Comorbidity of chronic pancreatitis and metabolic syndrome: mechanisms of development

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There is a large number of studies devoted to the mechanisms of development of chronic pancreatitis (CP), but insufficient attention is paid to considering the question of the possible role of the pancreas in the occurrence of metabolic and hormonal disorders in COP in comorbidity with metabolic syndrome (MS), given its universality, as an organ of mixed secretion [4, 5].

In the case of CP in connection with violations in the activities of the pancreas damaged both secretory and in vitro glands, which is important in the regulation of homeostatic mechanisms. It should be noted that transient hyperglycemia develops in acute pancreatitis. This is due to edema in the pancreas, inhibiting the effect of trypsin on insulin products. With the development of CP for 3 years, glycemia develops rapidly, and from 3 to 5 years, glucose intolerance is more often detected. If the terms of the course of CP go through 5-10 years, diabetes mellitus (DM) may develop, which is an integral part of the MS [6].

Consequently, the lack of endocrine function of the PP clinically manifested by metabolic disorders due to the disruption of the insulin regulation mechanism. Insulin is a hormone that causes vasodilatation in healthy, and in vascular conditions (with hyperglycemia and hyperinsulinemia), vasoconstriction. In addition, insulin is actively involved in energy and lipid metabolism [14], in the development of hypertensive syndrome, resulting in an increase in the intracellular content of Ca2 in β-cells of pancreas, contributing to the formation of compensatory hyperinsulinemia in CP. This mechanism can have an important role in the formation of insulin resistance as the main mechanism of MS development in CP. At the same time, sensitivity to insulin is initially reduced, insulin receptors are then blocked, and

glucose and fats, which come from food, are deposited with adipose tissue [17]. It also increases the formation of insulin resistance in patients with CP, hyperinsulinemia becomes constant. Permanent hyperinsulinemia depletes the secretory apparatus of β-cells, affects the progression of carbohydrate metabolism disorders from moderate increases in glucose concentration initially on nocturnal, and then after nutritional loading, and, lastly, contributes to the development of type 2 diabetes [20].

On the other hand, hyperinsulinemia complicates the decomposition of fats, which is one of the mechanisms that promote the development and progression of obesity in patients with CP. Studies have shown that a significant increase in the mass of visceral adipose tissue is associated with MS. It has been established that visceral fat tissue has a wider network of capillaries than fatty tissue of another localization and is directly connected to the portal system, opening the possibility for the systemic action of adipocytes to the tissue not only of the liver, but also of the pancreas, contributing to the development of their steatosis [10, 11].

Due to the high density of β-adrenergic receptors (especially type β3), corticosteroid and androgen receptors, as well as a relatively low density for alpha-2-adrenergic receptors and insulin receptors, the sensitivity of visceral adipose tissue to the lipolytic action of catecholins is formed and low sensitivity to the anti-lipolytic activity of insulin (especially in the postprandial period). Such a mechanism is possible for the comorbid flow of CP from the MS with the subsequent formation of obesity due to the fact that cortisol stimulates cortisol-dependent lipoprotein lipase on the capillaries of the fat cells of the upper half of the trunk, the abdominal wall, and on the capillaries of visceral fat cells. As a result of increasing fat deposition, hypertrophy of fat cells and abdominal obesity develops [19].

It should be noted that hypertensive patients may develop in parallel with arterial hypertension, due to the fact that not only the expansion of adipose tissue activates the renin-angiotensin-aldosterone system, but also at the local level (at the level of the tissue of pancreas) in the CP, the regulatory function of this system is violated. Due to such a mechanism, the sensitivity to insulin is reduced, and in the future, after a certain period of time, the DM may develop. Its development can

contribute to the persistence of oxidative stress, which affects cellular signals, cell growth, proliferation and expansion of the intracellular matrix in the CP [19]. The excess of circulating aldosterone damages the function of β-cells of the pancreas, disrupts the transmission of insulin signal, increases the production of proinflammatory adipocyne by adipose tissue, forms endothelial dysfunction, which is of great importance for the development of arterial hypertension with such a comorbidity of the course of CP. In addition, together with insulin, glucagon, adrenaline and adipose tissue hormones, glucocorticoids, hormones of the thyroid gland, male and female sex hormones are involved in the regulation of endocrine processes in the CP. Their significance in the development of liver and liver steatosis is evident in recent years [25].

Therefore, in the course of the comorbid flow of CP and MC for clinical practice (treatment, rehabilitation), it is necessary to counteract the development and progression of insulin resistance, which subsequently affects the imbalance of not only carbohydrate but also fatty metabolism, promotes the development of liver and liver steatosis, endothelial dysfunction, atherosclerotic changes in cardiovascular system, which leads to serious complications. Moreover, the manifestations of MS in diseases of the digestive system, such as insulin resistance, dyslipidemia, obesity, hemodynamic disturbances, the tendency to hypokaligitis occur in 29.1-89.3% of cases. The highest percentages of obesity were found in 89%, dyslipidemia — 55%, metabolic ECG changes — in 45% of patients with CP in combination with gastroenterological diseases such as erosive gastritis, gastroesophageal disease (GERD), gallstone disease, chronic cholecystitis [15].

In addition, it has been established that endocrine disruptions affect the external secretion function of the gland, with its development of enzyme insufficiency, enteropancreatic, and subsequently trophological syndrome. It is important that the same process will also contribute to diabetes, steatosis, obesity (which are components of MS). Development of enteropancreatic syndrome, caused by external secretion insufficiency, excess bacterial growth in the small intestine, dysbiosis of the large intestine. In turn, it is believed that dysbiosis is also one of the mechanisms of the development of MS [18]. Violation of the depth of etching in the

duodenum and other parts of the small intestine contributes to the ingestion of food glands that are not prepared for disposal. That is, for the enzyme insufficiency at the CP, the hydrolysis of nutritional nutrients under the action of the small and pancreatic enzymes is insufficient, which results in the intake of insufficiently digestible proteins in the large intestine. As a result, proteolytic microflora is activated, which activates the processes of rotting, the formation of a large number of toxic substances (ammonia, mercaptopurines, indole, scalpel). Such processes lead to dysbiosis with the development of chronic low-intensity inflammation and to reduce the antiviral and antitumor immunity, hypovitaminosis. Early clinical symptoms of hypovitaminosis B1 and B6 from the digestive system are manifested by decreased appetite, nausea, constipation. From the nervous system, clinical symptoms are headache, irritability, memory impairment, drowsiness. In addition, in part of patients with CP (for example, at the CP of alcoholic genesis, MS), the permeability of the intestine increases, which promotes the translocation of lipopolysaccharide of gram-negative enterobacteria into the total blood flow. Following this, the tissue of the liver and lungs is damaged. Confirmation of such conclusion is experimental researches, which testify to the formation of large vesicles, the presence of immature zigogen granules, a sharp expansion of the endoplasmic reticulum of acinar cells [8]. The work of recent decades has shown that intestinal bacteria in a CP can trigger obesity, insulin resistance due to the activity of the lipopolysaccharide, which can cause inflammation through the formation of the CD14 receptor (TLR) complex, namely TLR4. Reducing TLR4 reduces obesity caused by insulin resistance. In this process, TLR2 is involved, its deficit contributes to the development of diabetic nephropathy, diabetic vasculopathy. It is precisely in such cases (especially for the comorbidity of CP with MS) the function of microbiota is important as a "metabolic organ," which affects energy homeostasis and body weight control, which requires appropriate analysis (for the correct treatment tactic). At the same time, nutrition is a key mechanism for modeling the intestinal microbial, which is important for the formation of a strategy for medical rehabilitation of patients with obesity [16].

According to L. B. Lazebnik and L. O. Zvenigorodskaya (2009), MS is the basis of polymorbidity in gastroenterology; characterized by changes in the structure

and function of the digestive system, which are caused by microcirculatory disorders and the absence of a clear clinical picture, as well as cross-sections of the syndromes. Microbes can affect the formation of eating behavior through the chain of “microbe — gut — brain” [9]. They synthesize the exact analogs of hormones that are involved in the mood, behavior of patients with CP and MS (yes, serotonin has an "intestinal" source of education) [13]. Consequently, the intestinal microflora is essential for normal metabolism, and a low calorie diet (especially prolonged) can change the intestinal microbiota in the negative direction (especially for the comorbidity of CP with MS).

It should be noted that a person microbiota reacts differently to the components of food, including the long-term use of products at the same composition, which was and is typical for patients suffering from CP. When making recommendations, it should be emphasized that bacteria like Bacteroides are positively correlated with protein rich foods, and Prevotella is associated with a diet rich in fiber [1]. In turn, the risk of developing obesity and type 2 diabetes is established in cases where the Firmicutes/Bacteroidetes ratio increases [3]. A decrease in the number of Bifidobacterium is observed in type 2 diabetes, obesity, and excess body weight. This is important for the design and development of an individual nutrition project, especially with the comorbidity of the CP with MS. But it is also important that the level of Bifidobacterium and Faecalibacterium prausnitzii correlates with anti-inflammatory action [1, 12] and can prevent the metabolic disturbances in patients with chronic instability in the presence of insulin resistance. A decrease in the number of Faecalibacterium prausnitzii was established for type 2 diabetes [21].

It is believed that the microflora suppresses the expression of 4-angiopoietin antagonist of lipoprotein lipase (LPL) in response to an excess of food intake, increases the activity of LPL and deposition of fat in adipocytes. Lipoprotein lipase (LPL) play a key role in the hydrolysis of triglycerides and release of fatty acids for transport to adipocytes. After entering adipocytes, fatty acids are re-esterified into triglycerides and stored as fat. In this case, fatty tissue, intestines, and liver secreted 4-angiopoietin LPT antagonist (FIAF), which prevents the accumulation and storage of triglycerides in the form of fat.

It is well-known that adenosine phosphate-activated protein kinase (AMRC) is an enzyme that plays an important role in energy homeostasis. So, in order to compensate for energy deficit, the activity of AMRC increases, fatty acid oxidation, glucose uptake, insulin secretion are stimulated, and cholesterol synthesis, triglycerides and lipogenesis are inhibited [26].

The microbial altered by the host suppresses the activity of AMRC, affecting the oxidation of fatty acids and becoming a factor in the formation of obesity and insulin resistance [23]. For example, high fat assimilation correlates with an increase in the gram-negative/gram-positive bacterial factor, which can lead to endotoxemia and metabolic stress, and to metabolic diseases such as CP and MS. Most often, the number of gram-negative Bacteroides-like bacteria, representatives of the Eubacterium rectal and Clostridium coccoides and bifidobacteria [24] is reduced.

Thus, in patients with CF with MS and intestinal dysbiosis, endotoxemia, which can be formed due to the microflora, causes depression of the reticuloendothelial system, inhibition of the antioxidant system of protection, the increase of modified lipoproteins in the blood. Synthesis of bile acids in this case decreases, and the metabolism of the liver switches to the synthesis of cholesterol [7]. Thus, in patients suffering from CF with MS formed “vicious” circle: violation of microecology of the intestine — accumulation of endotoxins — violation of enterohepatic circulation of bile acids — liver dysfunction — lipid metabolism disorders — fatty liver infiltration and pancreas, liver fibrosis — progression of dyslipidemia — maintenance and progression of intestinal dysbiosis [2].

Thus, the role of microbiota in metabolic disorders in CP can be considered in several aspects: as an adaptation factor (due to, for example, insulin, a pancreatic polypeptide) as a trigger factor that regulates energy metabolism, metabolism of carbohydrates and proteins with other endocrine organs, forming insulin resistance, atherogenic dyslipidemia (worsening the course of coronary heart disease, contributing to the development of abdominal ischemic disease in patients with CP and MS); as a factor without which the digestive process cannot occur (including in the stomach, duodenum and small intestine). But for clinical practice, it is very important to determine the nature of intestinal dysbiosis in such patients. It is divided

into defective, rotten, enzyme, fungal and dysbiosis, associated with sensory impairment. Dysbiosis, which is associated with excessive growth in the small intestine due to external secretion of the pancreas deficiency, is considered enzyme. It is often observed in irritable bowel syndrome (which is important for medical and rehabilitation measures in patients with comorbidity of CP and MS). Since chronic systemic inflammation is the only mechanism for the progression of such comorbidity, the decrease or loss of tolerance of the immune system to intestinal microbiote is also important. This reduces the number of probiotic bacteria, increases the number of potential pathogens, changes in intestinal motility, inflammation of the intestinal mucosa develops. Therefore, it is quite right to further investigate the role of microbiota in the formation of comorbidity/multimorbidity of CP and other diseases of internal organs with MS in order to differentiate treatment, prevention and rehabilitation of such patients.

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In this article, the authors analyze a number of known and probable mechanisms involved in the formation of metabolic disorders upon chronic pancreatitis in comorbidity with metabolic syndrome. The issue of involvement of pancreatic endocrine apparatus in development of insulin resistance upon chronic pancreatitis, namely, the role of such a hormone as insulin, is highlighted. The role of this hormone in development of disorders of fat metabolism, obesity and arterial hypertension is presented. The authors emphasize the role of adrenal hormones, estrogen in the pathogenesis of both diseases. The issue of effect of endocrine function disorders on the state of external pancreatic secretion with subsequent development of disorders in the microbiota composition is considered (which also contributes to the progression of both diseases).

The data on presence of a possible relationship between the composition, functional activity of the intestinal microbiota and development of metabolic syndrome, chronic pancreatitis are given. The significance of intestinal microbiota in the maintenance of various vital processes of a healthy person, food digestion, as well as synthesis, metabolism, recycling, utilization of various biologically active substances (vitamins, hormones, steroids, immunoglobulins) and elimination of toxins is revealed. The role of microorganisms in the formation of feeding behavior via axis “intestinal microbiome — intestine — brain” is analyzed. Modern ideas on the ability of microorganisms to provoke formation of metabolic disorders upon chronic pancreatitis are presented. The data confirming connection of certain dysbiotic changes (increased ratio of *Firmicutes/Bacteroidetes*, reduced number of *Bacteroidetes* and increased number of *Firmicutes*) with development of obesity,

overweight, type 2 diabetes mellitus (known risk factors of metabolic syndrome) is given. It is suggested to prevent formation of metabolic syndrome in chronic pancreatitis by increasing the number of specimens of *Bifidobacterium* genus and *Faecalibacteriumprausnitzii* strains in the intestine.