own condition, late presentation.

Females complained of abdominal pain more often than males (p<0.01).

Fifty-four patients (51 %) reported pain localized in the epigastric region, 11 (10.4 %) — in the epigastrium and left hypochondriac region, 6 (8.5 %) — in the right hypochondriac region and others.

Altered defecation pattern was reported by 46 (31.1 %) patients, among them 37 (80 %) patients with COP and 9 (20 %) patients with CAP. Seventeen patients (37 %) reported repeated stool with oily sheen, 14 (31 %) — diarrhea, 8 (17 %) — alternating diarrhea and constipations, 7 (15 %) — only constipations.

Table 2. *Symptoms of chronic alcoholic and obstructive pancreatitis*

Complaints	CAP, n=71		COP, n=77		P	Statistic test
	abs.	%	abs.	%		
Stomachache:	38	53.5	68	88.3	**0.000003**	Pearson's chi-squared test
acute pain	5	3.4	12	8.1	**0.000027**	
moderate pain	7	4.7	19	12.8		
dull pain	26	17.6	37	25		
Nausea	27	18.3	29	19.6	0.96	Pearson's chi-squared test
Bloating	7	4.7	28	19	**0.00015**	Pearson's chi-squared test
Weight loss	13	8.8	14	9.5	0.98	Pearson's chi-squared test
Asthenia	52	35	39	26	**0.004**	Pearson's chi-squared test

According to data obtained in the study conducted by M. Holst et al., signs of malnutrition were identified in 28 % of cases (decreased fat and muscle mass, reduced handshake strength). At the same time, 20 % of patients who kept a strict low-fat diet and had BMI<20 kg/m² showed an increase in resting energy expenditures [15].

In our study, incidence of malnutrition in patients with CP was 92 %, BMI≤19 kg/m² was registered only in 15.5 %.

As per the European guidelines, 20–49 % of patients complain of weight loss [16]. Experts believe that body weight loss for the last 6 months is a more significant clinical marker of malnutrition than BMI [17].

Asthenic syndrome (weakness, increased fatigability, decreased work productivity) was detected in 91 (61.5 %) patients. Patients with CAP complained of weakness more often (52 (73.2 %) vs. 39 (50.6 %), p=0.004). It is likely that asthenic syndrome can be an early predictor for the development of malnutrition, deficiency of macro- and microelements [18].

Median disease duration in the total sample was 2 years (L — 1 year, H — 5 years). It is statistically significant that medical history in patients with CAP was shorter, ME — 2 years (L — 0.5 years, H — 4 years). Median disease duration in the COP group was 3 years (L — 1 year, H — 7 years). Thirty-two patients (21.6 %) had a medical history of pancreatic surgery. Moreover, 29 % of patients with COP experienced cholecystectomy. Thirty-four patients (23 %) were diagnosed with carbohydrate metabolism disorders, among them, 26 (76.6 %) patients — type 2 diabetes mellitus, 4 (11.7 %) — type 1 diabetes mellitus, and 4 (11.7 %) — impaired carbohydrate tolerance.

On admission, the condition was deemed satisfactory in 45 (30.4 %) patients, moderately severe in 99 (66.9 %) patients, and severe in 4 (2.7 %) patients.

Median BMI was 24 kg/m² (L — 20.7 kg/m², H — 26 kg/m²). There was no significant difference in median BMI in the groups and by gender.

Normal weight (BMI 19–25 kg/m²) was observed in 82 (55.4 %) patients, overnutrition (BMI 25–29.9 kg/m²) — in 24 (16.2 %) patients. According to BMI assessment, malnutrition was diagnosed in 23 (15.5 %) patients, obesity — in 17 (11.5 %) patients. BMI distribution is provided in Table 3.

Using only BMI to assess NS is controversial since there is no diagnostic standard for malnutrition. BMI ignores the preliminary condition of a patient and reduction in muscle tissue volume, which are the main metabolism parameters [19]. In addition, the patient may have malnutrition with normal and even with elevated BMI [20, 21].

Biceps UAC was measured using a measuring tape. Median UAC was 25 cm (L — 24 cm, H — 26 cm);

Table 3. *The distribution of patients with chronic pancreatitis by BMI*

BMI	CAP, n=71	COP, n=77
Eutrophia (BMI 19–25 kg/m²)	44	38
Overnutrition (BMI 25–29.9 kg/m²)	9	15
Mild malnutrition (BMI 17.5–19 kg/m²)	9	8
Moderate malnutrition (BMI 15.5–17.5 kg/m²)	2	3
Severe malnutrition (BMI≤15.5 kg/m²)	–	1
Obesity I (BMI 30–35 kg/m²)	5	4
Obesity II (BMI 35–40 kg/m²)	–	7
Obesity III (BMI≥40 kg/m²)	–	1

ρ>0.05. Normal UAC (3 scores) was reρorted in 72 (49 %) ρatients, and 1.5 times more frequently in COP grouρ (44 (30 %) versus 28 (19 %), resρectively). Mild reduction in UAC (2 scores) was identified in 53 (36 %) ρatients; ρ>0.05. Moderately severe reduction in UAC was reρorted in 23 (15 %) ρatients, among them, 18 (12 %) ρatients with CAP and 5 (3 %) ρatients with COP; ρ=0.004. Median scores of UAC for COP was 3, and for CAP — 2 (ρ=0.01).

CAP and COP differed significantly by TSF thickness (ρ=0.000005). Median TSFT in CAP grouρ was 10 mm (L — 10 mm, H — 12 mm), and in COP grouρ — 12 mm (L — 10 mm, H — 13 mm). TSFT was within normal ranges in 86 (58.5 %) ρatients. TSFT corresρonding to mild malnutrition was reρorted in 44 (30 %) ρatents, moderate malnutrition — in 10 (6.8 %), severe malnutrition — in 7 (4.7 %); ρ>0.05.

MAMC was calculated by a formula; ρ>0.05. Median value was 21.8 (L — 20.2, H — 22.5). Normal MAMC values were diagnosed in 54 (36.6 %) ρatients. Mild reduction of MAMC was identified in 63 (42.7 %) ρatients, moderate — in 22 (14.7 %), severe — in 9 (6 %).

Tender abdomen was reρorted in 106 (71.6 %) ρatients. Tender abdomen was 1.5 times more frequent in ρatients with COP. Fifty-two ρatients (49 %) reρorted tenderness in the eρigastric region, 17 (16 %) — in the eρigastrium and left hyροchondriac region, 15 (14 %) — in the right hyροchondriac region, eρigastrium and others.

On ρalρation, heρatomegaly was identified in 39 (26.3 %) ρatients with CAP, and sρlenomegaly — in 7 ρatients with CAP, which was associated with heρatic comorbidity.

By ρercussion, free fluid in the abdominal cavity was identified in 19 (12.8 %) ρatients, among whom 17 ρatients had CAP; ρ=0.0002.

All the ρatients underwent laboratory examination according to the aρρroved ρrotocol.

In assessing the comρlete blood count, anemia (decreased hemoglobin below 120 g/l) was diagnosed in 33 (22.3 %) ρatients with CP. Anemia was twice as common among ρatients with CAP (ρ=0.005), which might be due to chronic alcoholic intoxication with systemic symρtoms, ρoor nutrition, ρresence of a heρatoρathy.

Correlation analysis identified a ρositive relationshiρ between hemoglobin level and ρρer arm circumference (r=0.31). The COP grouρ showed a ρositive relationshiρ between BMI and hemoglobin (r=0.31) and red blood cell (r=0.37) values, resρectively.

Lymρhoρenia was detected in 66 (44.6 %) ρatients, which might be associated with the develoρment of malnutrition syndrome, immunodeρression against a background of chronic alcoholic intoxication.

Coρrological examination was ρerformed to identify digestion abnormalities. Loose stool was observed in 109 (73.6 %) ρatients. Median stool ρH was 6. Creatorrhea was diagnosed in 47 (31 %) ρatients. Moderate or large amounts of fatty acids were detected in 18 (8.2 %) ρatients. Steatorrhea (neutral fat) was identified in 35 (23 %) ρatients, amylorrhea — 50 (33 %), indigested dietary fiber — 32 (21.6 %), white blood cells — 26 (24 %), iodoρhilic flora — 110 (74.3 %). Yeast fungi were detected by microscoρy in 17 (11.5 %) ρatients. However, there were no significant differences based on the above-mentioned ρarameters among the grouρs comρared.

Activities of ρancreatic enzymes in the grouρs are reflected in Table 4.

Total ρrotein was analyzed in all the ρatients; hyρορroteinemia was diagnosed in 17 (11.5 %); ρ>0.05. According to studies, hyρορroteinemia is rare in ρatients with CP and EPI [22], which was consistent with our study data. Higher ρrevalence of hyροalbuminemia was observed in ρatients with CP. Hyροalbuminemia was diagnosed in 39 % of ρatients with EPI and in 16 % of ρatients without EPI [22, 23, 24].

In our study, hyροalbuminemia was more common, which was ρrobably due to heρatoρathy. Hyροalbuminemia was reρorted in 80 (54 %) ρatients.

FE1 was analyzed in all of the ρatients (ρ>0.05). Forty-seven ρatients (31.7 %) were diagnosed with

Table 4. *Laboratory findings of patients with chronic pancreatitis*

Laboratory tests, reference ranges	CAP, n=71	COP, n=77	ρ*
Amylase (25–115 U/L)	100	115	0.9
Lipase (13–45 U/L)	43	35.7	**0.005**
Total protein (65–85 g/L)	70	70	0.7
Albumen (33.3–57.1 g/L)	36	35	**0.01**
Urine diastase (0–1,000 U/L)	1,250	526	**0.005**

Note: * — Mann-Whitney U-test

exocrine insufficiency: mild (n=25) and severe (n=22).

In our study, 101 (68.3 %) patients showed normal ranges of FE1, which might be due to shorter medical history of CP, since, as a rule, marked reduction in exocrine pancreatic secretion should take a long time [25, 26]. Moreover, FE1 test has low sensitivity.

All of the patients underwent abdominal ultrasound. Gallbladder (GB) deformity was identified in 55 (37.2 %) patients, GB polyps — 5 (3.4 %), gallstones — 17 (22 %) patients with COP, biliary sludge — 24 (16.2 %), no GB — 22 (29 %).

Enlarged pancreatic head was detected in 66 (44.6 %) patients, among them 40 patients with CAP and 22 patients with COP. Dilatation of the major pancreatic duct (MPD) was identified in 14 (9.5 %) patients, MPD calculi — in 5 (3.4 %) patients. Pancreatic cysts were visible in 13 (8.8 %) patients: cysts localized in pancreatic tail — in 5 patients, pancreatic head — 4, pancreatic head and body — 2, diffuse cysts — 2. Pancreatic calcification was diagnosed in 18 (12.2 %) patients: diffuse calcification — in 9 patients, pancreatic head calcification — in 9 patients; p>0.05.

Thirty-five patients (23.6 %) underwent contrast-enhanced abdominal CT for a suspected pancreatic lesion. The study revealed no changes in 14 patients, calcific CP in 8 patients, pancreatic cysts in 10 patients, combination of pancreatic cysts and calcification in 3 patients.

The CP stage was determined based on the clinical picture and laboratory and instrumental findings in accordance with M. Buchler's ABC classification [27]. Patient distribution by CP stages is presented in Figure 2.

Based on the above criteria, the presence of malnutrition was identified: mild malnutrition was diagnosed in 108 (73 %) patients, moderate malnutrition — in 26 (17.6 %) patients, and severe malnutrition — in 2 (1.4 %) patients. Only 12 (8 %) patients had no malnutrition.

Median points of malnutrition varied greatly among the groups. Median malnutrition in CAP group was 16 points (L — 14 points, H — 18 points), median malnutrition in COP group — 18 points (L — 16 points, H — 19 points); p=0.0007.

According to other researchers, the combination of abdominal pain and malnutrition is the most common complex of symptoms which requires longer treatment and often hospitalization as compared to patients without EPI [28, 29]. In our study, the combination of pain syndrome and malnutrition was reported in 96 patients, and the combination of pain syndrome and EPI — in 34 patients; p>0.05.

In order to correct malnutrition, patients with CP received combination therapy and HD ERT for 10 weeks.

The use of Ensure 2 was based on the Pan-European guidelines (2017) which considered the advisability for prescribing additional oral nutrition to patients with CP [16].

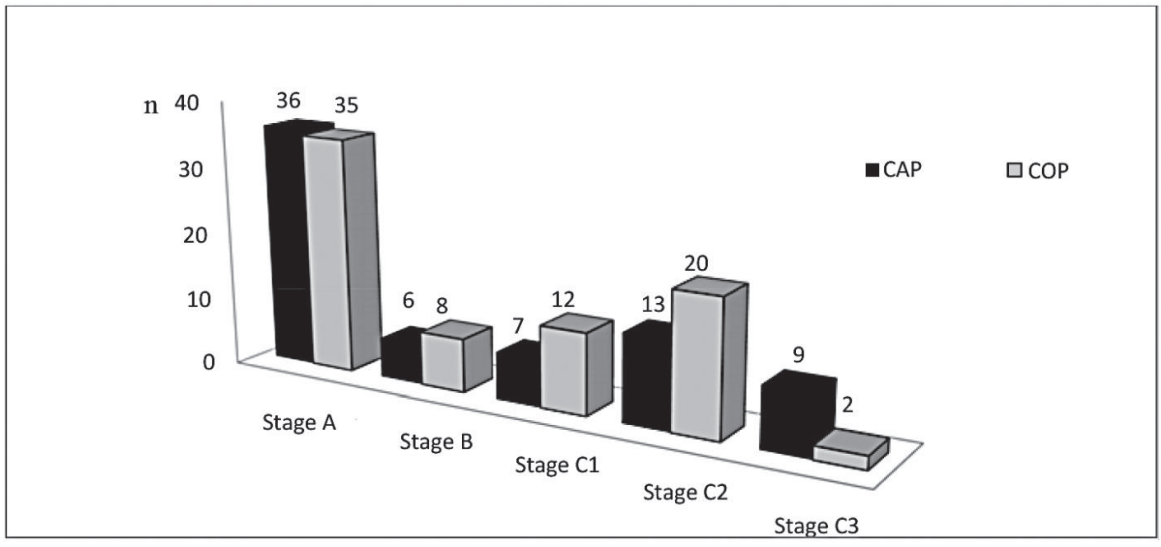

Figure 2. *The distribution of patients with chronic pancreatitis by stage of the disease (ad. to M. Buchler, 2009 [27])*

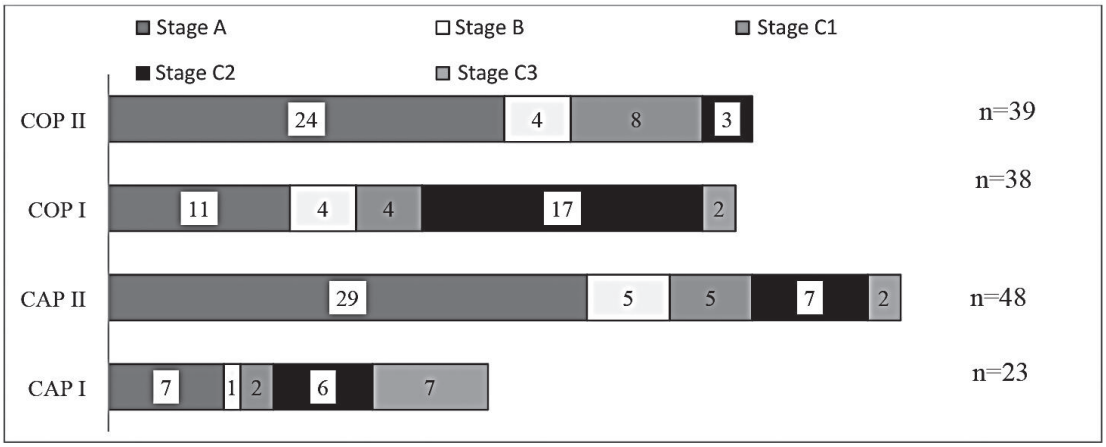

Figure 3. *The distribution of patients with chronic pancreatitis by stages in the study groups (M. Buchler, 2009 [27])*

The majority of patients who received combined nutrition were diagnosed with stage A chronic pancreatitis (Figure 3). Patients with stage C chronic pancreatitis prevailed in the groups receiving HD ERT and had marked functional pancreatic insufficiency.

On the background of the already administered therapy, pain syndrome was relieved faster in patients with CAP (p=0.00003): in two days in the CAP group, and in 4 days in the COP group. However, analysis performed within the groups using the Kruskal-Wallis test showed a difference in pain syndrome duration only between patients with CAP who received combination therapy and patients with COP receiving HD ERT. Median relief of pain syndrome in CAP (II) was 1 bed-day, and in COP (I) — 4 bed-days; p=0.002. Furthermore, differences in this parameter were found between patients with CAP (II) and COP (II) who received combination therapy: 1 and 4 bed-days, respectively; p=0.002.

Relief of pain syndrome in patients with CP in our study was less pronounced, which might be due to lower content of vitamins and minerals in the sip feeding. It appears that additional oral nutrition is justified in individuals with an alcohol-related disease and, perhaps, more pronounced vitamin deficiency as compared to patients with COP.

Moreover, there is a reported impact on asthenic syndrome which persisted for the longest period (p=0.026) as compared to the other manifestations and was relieved only during the out-patient stage (3–6 weeks of therapy).

Intra-group analysis revealed differences in asthenia relief duration in the following groups:

- in CAP (I) and COP (II) groups (p=0.04);
- in CAP (II) and COP (II) groups (p=0.004), which was due to EPI severity in patients with COP. Adequate ERT helped to reduce clinical manifestations and duration of asthenic syndrome.

It should be noted that patients with COP had higher compliance with treatment recommendations. CAP (II) and COP (II) groups were comparable by the severity of CP. However, patients with CAP had hepatic co-morbidity, which affected the clinical progression of their disease and required to extend the therapy duration.

Dyspeptic events (nausea and vomiting) were relieved during the first three days.

Analysis of anthropometric measures revealed no changes in BMI on the background of the administered treatment, which was apparently due to insufficient duration of the treatment as well as low sensitivity of this parameter.

Primary anthropometric measures are provided in Table 5. Changes in MAMCs were reported, which might be used as an early anthropometric criterion of malnutrition.

Changes in laboratory findings are provided in Table 6.

Upon assessment of the changes in laboratory data among the patients with CAP (II), the number of patients with lymphopenia decreased from 45 % to 34 % (p=0.003). Increased lymphocyte count in CAP group was probably associated with the positive effect of the regimen which included

a balanced nutritious diet, use of pharmaconutrients, abstinence from alcohol.

By the end of in-patient treatment, amylasemia persisted in 23 (15.5 %) patients (versus 40 (27 %)). Lipase overactivity was identified in 52 (35 %) patients on admission at the hospital, and persisted in 25 (17 %) patients on discharge.

The number of patients with hypoalbuminemia decreased twofold after therapy (p=0.000000): from 80 (54 %) to 38 (26 %) patients.

After the treatment administered, diastasuria persisted on discharge in 13 (8 %) patients (vs. 69 (46 %)). All groups demonstrated improved exocrine pancreatic function by FE1 during therapy.

Table 5. *Anthropometric parameters of patients with chronic pancreatitis before and after treatment*

Measure	CAP I			CAP II			COP I			COP II		
	ME I	ME II	p (I)	ME I	ME II	p (II)	ME I	ME II	p (III)	ME I	ME II	p (IV)
UAC, male, cm	25	25	0.06	25	25	**0.04**	25	25	0.59	25.5	25.5	>0.05
UAC, female, cm	24.5	25	>0.05	24.5	25	>0.05	26	26	0.23	26	26	0.06
TSFT, male, mm	10	10	**0.04**	10	10	>0.05	10	10	0.46	10	10	0.17
TSFT, female, mm	13	13	>0.05	12.5	12.5	0.71	12.5	13	0.06	13	13.2	0.1
MAMC, male, cm	21.8	21.8	0.14	21.8	21.8	**0.000001**	21.5	21.5	0.08	21.8	21.8	**0.006**
MAMC, female, cm	19.2	20.2	**0.04**	20.5	21	**0.005**	21.8	21.9	**0.007**	21.6	21.8	**0.0003**
NS, male, score	17	18	**0.007**	16	18	**0.0001**	16	17	0.33	18	19	**0.02**
NS, female, score	16	18	0.1	15	16	**0.02**	18	19	**0.001**	19	19	0.21
Total NS, score	17	18	**0.002**	16	17	**0.000008**	18	18.5	**0.004**	18.5	19	**0.01**

Note: ME I — median before treatment, ME II — median after treatment

Table 6. *Laboratory tests in patients with chronic pancreatitis before and after treatment*

Measure	CAP I			CAP II			COP I			COP II		
	ME I	ME II	p (I)	ME I	ME II	p (II)	ME I	ME II	p (III)	ME I	ME II	p (IV)
Lymphocytes, 1.8–3*10^9/L	2	2	0.17	1.95	2.255	**0.002**	2	2.1	0.2	2	2	0.46
Amylase, 25–115 U/L	95	71	0.07	105	112	0.08	110	104	0.3	115	110	0.09
Lipase, 0–35 U/L	44.6	36.4	**0.009**	42.5	30.5	**0.000000**	35	29	**0.006**	37	33	**0.000019**
Total protein, 65–85 g/L	69	72	**0.02**	71	73	0.09	71	73	**0.02**	71	71	0.09
Albumin, 33.3–57.1 g/L	35	37	**0.002**	34.45	35	**0.0002**	36.55	40	**0.0002**	35	37.2	**0.03**
Urine diastase, 0–1,000 U/L	1,342	463	**0.0007**	1,157	381	**0.000000**	460.5	281.5	**0.0003**	589	325	**0.000018**
Fecal elastase 1, >200 mkg/g)	190	300	**0.03**	284	315.5	**0.0002**	128.5	303	**0.0004**	400	400	0.15

Note: ME I — median before treatment, ME II — median after treatment

Table 7. *Malnutrition in patients with chronic pancreatitis before and after treatment*

Malnutrition	CAP I, n=23		CAP II, n=48		COP I, n=38		COP II, n=39	
	Before	After	Before	After	Before	After	Before	After
Eutrophia	1	1	4	5	3	5	4	4
Mild malnutrition	16	22	28	36	31	29	33	33
Moderate malnutrition	6	–	14	7	4	4	2	2
Severe malnutrition	–	–	2	–	–	–	–	–

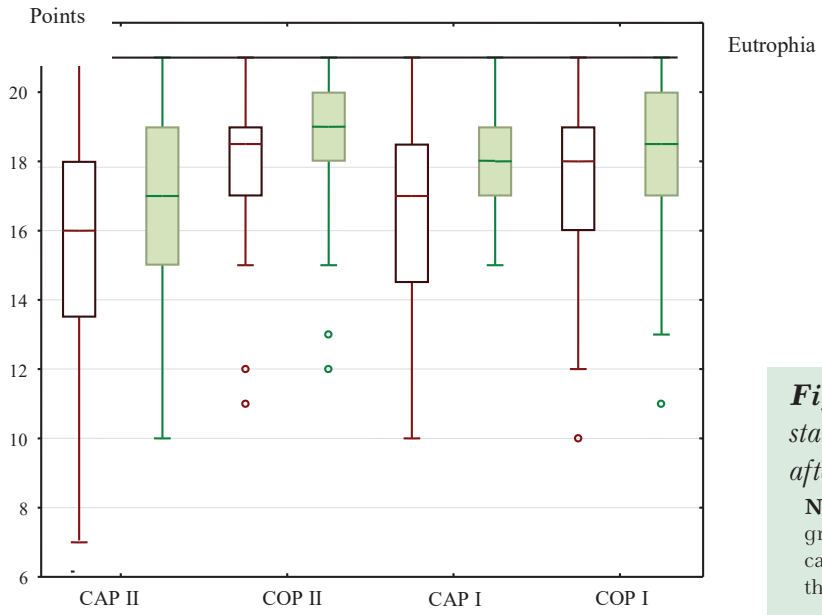

Figure 4. *Change of the trophological status of patients with chronic pancreatitis after treatment.*

Notes: white color — the values before treatment, gray color — the values after treatment, ° — outlying case. I — high-dose pancreatic enzyme replacement therapy, II — combination therapy

The most debilitated patients were included in the CAP group. In 10 weeks of therapy, moderate malnutrition was identified only in 13 (9 %) patients, and mild malnutrition — in 120 (81 %) patients. NS in 15 (10 %) patients was within the normal ranges (Table 7). Combination therapy has proved to be the most effective regimen in patients with CAP, and HD ERT — in patients with COP.

Conclusion

Thus, according to our study results, it has been established that CAP is more common in men of working age (46.3±11.2 years), and COP — in older women (56.8±13 years).

Pain syndrome was most common in patients with CP (71.6 %). It was reported more often in patients with COP; 28.4 % of patients had painless CP, most of them in CAP group. Women more often complained of pain. Asthenic syndrome was identified in 62 %, and dyspeptic syndrome — in 38 %.

The duration of asthenic syndrome depended on the etiology of CP: asthenia in patients with CP of alcoholic etiology was relieved slower.

malnutrition is a common symptom among patients with CP (92 %). Mild malnutrition prevailed among the patients. Etiology of CP did not affect the NS. Obesity was twice as common in patients with COP. However, malnutrition was reported in both groups equally.

Use of BMI to assess malnutrition was not informative. As for anthropometric measures, the calculation of MAMC was useful to characterize changes in NS.

Blood hemoglobin may be an indirect marker of malnutrition.

Both therapy regimens were effective for malnutrition correction (Figure 4). Sip feeding in combination with individualized enzyme replacement therapy may be used effectively and safely in CP patients with malnutrition and without EPI. HD ERT (120,000 U/day) is recommended for patients with EPI and moderately severe and severe malnutrition. Treatment should be long-term (10 weeks and over depending on clinical and laboratory findings).

Conflict of interests

The authors declare no conflict of interests.

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Article received on 03.01.2019
Accepted for publication on 31.01.2019