COMORBID CHRONIC PANCREATITIS AND CORONARY HEART DISEASE: ON THE POSSIBLE MECHANISMS OF DEVELOPMENT AND PROGRESSION

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Diseases of the pancreas, including chronic pancreatitis (CP) constitute not only gastroenterological, pancreatological problem, but also the issue of all internal medicine. Confirmation of the importance of its studying is the fact of presence in Europe of 3 million patients with CP. In the general structure of digestive diseases in Ukraine the proportion of CP also increased (10.5%), especially the number of cases with primary chronic course [36] and frequent attacks. The cases of CP, accompanied by structural changes, associated with exo- and endocrine pancreatic insufficiency, a significant decrease in quality of life, the development of type 2 diabetes, and/or pancreatogenic origin, tumors of the pancreas also became more frequent.

Upon recurrent course of CP, in 30% early complications with mortality of 5.1% develop, connected not only with the combination of gastroduodenobiliary zone diseases, but also with another pathology of internal organs, in particular the cardiovascular system. Experts point out the importance of the study of disease and comorbidity, emphasize that syntropic comorbid lesions are the factors determining medical tactics and prognosis, moreover, a multiplicity of diseases has already been observed in teenagers and aged under 30 today [27]. In young people there is increasing proportion of early signs of metabolic syndrome, obesity [38], the development of the atherosclerotic process and preclinical forms of coronary heart disease (CHD) [12].

Therefore, this problem is urgent and acquires meaning when upon comorbidity of diseases characterized by substantial prevalence and factors of fatal cardiovascular complications. They include CP, CHD and chronic heart failure

(CHF). The prognosis of CHF remains disappointing as its lethality has reached 50% for 5 years. According to the literature, CHF with preserved left ventricular ejection fraction is detected in 40-55%, often develops on the background of essential hypertension (AH) and/or CHD, while risk and progression of CHF are significantly increased upon combination. It should be noted that the concomitant obesity, diabetes, chronic renal failure, etc. serve as the additional risk factors. Peculiarities of clinical course of CHD isolated form and its combination with hypertension are stated. Isolated CHD is characterized by severe symptoms, reducing exercise tolerance, the degree of left ventricular hypertrophy in greater extent than upon combination with hypertension [20].

Among the common etiological factors of CP, CHD and CHF, tobacco, alcohol, microbial and non-microbial factors, failure of a healthy way of life (especially the lack of physical activity) are of great importance. According to surveys conducted by the National Institute of Therapy n. a. L. T. Malaya, lack of physical activity is set in 38% of men and 54% of women in Ukraine, it does not depend on age. Typically, even in 50% of those aged 18-24, the level of physical activity is insufficient. Consequently, at a young age not only the risk of cardiovascular events is formed, but also digestive diseases (gastroesophageal reflux disease, biliary diseases and CP). In addition, studying the mechanisms of CP, CHD and CHF comorbidity remains relevant. One of the key mechanism is considered a low-intensity chronic generalized inflammatory reaction (low or sufficient intensity), which determines the progression of atherosclerosis in coronary vessels, myocardial tissue, pancreas and combined with general biological process of immune system response to injury. It is considered from the point of view of pathogenetic link of forming comorbidity diseases, complications, including the fatal cardiovascular ones.

Detailed examination and study of the epidemiological data may enable to develop appropriate methods of treating, preventing, recommendations for modification of cardiovascular risk factors, taking into account the comorbidity of these diseases, significantly contribute to the prevention of the progression of CHF, CP complications (ischemic pancreatitis), CHD.

The aim of the literature review was to show the clinical and pathogenetic mechanisms of CP in combination with CHD and CHF.

The common pathogenetic links of the development and progression of CP, CHD and CHF can include oxidative [41], carbonyl and nitrosol stresses [26], low-intensity chronic inflammation [22], atherogenic dyslipidemia (especially hypertriglyceridemia) [4], insulin resistance (IR) [46], enhancing the development and persistence of atherosclerotic processes in the vessels [2]. Attention is paid to the endothelial dysfunction, impairing the microcirculation [45] and hemostatic process [9], contributing to the ischemia and maintenance of tissue hypoxia (taking into account the mechanisms of chronic DIC syndrome).

CHD and CP combination is characterized by more severe course, atypical pain, especially in the left side of the chest, creating difficulties in the diagnostic process, defining the high mortality and late adequate therapy [16]. Abdominal pain and dyspeptic syndromes wherein are associated with anginal attacks, worsening quality of life of patients [43]. In addition, the neuro-reflex pain reactions and dietary exposure under the existing pancreatic pathological decrease exercise tolerance to an even greater degree due to the viscero-visceral reflexes and abnormal hemodynamic response [39]. Hypertrophy of the left ventricle, increased homocysteine, lipoprotein α, triglyceride or fibrinogen concentrations, presence of pathogens and markers of inflammation in the body, increased procoagulants (plasminogen, factor VII, plasminogen inhibitor type 1, and Willebrand factor) are also common [28]. In patients with CP in combination with CHD [12] intensity of proteolysis has been significantly increased (according to O. Zazdravnova et al.) about 2 times in comparison with a group of healthy. This fact suggests the possibility of rise and formation of apoptotic activity in pancreatic tissue. The authors also detected significant decrease of fibrinolytic potential, creating the conditions for the formation of microscopic platelet and fibrin clots in the system hemomicrocirculation, development and progression of chronic DIC syndrome in these patients. With the progression of the pathological process in the pancreas, these mechanisms are disturbing the local blood circulation, followed by increase of

ischemia, hypoxia, membrane permeability, destruction of acinar cells and releasing of pancreatic enzymes in the blood flow [15]. Even a minimal intake of enzymes generates structural changes in the tissue, helping the fibrosing of parenchymal tissue with the development of exo- and endocrine insufficiency up to the symptoms of maldigestion and malabsorption [42].

The unifying mechanism of these processes may be named as the chronic systemic inflammation as a low-intensity immune system response to injury [15, 33]. Positive correlation between the increasing C-reactive protein (CRP) in the blood and coagulation system activation (due to stimulation of the tissue factor release from monocytes, that initiates the coagulation and neutralizes platelet-activating factor, thus contributing atheromatosis and thrombus formation) is proved, which is inextricably linked with the persistence and progression of chronic inflammation, in particular ischemic pancreatitis [7].

It is possible that a change in pH or redox homeostasis, accumulation of the products of proteolysis and/or oxidation of proteins and lipids can inhibit the ability of the fibrinolytic system to maintain a sufficient level of thrombolytic efficacy [9]. This mechanism is peculiar to fibrin degradation products, the increase of which occurs not only in atherosclerosis, but also in CP, chronic relapsing pancreatitis. Its value consists in the binding of a certain amount of prostaglandins for the purpose of removing them from the bloodstream [28]. Presumably, this mechanism may be common for CP, as well as for its combination with CHD, CHF. The pancreas is very sensitive to ischemia, atherosclerotic and thrombotic processes [29], and can itself be a source of metabolic disorders [44], causing hemodynamic disorders with subsequent deployment of ischemic pathological processes in it [10, 13].

Cytokines' cascade is believed as the main pathogenetic link of the low-intensity inflammatory response of the immune system, upon CP and CHD comorbidity, since it regulates the reaction of the proteins of the inflammatory response. The role of CRP is studied adequately, especially in the pathogenesis and progression of atherosclerotic and atherothrombotic processes [8]. Given common biological CRP role performing mediator, transport, immunomodulatory function, we

can assume its direct presence locally not only in the tissue of the pancreas in CP [7], but in the structures of the coronary vessels, myocardium and atherosclerotic plaques [23] upon their comorbidity.

V. V. Velkov found that activation of complement, monocytes, stimulation of adhesion molecule expression (sICAM-1, sVCAM-1, E-selectin) on endothelial surface, binding and modification of LDL with the participation of CRP were the signs of early stage of vascular wall damage and the formation of endothelial dysfunction, which was an obligatory part of the progression of the atherosclerotic process in the blood vessels [8], upon comorbidity of these diseases, including CHF.

Consequently, according to modern views, CRP is not only a sensitive marker of inflammation, but also plays an important role in the pathogenesis and progression of vascular damage, occurence and destabilization of atherosclerotic plaques and thrombotic vascular occlusion. K. Yasojima et al. [56] demonstrated that the level of CRP in atheroma was 7 times bigger than its concentration in the liver. High level of this protein was detected in the tissue of an aortic aneurysm [25]. It should be noted that CRP along with traditional risk factors is considered as an independent predictor of diseases and their complications [37], an independent risk factor for CHF, diabetes type 2. This requires the conformation changes in the structure of CRP associated with the destruction of both endothelial cells and cardiomyocytes, accompanied by cardiac, vascular, cardiopulmonary and other systems and organs (gastroduodenal zone, liver and pancreas) [40].

Cytokines (IL-1, IL-6, TNF-α), Gram-negative bacteria lipopolysaccharide, relevant mediators (anaphylatoxins, glucocorticosteroids) start and control the synthesis of CRP [22]. Cytokines are the primary promoters of certain genes whose work activates in inflammation, while glucocorticoids play the role of modulators of cytokine action. Activated cytokines (IL-1, TNF-α IL-6, interferons), increasing the production of glucocorticoids, stimulate leukocytosis, contribute to an increase in ESR, fever, activation of the complement and coagulation processes, reduction of serum iron and zinc [28], which is very important for destabilization of acinar and β-cells of the pancreas.

In conditions of chronic inflammation, infection or damage (that accompany CP course in conjunction with CHD, CHF), plasma CRP is synthesized by hepatocytes under the influence of cytokines of "first generation" — IL-1, IL-6. They have inflammatory properties and can activate the transcription of nuclear factor system — NF-kappa-B. CRP promoter gene contains regulatory elements interacting with interleukins. Regulation of protein synthesis occurs both at the level of transcription and at the post-translation stage [50]. However, in contrast to short-living cytokines and characterized by daily fluctuations, CRP levels are stable due to the long period of this protein's extraction from organism.

Low-intensity inflammation (defined in terms of a high-sensitive CRP) allows to predict the risk of atherosclerotic complications (myocardial infarction, insult) in patients with CP, especially ischemic one [18]. American Heart Association recommends the following criteria for evaluating the ratio of the level of high-sensitivity CRP and cardiovascular risk: less than 1 mg/L — low risk, 1-3 mg/L — medium risk, more than 3 mg/L — high risk [57]. Independent experts believe that this test can be used in practically all healthy adults for the purpose of allocating risk groups for preventive measures, especially the medical ones aimed at the prevention of CHD complications, taking into account the combined course with CP [32].

Role of the lipid metabolism in the development not only of CHD, but CP is proved [31, 47, 48], which contributes to the development or progression of IR [54]. It should be emphasized that IR is activated by fatty acid oxidation monocytes at the normal level of glucose in the cytosol and at the blockade of lipolysis [35]. Upon increasing level of non-esterified fatty acids in the intracellular medium, cells passively absorb and immediately oxidize them. The process is typical both for the biological function of adaptation, biological stress response, as well as inappropriate biological function of digestion (upon high content of palmitic fatty acid, transfer reaction of fatty acids to the cells and the blockade of apoE/B 100-endocytosis). It is carried out upon biological function of inflammation, lipid-redirecting CRP synthesis that as a vector forwards fatty acids from myocytes to interstitial cells, implementing

systemic inflammatory processes [35], not excluded — upon the chronic course of CP and CHD comorbidity.

The described mechanism increases the activity of all the loose connective tissue cells by connecting to an exchange of myocardial cells, causing structural changes in the myocardium at each CP attack (in our case) and activating the atherosclerotic process, forming CHF, contributing to the progression of its functional class.

O. V. Korkushko et al. [30] showed that an imbalance in sympathetic and parasympathetic nervous systems in the elderly characterized the state of stress, leading to myocardial ischemia, hypertension, impaired glucose tolerance [21, 51]. However, it disturbs not only carbohydrate metabolism with the IR development, but the lipid one [49].

The connection is stated between obesity, IR, and liver enzymes activity [17], which may change upon CP and non-alcoholic fatty disease of the liver, pancreas (which becomes a cause of CP) [34], upon diabetes, CHD, CHF [28]. Thus, according to O. V. Stepanova, men without diabetes level of gamma-glutamil transferase (GGT), and not ALT or AST, is inversely related to insulin sensitivity independently on the abdominal obesity and is a sensitive IR marker. At the same time, the level of GGT in women is positively correlated with the ratio waist/hips, but not with insulin sensitivity. Ascertained gender characteristics indicate that GGT may be a marker of liver fat accumulation. Gender differentiation may indicate the distribution of fat and be used as a significant causal factor in the development of fatty liver disease in women [14].

Hyperglycemia in IR at first causes compensatory hyperinsulinemia, which increases glucose uptake by peripheral tissues and reduces the formation of hepatic glucose [19]. Correspondingly, in IR progression, β-cells of the pancreas produce insufficient amount of insulin for its compensation. The resulting relative deficiency of insulin, in turn, enhances hyperglycemia. Upon the depletion of reserve possibilities of the pancreatic β-cells, hyperinsulinemia leads to increased levels of free fatty acids and glucose, strengthening IR, causing a deficiency of intracellular

glucose [24]. There is a transition to an alternative energy substrate — fatty acids — and enhanced hepatic glucose production. Increasing free fatty acids' production reduces glucose uptake to a greater extent [54].

Hyperglycemia and hyperinsulinemia are proved to be the factors affecting the dysfunction of endothelial cells due to the activation of the sympathetic nervous system, increasing synthesis of prostaglandins, endothelin-1, angiotensin-converting enzyme with increased activity of protein kinase C in these cells [6, 54]. There are two views on the causes of endothelial dysfunction in IR [46]. Authors, who hold first point of view, consider that endothelial dysfunction develops because of hyperglycemia, arterial hypertension, atherogenic dyslipidemia, while other authors consider that it is the cause of IR and the associated hyperglycemia, hypertension and atherogenic dyslipidemia [5, 52]. Nevertheless, these theories have no effect on the approaches to therapy improving the functioning of the endothelium, because preparations are prescribed to improve the exchange of nitric oxide, which is pathogenetically justified.

Molecular genetic studies of polymorphism of genes, involved in the regulation of carbohydrate metabolism, led to the deeper understanding of the mechanisms of development of metabolic disorders in other diseases [53]. Peroxisome proliferators-activated receptors (PPAR-α, PPAR- b, PPAR-γ) have direct relevance to the development of obesity, diabetes and cardiovascular disease that is associated with natural polymorphism of genes, external causal factors, level of fats consumption [11]. Receptors of genes (according to O. Y. Babak et al. [3]) represent transcription factors from the nuclear hormone receptors family. They control the activity of many genes and are not only central regulators of lipid and carbohydrate metabolism, development and differentiation of adipose tissue, but also modulators of gene expression in many tissues — adipocytes, epithelial cells, lissocells of the vascular endothelium and macrophages under the influence of Pro-Pro genotype of PPAR-γ gene.

Thus, one aspect of IR formation is to reduce gene expression of nuclear PPAR receptors family, especially of PPAR-γ type, which contribute to depositing of fatty

acids, increase leptin gene expression, glucose transporter gene, decrease IR, which is very important in the prognosis of comorbidity course of CP with CHD and CHF. Patients with Pro-Pro genotype had the highest atherogenicity of blood plasma with a reduction in HDL and increased total cholesterol, which is functioning as the formation of atherosclerosis. It is important that PPAR-γ1 and PPAR-γ2 isoforms can affect hemodynamic factors, causing the risk of cardio-vascular system lesions, including the development of CHF.

So, peculiarities of the inflammatory response (systemic chronic low-intensity one) for damage are: intensity of response of IL-6, CRP, type of cytokine cascade, reaction of complement system and cell-mediated immunity, severity of atherogenic dyslipidemia, IR, which promote the development of atherosclerosis, atherothrombosis. In addition, state of gene regulation of these processes (endothelial NO-synthase [1], endothelial oxidative stress, hemostatic reactions), state of endocrine and exocrine pancreatic function, functional and structural lesions of the liver represent big importance.

Thus, the above mentioned pathogenesis links may be employed both in CP and its combination with CHD. It is not excluded that CHD, which is caused by the progression of oxidative, carbonyl, nitrositive stress, hypoxia, endotoxemia, may act as a mechanism for the development of both local chronic inflammation in the pancreatic tissue and systemic chronic one. Activation of cytokine cascade, acute phase proteins of inflammation, chronic DIC syndrome are important for both diseases, as microthrombosis promotes angiogenesis, apoptosis, and the final stage of inflammation — fibrosis. All this requires a detailed study, but the significance of these mechanisms of such disease comorbidity remains understudied. There is a need to identify a number of common pathogenetic links to refine mutually aggravating mechanisms for the development of effective therapeutics, prevention and rehabilitation measures to improve the quality of life of patients.

References

1. Алельний поліморфізм гена ендотеліальної NO-синтази при серцево-судинних захворюваннях / О. О. Мойбенко, В. Е. Досенко, Я. М. Лутай [та ін.] // Доповіді національної академії наук України. — 2005. — № 12. — С. 173–176.
2. Архій Е. Й. Особливості змін процесів травлення, лабораторних та імунологічних показників при хронічних захворюваннях підшлункової залози, поєднаних з ішемічною хворобою серця та захворюваннями гепатобіліарної системи / Е. Й. Архій, Т. В. Мишанич, О. М. Москаль // Гастроентерологія : міжвід. зб. — 2012. — Вип. 46. — С. 56–62.
3. Бабак О. Я. Вплив поліморфізму генів PPAR-гамма на клінічні вияви хвороби у пацієнтів з інсулінорезистентністю та артеріальною гіпертензією / О. Я. Бабак, Г. Д. Фадєєнко, Н. В. Ярмиш [та ін.] // Укр. терапевт. журн. — 2010. — № 2. — С. 35–38.
4. Бабінець Л. С. Порушення екскреторної функції підшлункової залози як фактор формування мінеральної недостатності при хронічному панкреатиті / Л. С. Бабінець // Укр. морфол. альманах. — 2006. — № 2. — С. 7–10.
5. Бабінець Л. С. Роль про- та антиоксидантного статусу і тютюнопаління у формуванні трофологічних розладів при хронічному панкреатиті у поєднанні з хронічним обструктивним захворюванням легень / Л. С. Бабінець, О. С. Квасницька // Вестник Клуба Панкреатологов. — 2012. — № 4. — С. 6–8.
6. Бойчак М. П. Эндотелиальная дисфункция при заболеваниях сердечно-сосудистой системы и возможности ее коррекции ингибиторами ангиотензинпревращающего фермента / М. П. Бойчак // Therapia. — 2010. — № 9. — С. 79–82.
7. Бурдули Н. М. Агрегационные свойства тромбоцитов у больных хроническим панкреатитом и возможности коррекции их нарушений / Н.

М. Бурдули, С. К. Гутнова // Клин. лаб. диагностика. — 2009. — № 4. — С. 19–20.

8. Вельков В. В. С-реактивный белок — «золотой маркер», многозначительный и незаменимый. Новое в клинической лабораторной диагностике атерогенеза: С-реактивный белок, холестерины, аполипопротеины / В. В. Вельков. — Пущино, 2005. — 110 с.
9. Гемостазіологічні зміни та деякі параметри ліпопротеїнового спектра за умов атеросклеротичного ураження мезентеріальних артерій у хворих на ішемічну хворобу хворобу серця / М. Ю Коломоєць, Є. П. Ткач, В. М. Ходоровський [та ін.] // Укр. терапевт. журн. — 2008. — № 3. — С. 13–16.
10. Губергриц Н. Б. Метаболическая панкреатология / Н. Б. Губергриц, А. Н. Казюлин. — Донецк : Лебедь. — 2011. — 464 с.
11. Диабет и кардиоваскулярная медицина: эпидемиологические, молекулярные аспекты и влияние окружающей среды / И. Зиммет, Керр-Байлес, К. Уалдер [и др.] // Діабет і серце. — 2009. — № 1. — С. 49–55.
12. Заздравнов А. А. Возможные пути поражения поджелудочной железы у больных ишемической болезнью сердца / А. А. Заздравнов, Л. М. Пасиешвили // Гастроентерологія : міжвід. зб. — 2001. — Вип. 32. — С. 100–103.
13. Катеренчук І. П. Серцево-судинний континуум — фактори ризику та ендотеліальна дисфункція: завдання і можливості сімейного лікаря щодо впливу на первинні ланки / І. П. Катеренчук // Практична ангіологія. — 2008. — № 5. — С. 47–52.
14. Кендзерська Т. Б. Морфологічні зміни підшлункової залози при ішемічній хворобі серця / Т. Б. Кендзерська, Т. М. Христич, В. Т. Бачинський // Вестник Клуба Панкреатологов. — 2009. — № 1. — С. 75–80.
15. Кендзерська Т. Б. Прогностичні критерії хронічного панкреатиту та ішемічної хвороби серця / Т. Б. Кендзерська, Т. М. Христич, Є. І. Шоріков // Укр. терапевт. журн. — 2005. — № 1. — С. 22–24.

16. Кендзерська Т. Б. Шляхи корекції метаболічних змін та порушень системи гемостазу у хворих похилого віку на хронічний панкреатит із супутньою ішемічною хворобою серця : автореф. дис. на здобуття наук. ступеня канд. мед. наук : спец. 14.01.02 «Внутрішні хвороби» / Т. Б. Кендзерська. — К., 2003. — 190 с.
17. Клинико-морфологические изменения печени при атерогенной дислипидемии при лечении статинами / Л. Б. Лазебник, Л. А. Звенигородская, И. А. Морозов [и др.] // Тер. архив. — 2003. — Т. 75, № 8. — С. 51–55.
18. Клиническая картина, морфофункциональные параметры функция эндотелия у пациентов с систолической ХСН разных возрастных групп / И. А. Сукманова, Д. А. Яхонтов, Т. И. Поспєлова [и др.] // Цитокины и воспаление. — 2010. — № 3. — С. 7–11.
19. Лазебник Л. Б. Метаболический синдром и органы пищеварения / Л. Б. Лазебник, Л. А. Звенигородская. — М., 2009. — 184 с.
20. Либис Р. А. Особенности течения ХСН с сохраненной фракцией выброса левого желудочка у пациентов с эссенциальной артериальной гипертензией / Р. А. Либис, А. Г. Душина, Е. А. Олейник // Артериальная гипертензия — 2013. — Т.19, № 6. — С. 513–519.
21. Лупанов В. И. Ожирение как фактор риска развития сердечно-сосудистых катастроф / В. И. Лупанов. // Рус. мед. журн. — 2003. — Т. 11, № 6. — С. 18–24.
22. Медведев В. В. Клиническая лабораторная диагностика. Иммунный статус организма / В. В. Медведев, Ю. З. Волчек. — СПб. : Медицина, 2006. — 304 с.
23. Насонов Е. Л. С-реактивный белок — маркер воспаления при атеросклерозе (новые данные) / Е. Л. Насонов, Е. В. Панюкова, Е. Н. Александрова // Кардіологія. — 2002. — № 7. — С. 53–62.
24. Неалкогольная жировая болезнь печени и метаболический синдром: единство патогенетических механизмов и подходов к лечению / Л. Н.

Белоусова, В. В. Петренко, Е. И. Ткаченко [и др.] // Эксперим. и клин. гастроэнтерол. — 2008. — № 2. — С. 92–96.

25. Неспецифические маркеры воспаления в прогнозировании течения ишемической болезни сердца / Ф. Н. Палеев, И. С. Абудеева, О. В. Москалец [и др.] // Кардіологія. — 2009. — № 9. — С. 59–65.

26. Орловський В. Ф. Ефективність L-аргініну у комплексному лікуванні загострення хронічного панкреатиту / В. Ф. Орловський, Н. М. Кириченко // Гастроентерологія : міжвід. зб. — 2011. — Вип. 45. — С. 441–447.

27. Пархоменко Л. К. Нейрогуморальная регуляция внешнесекреторной функции печени и поджелудочной железы у детей с сахарным диабетом 1-го типа / Л. К. Пархоменко, А. В. Рылова, Е. А. Будрейко // Гастроентерологія : міжвід. зб. — 2011. — С. 132–140.

28. Паталах І. І. Система гемостазу та білки гострої фази запалення при тромбогенних патологіях / І. І. Паталах, С. О. Кудінов // Укр. біохім. журн. — 2008. — Т. 80, № 1. — С. 3–11.

29. Писаренко О. И. Участие NO-зависимых действия аполина в защите миокарда от ишемического и реперфузионного повреждения / О. И. Писаренко, Л. И. Серебрякова, Ю. А. Пелогейкина // Кардиология. — 2012. — Т. 52, № 2. — С. 52–57.

30. Состояние автономной регуляции сердечно-сосудистой системы при инсулинорезистентности и нарушении толерантности к углеводам у практически здоровых людей / О. В Коркушко, В. Б. Шатило, А. В. Писарюк [и др.] // Укр. тер. журн. — 2010. — № 2. — С. 5–10.

31. Стеатоз поджелудочной железы и его клиническое значение / В. Т. Ивашкин, О. С. Шифрин, И. А. Соколов [и др.] // Рос. журн. гастроэнтерол., гепатол., колопроктол. — 2006. — № 4. — С. 32–37.

32. Терещенко С. Н. Диастолическая сердечная недостаточность: разрешимы ли трудности диагностики и лечения? / С. Н. Терещенко, И. В. Жиров // Тер. архив. — 2009. — № 11. — С. 73–76.

33. Титов В. Н. Атеросклероз. Роль эндогенного воспаления, белков острой фазы и жирных кислот / В. Н. Титов, С. Г. Осипов. — М., 2003. — 168 с.
34. Титов В. Н. Глюкоза, гликотоксины и продукты гликирования протеинов: роль в патогенезе / В. Н. Титов, Н. В. Хохлов, Ю. К. Ширяева // Клин. мед. — 2013. — Т. 95, № 3 — С. 15–24.
35. Титов В. Н. Филогенез, становление переноса и поглощения клетками жирных кислот, биологической функции локомоции и действия инсулина. Патогенез синдрома резистентности к инсулину / В. Н. Титов // Клин. лаб. диагностика. — 2010. — № 6. — С. 3–17.
36. Фадеенко Г. Д. Ассоциированное течение хронического панкреатита и кислотозависимых заболеваний / Г. Д. Фадеенко, К. А. Сытник // Здоров'я України. — 2014. — № 2. — С. 22–23.
37. Функціональний стан ендотелію у хворих на пептичну виразку шлунка та дванадцятипалої кишки, поєднану з цукровим діабетом / О. Ю. Оліник, О. І. Федів, І. С. Давиденко [та ін.] // Бук. мед. вісник. — 2010. — Т. 14, № 4. — С. 66–69.
38. Функціональний стан печінки та показники ліпідного спектра крові у дітей і підлітків з ожирінням / Л. К. Пархоменко, Л. А. Страшок, О. А. Будрейко [та ін.] // Гастроентерологія : міжвід. зб. — 2011. — С. 125–132.
39. Хорошина Л. П. Поражение мезентериальных сосудов у пожилых / Л. П. Хорошина // Клиническая геронтология. — 2001. — Т. 7, № 7. — С. 34–38. Христич Т. Н. Абдоминальная ишемическая болезнь / Т. Н. Христич, Т. Б. Кендзерская // Острые и неотложные состояния в практике врача. Гастроэнтерология. — 2008. — № 2/1. — С. 44–51.
40. Христич Т. М. Дисфункція ендотелію судин у хворих на хронічне обструктивне захворювання легень із супутнім хронічним панкреатитом / Т. М. Христич, Я. М. Телекі, Л. Д. Кушнір // Гастроентерологія : міжвід. зб. — 2009. — Вип. 42. — С. 267–270.
41. Христич Т. М. Показники оксидативного, карбонільного стресу, антиоксидантного захисту і дисліпідемії в хворих на хронічний

панкреатит залежно від віку / Т. М. Христич // Гастроентерологія : міжвід. зб. — 2012. — Вип. 46. — С. 202–205.

42. Христич Т. Н. Клинико-патогенетические особенности сочетанного течения хронического панкреатита и ишемической болезни сердца / Т. Н. Христич, Т. Б. Кендзерская, М. В. Дяк // Гастроентерологія : міжвід. зб. — Д., 2004. — Вип. 35. — С. 374–380.
43. Христич Т. Н. Особенности клинического течения хронического панкреатита в сочетании с ИБС / Т. Н. Христич // Збірник наукових праць співробітників КМАПО ім. П. Л. Шупіка. — К., 2005. — С. 167–171.
44. Христич Т. Н. Поджелудочная железа при метаболическом синдроме / Т. Н. Христич, Т. Б. Кендзерская // Эксперим. и клин. гастроэнтерол. — 2010. — № 8. — С. 83–91.
45. Циммерман Я. С. Хронический панкреатит / Я. С. Циммерман // Вестник Клуба Панкреатологов. — 2009. — № 1. — С. 38–41.
46. Шестакова М. В. Дисфункция эндотелия — причина или следствие метаболического синдрома? / М. В. Шестакова // Рус. мед. журн. — 2001. — Т. 9, № 2. — С. 88–91.
47. Adiponectin deficiency enhanced the severity of cerulein-induced chronic pancreatitis in mice / T. Yamada, H. Araki, K. Watabe [et al.] // J. Gastroenterol. — 2010. — Vol. 45. — P. 742–749.
48. Altinel D. Lipomatous pseudohypertrophy of the pancreas: a clinicopathologically distinct entity / D. Altinel // Pancreas. — 2010. — Vol. 39. — P. 392–397.
49. Apparent hydroxyl radical production by peroxynitrite: implications for endothelium injury from nitric oxide and superoxide / J. S. Beckmann, T. W. Beckmann, J. Chen [et al.] // Proc. Nat. Acad. Sci. USA. — 2000. — Vol. 87. — P. 1620–1622.
50. Bhardway P. Рандомизированное контролируемое исследование антиоксидантов для облегчения боли у пациентов с хроническим

панкреатитом / P. Bhardway, P. K. Garg, S. K. Maulik // Вестник Клуба Панкреатологов. — 2010. — № 1. — С. 34–43.

51. Diabetes mellitus worsens antioxidant status in patients with chronic pancreatitis / D. Anilliot, E. Walters, J. P. Bonte [et al.] // Am. J. Clin. Nutrition. — 2005. — Vol. 81. — P. 1117–1125.
52. Goossens G. H. The role of adipose tissue dysfunction in the pathogenesis of obesity-related insulin resistance / G. H. Goossens // Physiol. Behav. — 2008. — Vol. 94. — P. 206–212.
53. Grundy S.M. Effectiveness and tolerability of sum statin plus fenofibrate for combined hyperlipideamsa (the SAFARI) trial // Am. J. Cardiol. — 2006. — Vol. 98. — P. 427–428.
54. A mouse model of metabolic syndrome: insulin resistance, fatty liver at non-alcoholic fatty pancreas disease (NAFPD) in C57BL / 6 mice fed a high fat diet / J. C. Fraulob, R. Ogg-Diamantino, C. Fernandes-Santos [et al.] // J. Clin. Diochem. Natur. — 2010. — Vol. 46. — P. 212–223.
55. Taubert D. Acute effects of glucose and insulin on vascular endothelium / D. Taubert // Diabetologia. — 2010. — Vol. 26. — P. 1026–1072.
56. Yip H. K. Levels and values of inflammatory markers in patients with angina pectoris / H. K. Yip, C. J. Wu, H. Hang // W. Int. Heart J. — 2005. — Vol. 46. — P. 571–581.
57. Yokus B. Effects of active and passive smoking on antioxidant enzymes and antioxidant micronutrients / B. Yokus, N. Mete, U. D. Cakir // Biotechnol. & Biotechnol. Eq. — 2005. — № 19. — P. 117–123.

Comorbid chronic pancreatitis and coronary heart disease: on the possible mechanisms of development and progression

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Key words: chronic pancreatitis, coronary heart disease, comorbidity, generalized low-intensity chronic inflammation, pathogenesis

The article reveals the possibility of some mechanisms of development, progression and complication of chronic pancreatitis comorbidity with coronary artery disease upon chronic heart failure. It also highlights the role of chronic low-intensity generalized systemic and local inflammatory reaction, atherogenic dyslipidemia, insulin resistance, endothelial dysfunction.