Important role of fat tissue hormones in development of comorbid chronic pancreatitis and obesity

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Key words: chronic pancreatitis, obesity, adipocytokines, low-intensity chronic systemic inflammatory response, type 2 diabetes mellitus, pancreatic cancer

To study the problem of lipid metabolism disorders in chronic pancreatitis, including obesity, in recent years attention has been paid not only to endocrinologists, but also to gastroenterologists [1, 3, 11], but a number of unresolved issues remain. For example, insufficient attention is paid to the consideration of the possible role of the pancreas (pancreas) in the development of metabolic and hormonal disorders in obesity, metabolic syndrome (MS), type 2 diabetes mellitus (DM 2 type), considering it as a universal organ implementing Not only exocrine, but also endocrine function.

In connection with violations in the activity of these functions in CP, both the secretory and incretory departments of the prostate are damaged, which is of great importance in the disturbance of homeostasis. Insufficiency of the endocrine function of the prostate is clinically manifested by the manifestation of metabolic disorders. It is believed that it is the endocrine cells of the pancreas that regulate the activity of the exocrine function. External obscure pancreatic failure (especially of mild and moderate severity) is observed not only in diseases of the prostate, including chronic heart failure, type 2 diabetes, but also in osteoporosis, uremia, after operations on the stomach, prostate, obesity and other pathological conditions.

The main clusters of obesity, MS, type 2 diabetes are the dysfunction of food-eating hormones, the functional state of the liver, the pancreas, microbial ecology of the small and large intestine. Accordingly, a number of problems arise that require a study of their role in the development and progression of certain syndromes and diseases. These include the activation of neuropeptides, the dysfunction of the endocannobioid system, eating hormones, the sympathetic nervous system, impaired release of insulin from the beta cells of the prostate, the violation of the processes of peroxidation and metabolism of liver lipids, the importance of free fatty acids in the development of insulin resistance (IR). In addition, attention is drawn to the study of the importance of microproteinemia, the interaction of hemostasis systems, the role of fibrinolysis, hyperuricemia, nitric oxide, adipokines and other cytokines that determine the common pathogenesis of CP and other diseases of the digestive, obesity, MS, and type 2 diabetes.

Manifestations of MS in diseases of the digestive system, such as IR, dyslipidemia of atherogenic origin, obesity by abdominal type, moderate arterial hypertension (AH), metabolic changes, disorders of central hemodynamics, tendency to hypocalygism occur in 29.1-89.3% of cases. The highest percentage of obesity (89%), IR (75%), dyslipidemia of the atherogenic profile (55%), metabolic changes on the ECG (45%) was recorded with CP, combined with erosive gastritis, gastroesophageal reflux disease (GERD), cholelithiasis, Chronic cholecystitis [10].

One of the hormones of the pancreas, which play an important role in the adaptive processes of the body, is insulin. It is a vascular hormone that in viable people causes vasodilation, and in pathological conditions (in the case of insulin resistance and hyperinsulinemia) vasoconstriction. Insulin is actively involved in lipid metabolism and energy [2], in the development of hypertensive syndrome, including by increasing sodium ion transporter expression in the epithelial sodium channels reduces the activity of Ca^{2+}-ATPase, thereby increasing the intracellular content of Ca^{2} in β-cells of the prostate, which contributes to the formation of compensatory hyperinsulinemia.

These processes first reduce the sensitivity, and then block the insulin receptors, and the glucose and fats that come with the food are deposited with the adipose tissue. This further reinforces the IR. Constant hyperinsulinemia depletes the secretory apparatus of the pancreatic beta cells, which leads to the development of a disturbance in the carbohydrate metabolism: from a moderate increase in the plasma glucose concentration firstly on an empty stomach, then after an alimentary load, and finally, to the development of type 2 diabetes. In turn, hyperglycemia causes impairment of the function of beta-cells of the prostate (the effect of glucose toxicity), closing the vicious circle.

On the other hand, hyperinsulinemia inhibits the breakdown of fats, which contributes to the progression of obesity. Studies have shown that a significant increase in the mass of visceral adipose tissue is combined with MS. It is noteworthy that unlike the fat tissue of the other localization it has a wider network of capillaries and directly connects with the portal system, providing opportunities for the systemic action of adipocytokines on the course of chronic systemic inflammation in the liver and the prostate [9].

Visceral adipocytes have high density β-adrenoceptor (especially β_3 types), and corticosteroid androgen receptor and relatively low for an alpha-2-adrenergic receptors and the insulin receptor. This determines the high sensitivity of visceral adipose tissue to the lipolytic action of catecholomines and low to the anti-lipolytic action of insulin (especially in the post-prandial period). The reasons for the development of abdominal obesity include age after 30 years, when the activity of the hypothalamus, the ACTH system with the release of cortisol increases, which leads to prolonged and excessive secretion. As a result, there is a characteristic fat

distribution resembling Cushing's syndrome. In parallel, there is arterial hypertension (AH) and a violation of glucose tolerance, with the possible development of diabetes. It is known that cortisol stimulates cortisol-dependent lipoprotein lipase on capillaries of fat cells in the upper half of the trunk, abdominal wall and visceral fat. As a result, fat deposition increases, fat cell hypertrophy and characteristic abdominal obesity develop [5, 12].

In turn, the expansion of adipose tissue activates the renin-angiotensin-aldosterone system, resulting in reduced sensitivity to insulin. As a result, persistent oxidative stress, which affects cellular signals, cell growth, proliferation and expansion of the intracellular matrix in CP [8]. Excess circulating aldosterone disrupts the transmission of the insulin signal to the cell and causes endothelial dysfunction, damages the function of the beta-cells of the prostate, reduces the sensitivity of skeletal muscles to insulin, increases the production of pro-inflammatory adipokines with fat tissue.

In addition, together with insulin, glucagon, adrenaline and hormones of adipose tissue, the regulation of endocrine processes involves male and female sex hormones, glucocorticoids, thyroid hormones.

The purpose of this review of the literature was to consider the role of fatty tissue hormones in the mechanisms of obesity development, including in CP, especially since in recent years obesity has been regarded as an independent etiological factor in the development of chronic pancreatitis and prostate cancer [6, 14]. This can be confirmed by the presence of specific transmembrane receptors to leptin, which are detected not only in adipose tissue, liver, kidneys, but also in the pancreas, heart and on the surface of platelets.

Adipokines, secreted by fatty tissue, are not just a reservoir of energy resources in the form of triglycerols (TG), but also a full-fledged endocrine organ.They participate in the regulation of appetite, thermogenesis, activity of pressor and hypotensive systems, in the metabolism of fats and carbohydrates, in stimulating the formation of pro-inflammatory cytokines, among which TNF-α is also considered an adipokine involved in the formation of chronic systemic inflammation.

The role of adiponectin and leptin in the pathogenesis of obesity has been studied to a greater extent. Adiponectin, a glycoprotein hormone discovered in 1995-1996, which uses myocytes and liver as the main targets of its influence, is sufficiently studied. In these tissues, it improves insulin sensitivity, has an anti-atherogenic effect. Adiponectin acts via the 5'AMP protein kinase (AMPK), which inhibits acetylcoenzyme-A-carboxylase and removes inhibition of β-oxidation by malonylcoenzyme A, increases the absorption of myocytes from fatty acids from blood and the rate of β-oxidation in muscles, stimulates glucose uptake and its catabolism in Muscles and liver.

Adiponectin has anti-inflammatory, angio, cardioprotective and antidiabetic effect. This is confirmed by a negative correlation with the level of glucose, insulin, TG, leptin, TNF-α (inhibiting its secretion). With decreasing adiponectin level, expression of TNF-α in adipocytes increases, contributing to the growth of MI of adipose tissue due to the expression of genes involved in the transcription of lipo- and adipogenesis factors.

It is believed that TNF-α, produced by fat tissue, lymphocytes and monocytes, is responsible not only for IR, the formation of a systemic slow chronic inflammation, but also for dysfunction of the beta-cells of the prostate, which is undoubtedly one of the main factors leading to the progression of lipoidosis, steatosis At association of CP with obesity, and type 2 diabetes. The activation of the production of this cytokine is influenced by the concentration of such an adipokin, such as apelin.

Apelin is a newly identified ligand for APJ receptors of the small intestine and hypothalamus, a propeptide containing 77 amino acid residues. It is split into several shorter peptides, which are ligands for the aphelin receptors. It is synthesized not only in adipocytes, but also in the stomach, heart, small intestine and hypothalamus. When injected into the ventricles of the brain, Apellin causes a decrease in food intake in both fed-up and hungry rats. These data confirm the possible role of apelin in the control of eating behavior [20]. The apelin-APJ complex is expressed in the gastrointestinal tract, affecting the exocrine function of the prostate, participating in the regulation of fibrotic processes in the liver, kidneys and heart. The hypothesis of the regulatory effect of the Apeline-APJ complex on fibrotic processes in the prostate is based on the detection of high expression of collagen-1-alpha, collagen 4, and protein levels in mice with CP. In contrast to the ability of apelin to inhibit the processes of fibrosis in the prostate, in the liver it stimulates them [22]. There have been studies indicating that amphetamine inhibits pancreatic activation of the transcriptional nuclear factor kappa-B in acinar and islet cells of the prostate [27], which demonstrates the protective effect of apelin on the prostate tissue in the presence of chronic low-grade inflammation. That is, the apelinergic system is an important component that allows to stop inflammatory and fibrotic changes in CP [18], caused (including) by hypoxia, ischemia of the organ [17]. Some authors consider the system "apelin-APJ as the main mediator of oxidative stress in various tissues, including in endotheliocytes, which suggests that the endogenous peptide apelin can be a factor in the appearance of pathologies associated with the mechanisms of development of not only non-alcoholic liver disease, steatosis Pancreas, but also the formation of MI, obesity, MS, type 2 diabetes. Its role in the formation of cardiovascular pathology (myocardial hypertrophy, heart failure, arterial hypertension, especially in type 2 diabetes) is noted, which is important for the treatment of the mechanisms

determining the clinical picture of CP associated with obesity, type 2 diabetes, MS, taking into account complications from the side Concomitant diseases.

An increase in the volume of visceral adipose tissue results in a systemic release of the resistin protein and pro-atherogenic interleukins. Enriched with cysteine 12.5 kDa, the resistin protein and molecules similar to it are a family of proteins that take part in the processes of inflammation and the development of resistance to insulin. It is an antagonist of adiponectin. It has both a paracrine and a telekinic action, since it has receptors, both in the adipose tissue itself and in the liver. The level of resistin increases with increasing body weight. A direct relationship between the level of resistin and levels of low-density lipoprotein (LDL), triglycerides, fasting glucose, C-reactive protein (CRP) and anthropometric data (BMI, waist and chest circumference), and a reverse relationship with the level of high-density lipoproteins (HDL), which is very important for clinical practice. The potential role of this adipokine as a link between obesity and type 2 diabetes is discussed [25], because in the conditions of hyperinsulinemia and a decrease in insulin sensitivity in adipose tissue, especially visceral, lipolysis is increased and the delivery of free fatty acids to the liver is increased. The liver is the first target organ of resistance, leading to the development of hepatic insulin resistance [13]. As a result, LDL cholesterol is increased, hypertriglyceridemia is formed and the content of HDL cholesterol is reduced (which is an "atherogenic triad"). Therefore, resistin can serve as an indicator for determining the severity of insulin resistance, obesity, atherosclerosis, the intensity of systemic inflammation and in comorbidity with CP.

Resistin serves as a promoter of fat cell maturation and acts as an autocrine regulator of prodiabetesogenic factors in adipose tissue. In addition, this adipocyte-specific hormone can be characterized as a proliferative, anti-apoptotic, proinflammatory and proangiogenic regulator [15, 16].

Resistin was isolated in 2001. It is secreted predominantly by preadipocytes, to a lesser extent — by mature adipocytes of abdominal localization and macrophages [26]. It is the activated macrophages that are the source of adult serum resistin, but the prerequisite is the presence of TNF-α and IL-6 cytokines [19, 21], which supports not only the local (in adipose tissue) but also the systemic nature of the chronic Low-level inflammatory process.

To date, the points of application of such hormones of the prostate as adipoline — a new adipokine, possessing anti-inflammatory and glucose-lowering properties, regulating the metabolism of carbohydrates and lipids in the liver and adipose tissue and reducing systemic inflammation have been discovered and are being studied.

The interest is represented by visfatin — a protein hormone, discovered in 2004. It is produced by visceral adipocytes and acts on those tissues in which there

are insulin receptors, although its receptors are different from insulin. Consequently, these synergistic hormones do not compete for binding sites on the membranes of target cells. Wisfatin stimulates the phosphorylation of intracellular proteins by tyrosine, including insulin receptor protein substrates. Its level increases in proportion to the degree of obesity, it controls the expression of adiponectin [24]. In a recent study, it has been shown that wisfatin activates human lymphocytes, enhancing the production of pro-inflammatory cytokines IL-1β, TNF-α and IL-6, as well as the synthesis of co-stimulating transmembrane molecules CD54, CD40 and CD80 [23].

Based on the published literature, most of the visceral adipose tissue hormones affect the prostate tissue through the immune system reaction, supporting the persistence of chronic systemic inflammation. Along with others, these include fatty tissue hormones such as leptin, resistin, wisfatin, adiponectin, adeline, adipolin. Various factors leading to the development of inflammatory changes with the death of acinar cells and the replacement of their adipocytes, contribute to the formation of fatty replacement (replacement — fatty replacement) with the subsequent development of steatosis of the prostate.Steatosis is a broader concept that includes parenchymal fat distribution (in acinar and islet cells), as well as RV lipomatosis, including that caused by inflammatory changes occurring in the organ. The development of such processes can eventually lead to the formation of fatty disease of the prostate. The term nonalcoholic fatty disease of the prostate gland predisposes the relationship of this state with obesity and other components of the metabolic syndrome, excluding congenital pathology. In this regard, apparently, non-alcoholic fatty disease of the pancreas should be on a par with non-alcoholic fatty liver disease an integral part of the metabolic syndrome [4, 7, 13]. This opinion is also supported by a significant increase in the number of patients with MI on the background of steatosis of the prostate. In this case, the conjugation of steatosis and dysfunction of the insular apparatus is considered against the background of the triglyceride-induced lipotoxic effect. We also consider the possibility of paracrine exposure to adipocytes on the insular apparatus of the prostate and the formation of dyslipidemia as mechanisms of the combined course of CP and obesity. The data presented show sufficient activity and increased research on the association of pancreatic steatosis, level of adipocytokines and endocrine pancreatic function in the context of a possible pathogenesis of non-alcoholic fatty disease of the pancreas and its involvement in the progression of MS.

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Aim of this paper is to consider the role of hormones of the adipose tissue in mechanisms of obesity, metabolic syndrome, type 2 diabetes mellitus upon chronic pancreatitis.

Materials and methods. The literature review indicates the value of visceral fat in the development of insulin resistance, dyslipidemia, including atherogenic one, taking into account the possible infiltration of pancreatic tissue by adipocytes. Participation of some adipocytokines of adipose tissue in the development of obesity upon chronic pancreatitis is highlighted. It is shown that in some cases the hormones of visceral adipose tissue, penetrating through the portal vein to the liver and then to the pancreas, aggravated the course of systemic chronic inflammation of the inherent chronic pancreatitis, promote steatosis and development of fatty pancreatic disease.

Conclusion. Literary sources indicate the leading role of visceral adipose tissue and its hormones in the formation of obesity in chronic pancreatitis. Due to the infiltration of the pancreatic tissue by adipocytes, lipoidosis and steatosis develop. With the progression of the process type 2 diabetes mellitus, fatty liver or pancreatic disease, or cancer of these orhans. Consequently, there is a need for serious differentiated preventive and curative measures aimed at promoting a healthy lifestyle to improve the quality of life of patients suffering from chronic pancreatitis.