

THE QUESTIONS OF A CHRONIC PANCREATITIS PATHOGENESIS AND ITS COMPLICATIONS

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Abstract. Biochemical studies were performed in 47 patients with pancreatic pseudocysts, aged $4.,58 \pm 7.38$ years, male / female ratio of 8.4: 1. All patients were operated on. Studies have shown that the level of IL-18 was higher in patients with type I pseudocysts 1.9 times with type II - 1.2 times and type III - 1.3 times compared with the control. Such a tendency was noted for IL-6 and IL-8 against increase of IL-10 in a 27.4-fold, respectively (I pancreatic pseudocysts type), 28.1 times (II pancreatic pseudocysts type) and 21.4 fold with III type of pancreatic pseudocysts. The content of IL-18 and glutathione peroxidase in blood in different types of pancreatic pseudocysts directly correlates with the severity of pancreatitis. We found a close correlation between the level of IL-18 and glutathione content in blood at an unfavorable prognosis of postoperative period.

All patients had development of endothelial dysfunction and endothelial damage, as svidetstvovalo a significant increase in plasma VEGF respectively 176.4% (I type pseudocysts), 129.2% (II type pseudocysts) and 54.2% (III type pseudocysts) relative to the control. These data suggest that this creates favorable conditions for the remodeling of the pancreas when the defect replaced cloth with lower levels of the organization, such as scar and repeated cell injury leads to greater activation of PSCs and increased production of extracellular matrix components.

Keywords: *pancreatic pseudocyst, matrix metaloproteinaze pathogenesis.*

The chronic pancreatitis (CP) concerns to group of chronic diseases of a pancreas (P), mainly inflammatory causes, with phase-progressing focal, segmentary or diffuse degenerate and its destructive changes of exocrine part, an atrophy of glandular elements (pancreocytes) and replacement by their fibrous tissue; changes in ducts system of P; cysts and calculus formation; different degree disorder of exocrine and endocrine functions. CP is polyetiologic disease of P which develops owing to attacks of acute pancreatitis (AP) or traumas of P. As for literatures testify, prevalence CP nearly 30 cases on 100 000 persons [1]. Priority directions of modern researches in pancreatology understand the mechanism of loss functioning of P tissue

and replacement by its connective tissue. The development of fibrous changes of P, as consequence of the dynamic cascade of cytokine, chemokine, factors of growth and many other factors, balance infringements between processes of synthesis and disintegration proteins of extra cellular matrix (ECM) with its accumulation and degradation [2]. Pancreafibrosis now it is considered as the leading pathological mechanism of development CP and its complications, and main role in this process perform pancreatic stellate cells (PSCs) [3, 4].

The hypothesis formulated by us became a basis for research carrying out that in hypoxia and ischemia conditions of P after its damage, angiogenic factors support endotheliocytes activation and proliferation, which comes to the end with processes neovascularization, and insufficient degradation of extracellular matrix is the cause of progressive fibrosis and remodeling P with development of complications. Thus we considered that remodeling of P is heterogeneous process which leads to changes in a connecting fabric and infringement of structure and function of P.

The work purpose – to define profibrogenic mediators, markers of endothelial dysfunction and hemostasis at patients with different types complications of pancreas pseudocysts.

Materials and research methods. The investigation is approved by Ethical committee. The participants have been completely informed. Researches was done at 47 patients in age average ($43,58 \pm 7,38$) years, a parity of the man / women 4:1.

Criteria of inclusion: pseudocysts of P on classification A. D'Egidio and M Schein: to I type are carried postnecrotic pseudocysts of P, which were formed after episode of acute pancreatitis or traumas of P; to II type – postnecrotic pseudocysts of P, which were formed owing to attacks of AP at patients with CP; to III type – retention cysts which arose after CP as a result of pancreas channels stricture [4].

Criteria of cutting off: in our research did not include patients with a liver pathology (hepatitis, cirrhosis, cancer) and cancer of P, the secondary arterial hypertension, accompanying endocrine, autoimmune, oncology pathology, with the expressed infringements of a warm rhythm and conductivity, with acute heart attack,

acute heart insufficiency, cardiomyopathy, accompanying mental diseases, narcotism, alcoholism.

All patients have been divided into three groups: the first – patients with I type pseudocysts of P, complicated by suppuration (12) and acute bleeding in a cavity of cyst (2); the second – patients with II type pseudocysts of P (12 – suppuration, 3 – bleeding in a cavity of cyst, 1 – rupture of cyst with a bleeding in abdomen cavity); the third – III type pseudocysts of P (17 patients the fibrous-degenerate pancreatitis complicated by development by secondary portal hypertension, mechanical jaundice, etc. Groups of patients were comparable ($\chi^2=1,234$, $p>0,05$).

Clinical investigation included estimation of complaints, gathering of the anamnesis of the basic disease and accompanying pathology, an estimation of anthropometrical indicators (height, weight, an index of weight of a body), electrocardiogram, definition of the basic clinical and biochemical parameters of the blood and urine, ultrasonic, CT, MRT, radiographic examination of stomach and intestine. Was done an estimation of inflammation factors, hypoxia and conditions of fabric reconstruction of P. Defined VEGF, MMP-9, its inhibitor TIMP-2 and a complex with inhibitor (MMP-9/TIMP-2 in serum blood with use immune-enzyme method: IL-6, MMP-9, TIMP-2 research by commercial diagnostic sets of firms R&D Diagnostics Inc. (USA): Human MMP-9 Quantikine ELISA Kit, category DMP900; Human TIMP-2 Quantikine ELISA Kit, category DTM200 <<http://www.rndsystems.com/Products/DTM200>>); Human IL-6 Quantikine ELISA Kit category D6050; Human TGF-beta 1 Quantikine ELISA Kit category DB100B. Definition of plasmatic level IL-8, IL-18 and IL-10 was carry out by immune-enzyme method and test systems manufacture «Bender Medsystems» (Austria). Glutathione peroxidase (GPO) blood activity investigated on spectrophotometer. A method principle: GPO (1.11.1.9) catalyzes oxidation reaction of restored glutathione in presence of a cymene substrate which is an oxidizer. Activity of enzyme defines on decrease of substratum G-SH in color reaction on hydrosulfide groups with Elman

reactant [5]. Malonic dialdehyde (MDA) in blood serum defined by spectrophotometric method on L.I. Andreevoj and co-authors (1988).

Statistical processing of results was carry out by software package "Biostatistics" (Russia). The correlation analysis applied to an estimation of communication of two quantitative values and was carrying out by Spearmen method and the one-factorial dispersive analysis.

Results and their discussion. Clinical displays and the laboratory characteristic are resulted in tab. 1. At 22 (46,8 %) patients hyperthermia was observed, at 16 (34 %) – jaundice, at 9 (19,1 %) – disturbance of duodenal patency, at 8 (17 %) – disturbance P and at 4 (8,5 %) – wirsungolithiasis, at 14 (29,8 %) – regional portal block. Complications are noted at all patients: pseudocyst of P suppuration at 100 % of the first group, obstruction jaundice at 23,5 % of the second and 57,1 % of the third group; disturbance of duodenal patency 7,1 % of patients of the second and 26,7 % – the third group; calcification of P at 24 % patients of the third group; wirsungolithiasis at 14,3 % patients of the third group; regional portal block at 14,3 % patients of the second and 21,4 % – the third group; compression of adjacent organs – at 42,9 % patients of the second group; association of different complications – at 28,6 % patients of the second and third group.

The basic concept of optimum complex of patients treatment which we use since 90th years old of last century, the maximum preservation of functional P reserve, which is based on use of four basic directions at all stages is: 1) the control of abdomen pain; 2) the treatment of maldigestion syndrome; 3) "management" of complications; 4) as it is possible preservation of organs parenchyma at surgical interventions on P. All patients have been operated. At I type pseudocyst of P have been used puncture drainage interventions under ultrasonic control (10 patients) and open operative interventions with external drainage of pseudocyst cavities and biological tamponade by omentum with external drainages, (4 patients). At II type pseudocysts of P have been executed – drainages interventions under control by ultrasonic (14), and at 2 patients – operative interventions with tamponade cyst cavities in as a result of bleeding in a cavity. Patients III type pseudocyst of P after

preliminary punctures under ultrasonic control was done resection of ventral parts of head of P by Frey (11 patients), a subtotal resection of head of P by Bern modification (3 patients) and cystodigestiv drainage (3 patients). From 47 analyzed patients has died 1 from arrosion bleeding.

Table 1.

**The clinical- laboratory characteristic of patients with pseudocyst of P
(Me (Q1-Q3))**

| Indicator / control | Groups of patients | | |
|---|--------------------------|----------------------------|--------------------------|
| | The first (n=14) | The second (n=16) | The third (n=17) |
| Age | 43,6 (26-55) | 45,4 (34-59) | 44,2 (32-57) |
| M/F | 12/2 | 12/4 | 14/3 |
| Body masses index, kg/m ² | 24 (21-28) | 23 (21-26) | 21 (20-26) |
| Blood leukocytes, × 10 ⁹ /l, 6,23 (5,2-8,5) | 14,8 (12,1-18,7)* | 9,7 (5,5-11,9)* ** | 8,2 (5,9-10,8)* |
| Blood amylase, gr/h×l, 17,3 (14,5-24,7) | 64,6 (60,2-73,8)* | 48,7 (24,7-62,1)* ** | 24,8 (21,1-28,9)* *** |
| General protein, g/l, 75,6 (65,9-81,3) | 63,1 (60,2-67,8)* | 64,5 (63,3-69,4)* | 65,2 (60,7-73,2)* |
| General bilirubin, mkmol/l 10,44 (9,1-16,2) | 22,4 (14,8-34,2)* | 27,2 (17,1-42,2)* ** | 44,8 (40,6-64,5)* *** |
| Alaninaminotransferase, ME×l, 27,8 (12,4-37,8) | 82,4 (36,7-94,8)* | 45,2 (40,2-57,3)* ** | 44,8 (39,9-52,7)* *** |
| Aspartataminotransferase ME×l, 29,44(14,2-35,6) | 95,4 (87,8-102,1)* | 97,2 (91,2-112,3)* | 96,5 (92,4-105,6)* |
| Blood glucose, mmol/l 5,13 (4,1- 5,9) | 7,2 (5,6-12,4)* | 9,2 8,7-14,3)* | 7,4 (7,1-12,3)* |
| Blood creatinin, mkmol/l 71,7 (64,2-98,4) | 85,5 (78,1-115,3)* | 89,5 (81,3-93,8)* | 77,9 (62,6-89,7)* *** |
| IL-18, pg/ml 235,7 (213,4-267,8) | 438,4 (363,01-488,7)* | 292,06 (256,45-305,2)* | 299,7 (247,6-324,7)* |
| IL-10, pg/ml 3,2 (0-8,6) | 87,59 (64,97-111,7)* | 89,76 (55,61-98,9)* | 68,36 (33,37-85,2)* |
| IL-18/ IL-10 3,7 (0-31,1) | 5 (5,6-4,4) | 3,3 (4,6-3,1) | 4,4 (7,4-3,8) |
| IL-6, pg/ml 34,5 (2,1-45,3) | 347,7 (214,5-424,2)* | 238,4 (193,5-367,3)* ** | 214,6 (145,7-254,3)* |
| IL-8, pg/ml 15,6 (3,8-22,1) | 198,6 (178,2-212,4)* | 99,02 (86,3-123,5)* ** | 87,8 (66,5-102,5)* |
| MDA, mkmol/l 2,11 (2,04-2,24) | 5,04 (4,77-5,34)* | 4,05 (3,45-5,1)* ** | 2,87 (2,45-3,11)* ** |
| GPO, mkkat/g x Hb, 6,12 (5,89-6,22) | 9,7 (8,91-12,1) | 11,25 (8,67-13,6) | 13,75 (12,1-16,8) |

The note: * – it is authentic with control; ** – it is authentic between 1 and 2 groups; *** – it is authentic between 2 and 3 groups (p <0,05).

Substantial increases of enzymes activity of LFT were observed at patients with different types of pseudocysts of P. As testify cited given (tab. 1), level of IL-18 was above in the first group of patients in 1,9 times, in the second – in 1,2 times and in the third – in 1,3 times in comparison with control ($p < 0,05$). The tendency is noted for IL-6 and IL-8 against increase IL-10 accordingly in 27,4 times (I type pseudocyst of P), in 28,1 times (II type pseudocyst of P) and in 21,4 times at III type pseudocyst of P. The possible increase in level IL-10 is attempted to reduce production pro-inflammatory cytokines which continues to last.

At the same time, level anti-inflammatory cytokines at patients III type pseudocyst of P on the average on 22 % was more low, than at patients with I type pseudocyst and on 26,1 % – than at patients with II type. IL-18, also known as the factor inducing IFN - γ (IGIF). It has initially been characterized as potential inductor synthesis IFN - γ T - and NK- cells.

IL-10, derivative Tx2, it can be considered as the antagonist of some the cytokines. So, IL-10 suppresses production IFN γ Th1. Besides, it brakes proliferative answer of T- cells to antigens and mitogens, and also suppresses secretion activated monocytes IL-1 β , IL-6 and TNF. At the same time IL-10 stimulates secretion Ig B- cells. IL-10 also can stimulate synthesis Ig E that conducts to development of hypersensitivity of immediate type. In the influence on cellular immunity IL-10 has synergistic action with IL-4. At various pathological conditions increase of level IL-10, this increasing is bad prognostic sign. IL-10, powerful transforming growing factor (TGF) β , regulate a regeneration phase, reduces fibrosis and atrophy.

Detailed studying of cytokines effect can be base for working out of medicines for treatment of acute and chronic pancreatitis [6]. So, by us it has been established that maintenance IL-18 and glutamic phase (GF) in blood serum, at various types pseudocysts of P, directly correlates with condition patients, and simultaneous decrease GF and increase IL-18 in comparison with indicators which were registered the day before, on 30 % and is more connected with the bad prognosis ($r = - 0,87$, p

$<0,01$). In our opinion, it testifies to deep depression of antioxidant protection, an exhaustion of its reserves as result of lipid peroxidation activation and oxidant stress. Modern researches have proved, that the pancreatitis is initiated as an inflammation condition, destruction of acinar and ducts cells, intra – and perilobular fibrosis and sclerosis parenchyma of P. According to experts, necrosis, apoptosis and fibrosis are dynamic processes and accompanied by polypeptide control which concerns TGF- β 1, one of which functions is balance regulation between the negative and positive processes occurring in P tissue [7]. At experimental researches it has been established that hyper production TGF- β 1 promotes induction at animals as pancreatitis, and an accompanying TGF- α -diabetes [8]. TGF- β 1 activates pancreatic stellate cells and strengthens them synthesis of extracellular matrix (ECM), including collagen I and III types. This cytokine inhibit degradation of (ECM) at the cost of specific metalloenzyme activity decrease [9]. TGF- β 1, which is key profibrosis cytokine, has been significantly raised at patients of all groups. Pseudocysts of P accordingly on 1807,5 %, 521,9 % and on 412,2 % in comparison with control group that, obviously, testifies to one of roles conducting it in development intra – and perilobular fibrosis irrespective of the trigger mechanism of pancreatitis development and its complications. However the maximum increase TGF- β 1 nevertheless was observed in group of patients with acute pseudocysts of P, were formed after 4-6 weeks from beginning of AP.

It is established that definition circulating TGF- β 1 can display various stages of a current of a pancreatitis and expressiveness of complications which develop in various terms from the disease moment. The obtained data will be coordinated with opinion of authors [5, 6, 9, 10, 11], which have proved that the transforming factor of growth β 1 (TGF- β 1) – is predictor which influences the processes of proliferation fibroblasts initiation, synthesis of components ECM, cooperation cells of an inflammation (first of all macrophages). In experimental works on animals the high expression of TGF- β 1 in acute phase of an inflammation and in a late stage of fibrosis is defined, and influence on immune system effects TGF- β 1, with inhibit functions prevailed. TGF- β 1 stimulates structure PZH change, it remodeling, has

important role in development fibrosis and potentiating apoptosis cells of P. This morphological reorganization can be a basis of pancreatitis pathogenesis.

It is known, that IL-6 is one of the most active cytokines, participating in inflammatory reaction. In researches which we have spent, level IL-6 has appeared considerably raised in all groups of patients with pseudocysts of P in comparison with control. In case of TGF- β 1 level research in blood, increase IL-6 was maximum at patients with I type pseudocysts of P, that will be coordinated with researches which discuss the status of cytokine as an ischemia biomarker [12, 13]. At all types pseudocysts of P the level of gelatinize B increased in relation to control group (fig. 1). At patients with I type pseudocysts of P the level of MMP-9 was raised on 73,5 %, at II type – on 64,7 % and at III type - on 45,5 % accordingly ($p < 0,001$). Concentration of the inhibitor matrix metalloproteinase (TIMP-2), was on the average on 51,6 % above at patients with I type pseudocysts of P, than at control group ($p < 0,001$); at patients with II type of distinction were doubtful; at patients about III type – level TIMP-2 was an average on 9,6 % more low, than an indicator in control group ($p < 0,05$) (fig. 2).

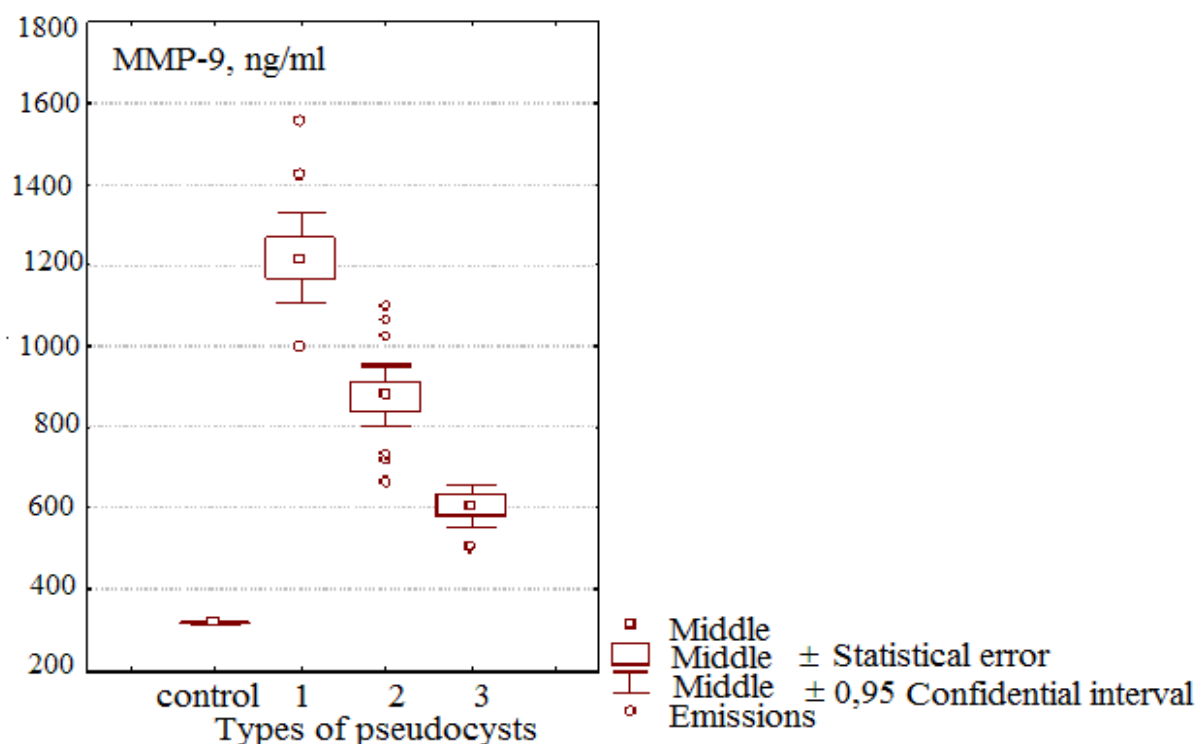


Fig. 1. Maintenance MMP-9 in a blood at patients with pseudocysts of pancreas

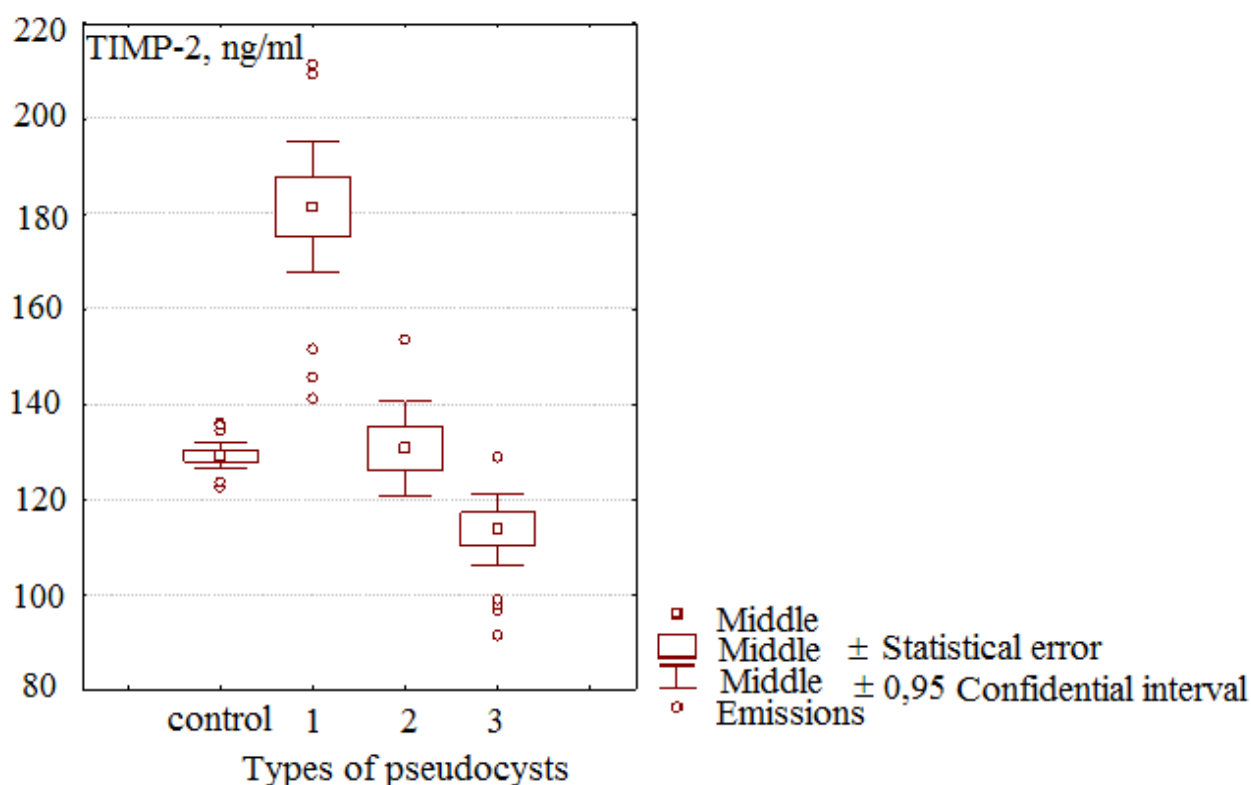


Fig. 2. Maintenance TIMP-2 in a blood at patients with pseudocysts of pancreas

Coefficient of MMP-9/TIMP-2 (coefficient of MMP-9 inhibition) was above at patients with I and II types pseudocysts of P, and has made accordingly 6,3 and 7,1 (in control group – 2,45) ($p < 0,001$). At patients with III type pseudocysts the inhibition factor on MMP-9 was more low, than in first two groups, but on 109,8 % exceeded indicators of control group ($p < 0,001$). Parity MMP-9 / TIMP-2 was above at patients of 2nd group and on 189,8 % exceeded indicators of control group, on 12,7 % – indicators which have been fixed in 1st group of patients and on 38,1 % – indicators which have been fixed in 3rd group of patients ($p < 0,05$) (fig. 3).

It is known that in the course of the development pseudocysts of P during the early period (the first 4-6 weeks from the beginning of acute pancreatitis), there passes a number of stages: 1) accurately prospective progressing inflammatory infiltrate 2) acute congestion of a liquid; 3) formation encapsulate congestions of the liquid with amylase and limited by fibrous tissue of peritoneum. Absence of epithelium allows differentiating pseudocyst and new cysts. Among the basic components which produce activated PSCs is collagen of I type and in smaller

quantities collagens of III and IV types, and also fibronectin, laminin, hyaluronic acid, etc.

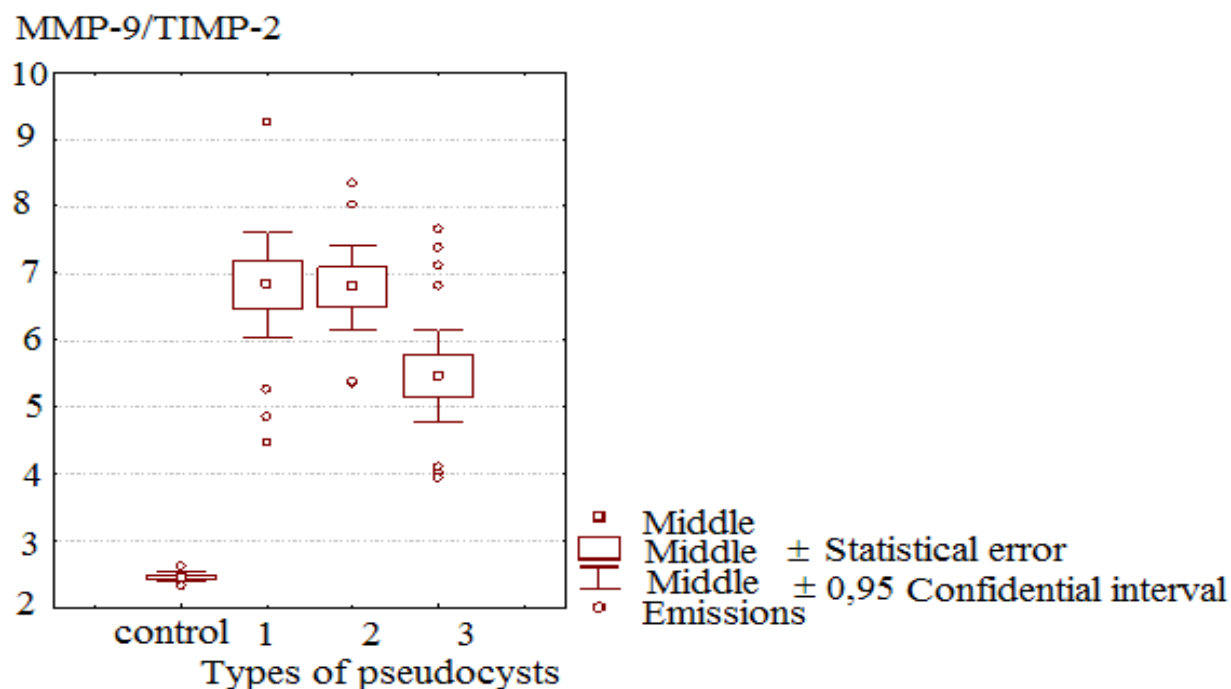


Fig. 3. Inhibition factors on MMP-9 at patients with different types pseudocysts of pancreas

For disintegration ECM answer metalloproteinase matrix – as endopeptidase group, which are made PSCs, and them proteolytic activity is regulated by tissue inhibitors – protein group, which the same produced by PSCs. Expression regulation of metalloproteinase occurs at three levels: 1) by genome; 2) by activation of proenzymes and 3) by inhibition of enzymes activity with the assistance of tissue inhibitors. Modulators of expression of MMP are TNF- α , IL-1 β , IL-8, IL-17, epidermal growth factor (EGF), transforming factor of growth (TGF), etc. All of them cause proof functions disturbance of various types of immunocompetent cells [14]. Osteocalcitonin, doxycycline, retinoids, glycosaminoglycans to inhibit by expression of MMP.

The expression of MMP is name the major factor in development of degradation ECM, "critical step" in it remodeling, the marker of inflammation activity, of fibrosis and sclerosis of P. Hyaluronic acid, tissue inhibitors MMP

(TIMP-1, 2), laminin, leptin, collagen of IV type, etc. are used as the indicators reflecting quantity of a connective tissue [15].

Activity of enzymes depends as on level of an expression of their genes, and presence of activators and inhibitors. MMP, basically, concern to "induced" enzymes which transcription submits to variety factors: steroid and thyroid hormones, cytokines, growth factors, chemical agents, etc. The exception makes MMP-2 which expression occurs on constitutional type, and regulation of activity of enzymes at post transmitting level is carried out by activation of zymogens or interaction with tissue inhibitors MMP [16, 17].

Contribution of PSCs to pathology of P is not limited to superfluous production of a connecting tissue, but also they stimulate growth factors, transforming factor (TGF- β), platelet (PDGF), etc. Besides, the bacterial infection and endocellular production of oxygen radicals [18] promote formation strengthening P fibrosis. Proliferation PSCs leads to formation of new blood vessels. These processes grow out of development P hypoxia and actions vasoactive mediators and cytokines: nitrogen oxide and other factors [19]. The process of angiogenesis is necessary for long adaptation of tissue in the conditions of damage, and the main mechanism of regulation of processes angiogenesis vasoactive is liberation of angiogenic factors.

Angiogenesis can be induced by processes an increase of concentration of stimulators and decrease level of inhibitors, or a combination of those and other processes. Thus, the essence of angiogenesis processes consists that after expansion of vessels and increase of their permeability occurs compression of endothelial cells and reduction of density of intercellular contacts. At pathological processes angiogenesis amplifies that can influence on the processes in ECM [20].

Vasculoendothelial growth factor (VEGF) – potential mitogen for epithelial cells of vessels. It strongly influences permeability of vessels, is powerful angiogenic tissue, participates in processes neovascularity at various pathological situations, is studied last years, including CP. Thus, the conducted researches have shown that the aggressive and heavy current at patients with pseudocysts of P (8 and more points on scale SOFA) associates with presence of higher values of level MMP-9, and

progressing fibrosis and development of complications in patients III type of pseudocysts associates with inhibition of TIMP-2. Thus the average level of a studied indicator, was not only more low, than at patients of the first and second groups, but also on the average on 9,3 % was below indicators of control group ($p < 0,05$). We had been spent studying of intragroup correlation communications between VEGF (indicator of hypoxia and damages of endothelium), MMP-9 and TIMP-2 to blood of patients with pseudocysts of P (tab. 2). The conducted researches have shown, that in at all types pseudocysts of P there was a positive communication only between level MMP-9 and VEGF: at I type it has made 0, 57 ($p < 0,05$); at II type – 0,76 ($p < 0,05$); at III type – 0,68 ($p < 0,01$). Results of research show that at all patients development endothelium dysfunctions with damage of endothelium to what substantial increase in plasma of blood VEGF accordingly on 176,4 % (1 group), 129,2 % (2 group) and on 54,2 % (3 group) in relation to control ($p < 0,05$ testified) was observed.

Thus, by means of the single-factor dispersive analysis it is possible to estimate the importance of distinctions between average values of indicators in four groups. Apparently from resulted data, at confidential probability of 0,95 % ($p < 0,05$) indicator MMP-9 significantly differs in all four groups. For TIMP-2 distinctions are observed only for the first and third groups of patients as among themselves, and in relation to control and to the second group. Average relations of MMP-9 / TIMP-2 are significantly various only for control group and the third group among themselves and in comparison with the first and second groups. High activity of MMP-9 and TIMP-2 at patients with I and II types pseudocysts of P, probably, is caused by compensatory reaction, directed on suppression destruction of collagenic network (basically - collagen IV) and on the prevention further reorganization of connecting tissue of P. At progressing fibrosis of P (the third group of patients) MMP-9 and TIMP-2 decreased in comparison with the first and second groups of patients. At III type pseudocysts of P the level of gelatinize was on 83,6 % above indicators of control group, but on 51,4 % and on 35,1 % more low, than at patients with I and II types pseudocysts of P. Thus average level TIMP-2 accordingly on 40,4 % and 11 % ($p < 0,05$) in the third group of patients was more low, than in the first and second

groups. It is known that MMP-9 is the induced enzyme which transcription depends on variety of factors: level of cytokines, factors of growth, chemical agents etc., and this enzyme plays an important role at chronic phases of various illnesses [21].

Table 2

Intragroup correlation communications between levels VEGF, MMP-9 and TIMP-2 at patients with pseudocysts of pancreas

| I type of pseudocysts of pancreas | | | |
|--|----------------|---------------|---------------|
| | VEGF | MMP-9 | TIMP-2 |
| VEGF | 1,0000 | 0,57, p<0,05 | 0,09, p>0,05 |
| MMP-9 | 0,57, p<0,05 | 1,0000 | -0,23, p>0,05 |
| TIMP-2 | - 0,23, p>0,05 | 0,09, p>0,05 | 1,0000 |
| II type of pseudocysts of pancreas | | | |
| | VEGF | MMP-9 | TIMP-2 |
| VEGF | 1,0000 | 0,76, p<0,05 | 0,25, p>0,05 |
| MMP-9 | 0,76, p<0,05 | 1,0000 | 0,24, p>0,05 |
| TIMP-2 | 0,25, p>0,05 | 0,24, p>0,05 | 1,0000 |
| III type of pseudocysts of pancreas | | | |
| | VEGF | MMP-9 | TIMP-2 |
| VEGF | 1,0000 | 0,68, p<0,01 | 0,07, p>0,05 |
| MMP-9 | 0,68, p<0,01 | 1,0000 | 0,3, p>0,05 |
| TIMP-2 | 0,07, p>0,05 | 0,24, p>0,05 | 1,0000 |

The regress of extracellular matrix occurs also because of apoptosis of PSCs. Further all depends on, whether action of the harmful factor (viruses, autoantibody, toxins, etc.) stops. If the pathogenic factor stop it works, there is collagen degradation. Such variant is favorable and similar supervision are described at patients with a syndrome of overload by iron and copper, alcohol-induced liver defeat, chronic virus hepatitis after virus elimination, hepatitis etc. [21]. These researches allow us to assume that in conditions of hypoxia and ischemia of P, as a

result of its damage by, angiogenic factors there is an activation and proliferation of endotheliocytes, which comes to the end by remodeling of vessels and neovascularization processes. Owing to infringements of balance between synthesis of proteins and their disintegration the structure pancreocytes of P is changes. Delay of processes of recycling of extracellular matrix components, which collects in a zone of damage of P, conducts to delay of a reparation processes and can be main cause of fibrosis with development of CP and its complications, including – as a result of repeated influence of factors exogenous and endogenous nature and activation PSCs, about what can increases in concentration TIMP-2 and increases of factors of inhibition MMP-9 at all types pseudocysts of P. Accordingly it creates favorable conditions for remodeling of P when, defect of organ parenchyma is replaced with a tissue, for example – scar, and repeated damage of cells conducts to bigger activation PSCs, that promotes formation of CP and its complications.

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Резюме. Проведено біохімічні дослідження у 47 хворих з псевдокістами підшлункової залози, у віці $43,58 \pm 7,38$ року, співвідношення чоловіки /жінки 8,4:1. Хворих було розподілено на три групи згідно класифікації псевдокіст підшлункової залози за А. D'Egidio та М. Schein (1991). Всі хворі були оперовані. Резекцію вентральної частини голівки ПЗ за Фреєм виконано у 11 пацієнтів, субтотальну резекцію голівки ПЗ за Бернською методикою – 3, дренажування порожнини кісти – у 14 (у поєднанні з протоковою системою ПЗ – у 3), пункційно-дренуючі втручання під контролем УЗД – у 10, відкриті

оперативні втручання та зовнішнє дренивання порожнини псевдокісти – у 4 хворих. З 47 пацієнтів, що аналізуються, помер 1 від арозивної кровотечі. Проведене дослідження підтвердило, що рівень IL-18 був вищим у хворих на I тип псевдокіст в 1,9 рази, на II тип – в 1,2 рази і на III тип – в 1,3 рази у порівнянні із контролем ($p < 0,05$). Подібна тенденція відзначена й для IL-6 та IL-8 на тлі підвищення IL-10 відповідно в 27,4 рази (I тип псевдокіст ПЗ), в 28,1 рази (II тип псевдокіст ПЗ) та в 21,4 рази при III типі псевдокіст ПЗ. Встановлено, що вміст IL-18 і глутатіонпероксидази в сироватці крові при різних типах псевдокіст підшлункової залози безпосередньо корелює з тяжкістю панкреатиту. Нами виявлено тісну кореляцію між рівнем IL-18 і змістом глутатіонпероксидази в крові при несприятливому прогнозі перебігу після операційного періоду: $r = -0,87$, $p < 0,01$

Дослідженнями підтверджена висока активність ММП-9 та ТІМП-2 у хворих на I та II типи псевдокіст ПЗ, що, можливо, зумовлено компенсаторною реакцією, яка направлена на пригнічення деструкції колагенової мережі (переважно – колагену IV) та попередження подальшої перебудови сполучної тканини ПЗ. При прогресуванні фіброзу ПЗ (третья група хворих) ММП-9 та ТІМП-2 знижувались у порівнянні з першою та другою групами хворих. При III типі псевдокіст ПЗ рівень ММП-9 був на 83,6% вище показників контрольної групи, але на 51,4% та на 35,1% нижчим, ніж у хворих на I та II типи псевдокіст ПЗ. При цьому середній рівень ТІМП-2 відповідно на 40,4% та 11% ($p < 0,05$) в третій групі хворих був нижчим, ніж в першій та другій групах. У всіх хворих спостерігався розвиток ендотеліальної дисфункції з пошкодженням ендотелію, про що свідчило значне підвищення у плазмі крові VEGF відповідно на 176,4% (I тип псевдокіст), 129,2% (II тип псевдокіст) та на 54,2% (III тип псевдокіст) по відношенню до контролю ($p < 0,05$). Отримані дані дозволяють припустити, що це створює сприятливі умови для ремоделювання підшлункової залози, коли дефект парехими заміщується тканиною з нижчим рівнем організації, наприклад – рубцем, а повторне ушкодження клітин веде до ще більшої активації PSCs і збільшення продукції компонента позаклітинної матриці.

Ключові слова: псевдокісти підшлункової залози, матриксні металопротеїнази, патогенез.

Резюме. Проведены биохимические исследования у 47 больных с псевдокистами поджелудочной железы, в возрасте $43,58 \pm 7,38$ лет, соотношение мужчины/женщины 8,4:1. Больные были разделены на три группы согласно классификации псевдокист поджелудочной железы по А. D'Egidio и М. Schein (1991). Все больные были оперированы. Резекция вентральной части головки ПЖ по Фрею выполнена 11 больным, субтотальная резекция головки ПЖ по Бернской методике – 3, дренирование полости кисты – у 14 (в сочетании с протоковой системой ПЖ – у 3), пункционно-дренирующие вмешательства под контролем УЗИ – у 10, открытые оперативные вмешательства и наружное

дренирование полости псевдокисты – у 4 больных. С 47 анализируемых больных, умер 1 от аррозивного кровотечения.

Проведенные исследования доказали, что уровень IL-18 был выше у больных с I типом псевдокист в 1,9 раза, со II типом – в 1,2 раза и с III типом – в 1,3 раза по сравнению с контролем ($p < 0,05$). Подобная тенденция отмечена и для IL-6 и IL-8 на фоне повышения IL-10 соответственно в 27,4 раза (I тип псевдокист ПЖ), в 28,1 раза (II тип псевдокист ПЖ) и в 21,4 раза при III типе псевдокист ПЖ. Установлено, что содержание IL-18 и глутатионпероксидазы в сыворотке крови при разных типах псевдокист поджелудочной железы непосредственно коррелирует с тяжестью панкреатита. Нами выявлена тесная корреляция между уровнем IL-18 и содержанием глутатионпероксидазы в крови при неблагоприятном прогнозе течения послеоперационного периода: $r = -0,87$, $p < 0,01$

Исследованиями подтверждена высокая активность ММП-9 и ТИМП-2 у больных с I и II типом псевдокист ПЖ, что, возможно, обусловлено компенсаторной реакцией, которая направлена на угнетение деструкции коллагеновой сети (преимущественно – коллагена IV) и предупреждения дальнейшей перестройки соединительной ткани ПЖ. При прогрессировании фиброза ПЖ (третья группа больных) ММП-9 и ТИМП-2 снижалась по сравнению с первой и второй группами больных. При III типе псевдокист ПЖ уровень ММП-9 был на 83,6% выше показателей контрольной группы, но на 51,4% и на 35,1% ниже, чем у больных с I и II типом псевдокист ПЖ. При этом средний уровень ТИМП-2 соответственно на 40,4% и 11% ($p < 0,05$) в третьей группе больных был ниже, чем в первой и второй группах.

У всех больных наблюдалось развитие эндотелиальной дисфункции с повреждением эндотелия, о чем свидетельствовало значительное повышение в плазме крови VEGF соответственно на 176,4% (I тип псевдокист), 129,2% (II тип псевдокист) и на 54,2% (III тип псевдокист) по отношению к контролю ($p < 0,05$). Полученные данные позволяют предположить, что это создает благоприятные условия для ремоделирования поджелудочной железы, когда дефект парехимы замещается тканью с более низким уровнем организации, например – рубцом, а повторное повреждение клеток приводит к еще большей активации PSCs и увеличению продукции компонента внеклеточного матрикса.

Ключевые слова: псевдокисты поджелудочной железы, матриксные металлопротеиназы, патогенез.

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