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RESEARCH OF LIPID EXCHANGE DIFFUSION OF MEDIUM-AGE PATIENTS WITH CHRONIC PANCREATITIS WITH DIABETES MELLITUS

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Abstract

Chronic pancreatitis refers to diseases in which both excretoric and incretoric sections of the pancreas are damaged, which in later stages leads to the development of concomitant diabetes mellitus (DM), which are not sufficiently studied in this pathology. This article presents a study of lipid metabolism in patients with chronic middle-aged pancreatitis with concomitant diabetes. It has been proved that the presence of DM significantly complicated the clinical course of chronic pancreatitis (CP) in the ballistic system M - ANNHEIM, which correlated with changes in the program ($r=0,67$; $p<0,001$), the criteria for ultrasound ($r=0,54$; $p<0,01$), the level of glycosylated hemoglobin ($r=0,66$; $p<0,001$). In patients with CP with concomitant diabetes the severity of the disease was more pronounced than in patients with CP: the average severity (C) predominated in 69,56% of patients in group 2, with 26,32% of the 1st, and cases of severe and severe severity. A direct reliable correlation between all the atherogenic indicators of the lipidogram and the age of the patients and the duration of the

course of the CP were found, which makes it possible to assume the age and duration of the CP by factors of the deepening of the dyslipidemia. In patients with CP in combination with DM and dyslipidemia, the lower index of fecal α-elastase level was established in comparison with the CP group: (157,15 ± 7,36) versus (112,86 ± 2,98), respectively ($p<0,001$) which proved a deepening of dyslipidemia in the development of excretory insufficiency of the pancreas.

Key words: chronic pancreatitis, diabetes mellitus, middle age, dyslipidemia, fecal α-elastase.

Introduction. The study of etiopathogenetic factors and clinical features of the combination of chronic pancreatitis (CP) and diabetes mellitus (DM) is an urgent problem due to its high prevalence, the formation of numerous metabolic changes that are progressing and severely subjected to correction. In accordance with the adapted clinical guidelines for CP since 2014, the incidence of CP in European countries is 4-8 cases, and the prevalence is 25 cases per 100 thousand population. In Ukraine, the epidemiological indicators of the incidence of CP in 3-4 times worse than in Europe, and the prevalence continues to increase. According to researches, in Ukraine, the level of morbidity of the pathology of the pancreas (MS) in 2012 amounted to 226 cases per 100 thousand population, prevalence - 2471 per 100 thousand population. Such a difference in the number of patients with CP in Ukraine and in other countries may be due to hyperdiagnosis in the diagnosis of CP, with a higher level of alcohol abuse, which is one of the main causes of the development of this pathology of software, as well as with unbalanced nutrition.

In the case of CP both excretoric and incretoric secretion units of pancreas are damaged, which at later stages leads to the development of concomitant diabetes, the course of which in this pathology has not been studied sufficiently. It occurs in 10-90% of patients with CP [5, 8]. Such a large difference in literature data on the frequency of diabetes at CP is associated with a different probability of development of endocrine disorders in various forms of pancreatitis [2, 4, 7]. It should also be taken into account that the development of endocrine disorders can contribute not only to absolute insulin deficiency, which is due to destruction and sclerosis of the incretory apparatus, but also constitutional tissue insulin resistance (IR), which occurs in the population in 10-12% of cases (this is higher in people with obesity). Interesting is the relationship of dyslipidemia, obesity and CP in the aspect that the violation of lipid metabolism and primary obesity complicates the course of CP and subsequent prognosis of this disease [1, 8]. According to the data of literary sources, at dyslipidemias

there are pathological changes in the functioning of all organs, including the software. Allocate even a dislipidemic variant of CP, which is most often combined with pancreas. In some scientific sources, there is evidence that CP with changes in lipid metabolism can be traced the most frequent combination with diabetes. Therefore, it was considered relevant to clarify the existence of interrelationships of dyslipidic changes in patients with a comorbid flow of CP with diabetes with a violation of endocrine and exocrine function of the software [3, 8, 10]. Until now, unclear factors of deepening of dyslipidemia in CP with combination with DM are still unknown, as well as the dependence of lipidogram parameters on severity of violations of excretory and inoculum function of pancreas.

The aim of the study is to evaluate the parameters of the lipidogram in patients with CP in conjunction with diabetes, identifying the factors for deepening dyslipidemia in such patients.

Materials and methods. We examined the indexes of 112 patients with a diagnosis of CP, of which -35 with CP and 77 - with a combination of CP and DM. The average age of patients was (49,9 ± 2,0) years, with such patients with CP - (45,3 ± 3,4) years, and patients with CP and DM - (53,6 ± 2,2) years Diagnosis CP and DM were verified according to generally accepted criteria in the clinic [6]. The severity of the course of CP was evaluated using the M-ANNHEIM system, taking into account the clinical stage, index and severity. In this case, the presence of excretory and inocular pancreatic insufficiency, structural changes in the software according to the ultrasound, coprogram, level of glycosylated hemoglobin in the blood, the number of complications was analyzed.

Non-invasive pancreatic test, which is considered as a "gold standard" - determination of the level of fecal α-elastase, proteolytic enzyme of the software [7, 9, 10], by the method of immunoassay analysis using the standard sets of the company Bioserv, was used to estimate the depth of the external-secretion insufficiency of the software Elastase 1-Elisa [1, 10]. The assessment of the parameters was carried out according to generally accepted international standards: expressed in terms of external secretion - <100 μg/g; external secretion of medium-grade - 100-150 μg/g; light weight - 150-200 μg/g; the normal function of pancreas without the phenomena of external secretion-> 200 μg/g [2, 3, 9]. The evaluation of blood α-amylase and α-amylase (diastase) parameters in the urine were also evaluated, which were determined according to generally accepted methods in the clinic. The norm was considered: the level of α-amylase in the blood (by Karavey method) - 12.0-32.0 mg / (hour x ml) and α-amylase (diastase) in the urine - 20.0-160.0 mg/(hr ml). To assess the endocrine insufficiency of

pancreas in the case of diabetes, glucose levels in the blood were determined by the glucose oxidase method, assuming a norm of 3.5-5.5 mmol/l

The parameters of serum lipidograms in the examined patients were determined using Lachema sets on the analyzer using the following methods: triglycerides (TG) - by reaction with methyl acetone and ammonium ions after ointment with potassium hydroxide, total cholesterol (TC) - by reaction of cholesterol esters after oxidation to hydrogen peroxide with phenol and 4-amino-antipyrine. The calculation of Low density lipoproteins was carried out using the Freudwald formula:

Cholesterol Low Density Lipoproteins = Total Cholesterol - cholesterol high density lipoprotein - (0.2 x). Lipoproteins of very low density = triglycerides / 2,2.
Atherogenicity = (total cholesterol – lipoproteins high density) / high density lipoprotein).

Infringement of lipid status was evaluated according to the level of total cholesterol, triglycerides, lipoproteins of low density, lipoproteins of very low density, lipoproteins of high density in accordance with the criteria of the third report of the experts of the National Program on Cholesterol (2001), phenotyped according to the classification of hyperlipidemia D.S. Fredrickson with modern additions [5, 7].

The evaluation of the coprogram was carried out with an increase in the amount of muscle fibers, vegetable fiber digestible, fatty acids, neutral fat, leukocytes, the appearance of mucus, eggs of worms. Each pathological symptom was evaluated as 1 point. The reliability of the differences in mean values was estimated by the Mann-Whitney U-criterion ($p < 0.05$).

Results and discussion. Patients were divided into 2 groups: patients with CP (35 patients) and CP with concomitant diabetes (77 patients). According to the M-ANNHEIM classification, all patients belonged to the diagnostic category of "defined" CP. Of the 112 patients studied, 38,10% of patients had II B, 7,14% of patients - II C, 45,24% of patients - III A and 9,52% of patients - III B clinical stage.

In the majority of patients with CP with concomitant DM - 52.17% - there was a proven out-of-secretory insufficiency, which corresponded to 2 points, in 47.83% - the presence of moderate out-of-secretory insufficiency (1 point). In patients with CP, 84.21% had a proven - (2 points) and 15.79% - light (1 point) out-of-secretory insufficiency. Patients without a lack of functions of pancreas in the study was not.

Endocrine insufficiency was evaluated for the absence or presence of diabetes and detected in 100% of CP with concomitant DM.

According to the data of the ultrasound, in 73.68% of the CP showed changes in the structure of pancreas, which corresponded to light severity (2 points for M-ANNHEIM), in

21.06% of patients - moderate (3 points). Significant changes in the structure of pancreas for ultrasound were noted in 5,26% of patients, which corresponded to a severe degree (4 points). Patients with CP with concomitant DM changes in ultrasound examination were expressed to a greater extent. In particular, in 43,48% of patients, changes in the structure of pancreas corresponded to a mild severity (2 points), in 56,52% of patients - moderate (3 points). Patients with CP and CP on the background of diabetes complications were found in 3 in 4 patients, respectively. 73.68% of patients with moderate (B) and 26.32% with average (C) severity were identified by M-ANNHEIM classification. However, among patients with CP and DM, 8.70% of patients with moderate (B), 69.56% with average (C), 13.04% with severe (D) and 8.70% with severe (E) degree of gravity.

In the analysis of indicators of lipidograms in patients with CP + CD, it was concluded that they had IIa, IIb and IV type of hyperlipoproteinemia according to the classification of D.S. Fredrickson-8 (9.8%), 31 (38.2%), 33 (40.7%), respectively, 9 (11.1%) were other types of hyperlipoproteinemia. It was found that hypertriglyceridemia was combined with other pathological changes in the lipidogram, which were more pronounced in the CP + DM group (Table 1).

Tab. 1 Analysis of parameters of lipidograms in CP and CP with DM

Indicator of lipidogram	Comparison group		
	Group of control (n=20)	CP (n=35)	CP+DM (n=77)
triglycerides, mmol/l	0,95±0,09	1,19±0,05 p<0,05*	2,72±0,07 p<0,001* p<0,001**
total cholesterol, mmol/l	4,72±0,11	5,15±0,24 p>0,05*	6,97±0,17 p<0,001* p<0,001**
Low density lipoproteins, mmol/l	2,92±0,12	3,66±0,29 p<0,05*	5,35±0,15 p<0,001* p<0,001**
Very low density lipoprotein, mmol/l	0,12± 0,03	0,54±0,02 p<0,001*	1,22±0,03 p<0,001* p<0,001**
high density lipoprotein, mmol/l	1,28±0,10	0,96±0,05 p<0,05*	0,81±0,02 p<0,001* p<0,05**
Atherogenicity coefficiento	2,20±0,10	3,6±0,21 p<0,05*	7,2±0,34 p<0,01* p<0,05**

Notes: 1. * the likelihood of a difference in the indicators for those in the control group; 2. ** Likelihood of difference between the indicators for those in the CP group.

The analysis of lipidogram parameters proved the presence of dyslipidemia in all patients with CP, but in the group with concomitant diabetes, patients with deeper violations of lipid homeostasis (significantly higher levels of total cholesterol, triglycerides, lipoproteins of low density, lipoproteins of very low density, lipoproteins of high density compared with the control group and the CP group) were detected. HDL as an antiatherogenic blood factor was within the normal range in the CP group, while in the CP + DM group, this indicator was significantly lower in relation to such control and CP groups.

It was found that in the CP + DM group, the level of total cholesterol was 1.82 mmol/l (35.3%) higher compared to that in the CP group ($p<0.001$). The same tendency was observed when comparing other atherogenic lipid fractions of blood of both groups. In particular, the triglyceride level in the CP + CD group was significantly higher in the CP group by 1.53 mmol / L, more than twice ($p <0.001$). The LDL-value in patients with dyslipidemia was 1.69 mmol / l (46.1%) higher than that in the group of patients without diabetes ($p <0.001$), the atherogenicity rate was twice that in this group of patients compared with the group of patients with CP ($p <0, 05$). The level of high density lipoprotein was significantly lower in the CP + DM group by 15.6% compared with the CP group ($p<0.05$).

Analyzing the data of the coprogram, the ultrasound and the level of glycosylated hemoglobin, the following changes were detected (Table 2). In patients with CP with concomitant DM changes in the program were significantly more significant than in patients without diabetes (5,45 ± 0,18) against (4,73 ± 0,14) points.

Tab 2. Dynamics of changes of the coprogram, data of ultrasound and blood glucose level in patients with CP and CP with DM

Laboratory and instrumental index	Group of patients with CP	
	CP (n = 35)	CP+DM (n = 77)
Coprogram, points	4,73±0,14	5,45±0,18*
ultrasound diagnostics	4,05±0,30	5,21±0,23*
Glycosylated hemoglobin,%	5,15±0,19	7,13±0,36*

Note: * - the reliability of the difference in the parameters in the CP + DM group for those in the CP group ($p <0,05$).

A similar trend was observed with respect to changes in the criteria for ultrasound scores in balls - (5.21 ± 0.23) vs. (4,05 ± 0,30) points. The level of glycosylated hemoglobin in patients with diabetes (7,13 ± 0,36) significantly exceeded that in patients with chronic obstructive pulmonary disease (5,15 ± 0,19) mmol/l.

Correlation and regression analysis revealed direct correlation between the severity of CP for M-ANNHEIM and changes in the coprogram ($r = 0.67$; $p<0.001$), ultrasound criteria ($r = 0.54$; $p<0.01$), the level of glycosylated hemoglobin ($r = 0.66$; $p <0.001$).

Table 3 shows data that establishes a link between the individual criteria of the CP and the parameters of the lipidogram.

Tab. 3 Analysis of indicators of excretory and inacrurate function of the pancreas and structural changes in the software for patients with chronic obstructive pulmonary disease

Indicator of pancreas function	Comparison Group		
	Group of control (n = 20)	CP (n = 35)	CP+DM (n = 77)
α-elastase, μg/g	218,7±8,74	157,15±7,36 p<0,001*	112,86±2,98 p<0,001* p<0,001**
Amylase of blood, mg/(hour × ml)	19,73±2,13	22,84±1,90 p>0,05*	18,24±2,14 p>0,05* p>0,05**
Urine amylase, mg / (h × ml)	91,46±3,28	67,16±2,14 p<0,001*	33,15±1,36 p<0,001* p<0,05**
Blood glucose level, mmol/l	4,28±0,16	6,79±0,48 p<0,001*	7,95±0,25 p<0,001* p<0,05**
Ultrasound diagnostics	–	3,41±0,20	3,02±0,10 p>0,05

Notes: 1. * the likelihood of a difference in the indicators for those in the control group.

2. ** Likelihood of difference between the indicators for those in the CP group.

It was proved that against the background of more pronounced pathological changes in the lipid status, deeper violations of external secretion of the pancreas in patients with CP are noted. This is evidenced by the level of α-elastase in the CP + DM group, which is significantly lower than that in the CP group and control group. The index of fecal α-elastase in the CP + DM group corresponded to the average severity of external secretion of the pancreas, while in the CP group, the milder severity of external secretion of the pancreas. In

16 (19.7%) patients with a dyslipidemia group, an isolated external secretion of pancreatic insufficiency. In the CP group, this figure is 55.5% (15 patients). The following percentage distribution of patients according to the degree of severity of external-secretory pancreatic insufficiency on the level of α-elastase is noted: in 21% (26.0%) patients in the CP + DM group, 11.9% were in the CP group, the average degree was 45 (55.5%) versus 11 (40.7%), light - in 15 (18.5%) versus 13 (48.2%) respectively.

It was also analyzed the existence of correlation between the lipidogram values and the main characteristics of CP in combination with DM, which are shown in (Table 4). Age of patient and duration of CP, according to the data, were in reliable direct moderate correlation bonds with practically all parameters of the lipidogram, with the exception of high density lipoprotein, where the inverse correlation connection was traced. It has been shown that the age and duration of CP leads to an increase in lipid metabolism disorders. The level of α-elastase was found to be in moderate or strong inverse correlation relationships with lipid profiles (cholesterol, triglycerides, very low density lipoprotein, high density lipoprotein), and a significant strong correlation correlation with HDL level was observed. Thus, the increase in external secretion of the pancreas (by the level of a-elastase) led to a deepening of lipid imbalance, and the level of dyslipidemia can serve as a predictor of the onset and progression of CP.

Tab. 4 Matrix of correlation relations between indicators of lipidograms of patients with CP with diabetes and the main characteristics of the disease (n = 77)

The couple in a regression relation	Age of a patient, years	Duration of CP, years	Level of α-elastase, μg/g	Ultrasound diagnostics
Total cholesterol, mmol/l	0,548 p<0,05	0,482 p<0,05	-0,416 p<0,05	0,306 p<0,05
triglycerides, mmol/l	0,615 p<0,001	0,639 p<0,001	-0,528 p<0,05	0,581 p<0,05
Low density lipoproteins, mmol/l	0,693 p<0,001	0,427 p<0,001	-0,410 p<0,001	0,457 p<0,05
very low density lipoprotein mmol/l	0,599 p<0,05	0,348 p<0,05	-0,528 p<0,05	0,530 p<0,05
high density lipoprotein mmol/l	-0,603 p<0,001	-0,526 p<0,001	0,633 p<0,05	-0,324 p<0,05

Notes: 1. n - the number of pairs in the correlation analysis.

2. p - degree of reliability of correlation dependence.

It was also proved that the parameters of lipidogram and ultrasound in points in patients with CP with diabetes mellitus are interdependent. Thus, the deepening of structural changes in the software contributed to the deepening of atherosclerotic changes in patients with CP in combination with diabetes.

Conclusions: 1. The presence of diabetes significantly compromised the clinical course of CP in the ball system M-ANNHEIM, which correlated with changes in coprogram ($r = 0.67$; $p < 0.001$), ultrasound criteria ($r = 0.54$; $p < 0.01$), the level of glycosylated hemoglobin ($r = 0.66$; $p < 0.001$).

2. In patients with CP with concomitant diabetes, the severity of the disease was more pronounced than in patients with non-urgent insufficiency: the average severity (C) was prevalent in 69.56% of patients in the second group, compared with 26.32% of the 1st, with There were cases of severe and severe severity.

3. A direct reliable correlation between all the atherogenic indicators of the lipidogram and the age of the patients and the duration of the course of the CP was found, which suggests that the age and duration of HP are factors of deepening of dyslipidemia.

4. Patients with CP in combination with DM with dyslipidemia have established a significantly lower level of fecal α-elastase compared with the CP group: 157.15 ± 7.36 versus 112.86 ± 2.98 respectively ($p < 0.001$), which has brought deepening of dyslipidemia with the progression of external secretion of the pancreas.

In the future of further research, we plan to analyze the trophological status of patients with a combination of CP and DM and the association of its parameters with the quality of life of such patients.

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