Pathogenetic aspects of lipid metabolism disorders upon chronic pancreatitis, approaches to their correction

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There are tendencies of integrative approach in medical science to the study of the pathogenesis and ways to optimize the diagnostics and treatment of many diseases. Among this nosology there are diseases due to metabolic disorders, including lipid homeostasis [1, 2]. These are definitely diseases such as atherosclerosis, gallstone disease (GSD), polyposis, dyskinesia of gall bladder and bile ducts, steatosis, angiogenic cochleovestibulopathy, diabetic angiopathy, digestive disorder syndrome, chronic pancreatitis (CP) and others [11]. Practitioners focus on lipid status primarily in cardiovascular diseases, endocrine disorders, obesity, atherosclerosis. But deep metabolic disorders, including lipid occur upon diseases of gastrointestinal tract.

It is known that the pancreas is an active and powerful regulator of many biological reactions in the body, so any pathological and functional changes even it always lead to varying degrees of severity of metabolic disorders. Changes in lipid metabolism, regardless of the underlying disease, are often associated with the so-called lipid triad: increased very low density lipoproteins (VLDL) or triglycerides (TG), atherogenic low density lipoproteins (LDL) and decreased high density lipoproteins (HDL). This triad underlies the pathogenesis of many diseases as well as oxidative stress in general. The scientific observations proved that lipotoxicity is a natural phenomenon with dyslipidemia, usually is associated with insulin resistance (IR), metabolic syndrome (MS) and diabetes mellitus (DM) type II.

In recent years, internal medicine clinic introduced the term "lipid distress syndrome" (LDS), which is also seen as a systemic metabolic process or system in the pathological reaction based on lipid metabolism (hyper- and dyslipidemia) [2, 7

9]. LDS phenomenon includes pathobiochemical and postmortem processes that go beyond a single body, causing the emergence of new or progression of existing disease. LDS consists of the many combined pathologies (ischemic heart disease, atherosclerosis of the arteries of the lower extremities, gall bladder cholesterosis, GSD, lipogenic pancreatitis, steatosis) [3]. All of these diseases have common etiopathogenetic factor — lipid imbalance and common pathogenetic mechanism — IR, which is a kind of marker of obesity, metabolic syndrome, diabetes, CP and others. Study proved that one of the early clinical manifestations of LDS was cholesterosis of gall bladder with violation of its motor-evacuation function disorder accompanied by synthesis of bile in the liver and slow arrival in the intestine [5, 12 13]. Out-bladder cholesterosis localization occurs, particularly in bladder duct, Wirsung's duct, which is the cause of CP, and therefore exocrine pancreatic insufficiency [10]. In the pathogenesis of hyperlipidemic pancreatitis also important vascular obstruction gland fat lobules, fatty acinar cells, cytotoxic emergence of a large number of free fatty acids (FFA), resulting from intensive TG hydrolysis under the influence of lipase [5]. Abdominal obesity is often accompanied by LDS and are pathognomonic sign of MS. MS is closely associated with LDS, they mutually cause each other and share many etiopathogenetic mechanisms, according to study interesting in light of the emergence and progression of many diseases and CP in particular.

In-abdominal visceral obesity dyslipoproteinemia is shown by increased levels of fatty acids, hypertriglyceridemia, lowering HDL cholesterol, increased LDL cholesterol levels, apolipoprotein B, increased ratio of LDL/HDL cholesterol. The fact is that LDL and VLDL reduce insulin production by cells of islets of Langerhans of the pancreas. Apolipoprotein B has contrinsular effect, which is common with insulin antigenic determinants and possibly competing with him for the specific insulin receptors [18, 19]. This phenomenon deepens IR and creates a vicious circle in the emergence of multiple pathological processes that union of the lipid metabolism, and often the clinical manifestations of MS.

Metabolic syndrome or syndrome X is an interdependence of number of metabolic (including carbohydrate and fat metabolism) mechanisms regulating blood pressure caused by IR [8]. Thus, MS is a set of not only metabolic but also clinical and hormonal disorders that is a factor of cardiovascular diseases, which are based on IR andcompensatory hyperinsulinemia [4].

Definition MS includes five features, including two types of dyslipidemia: increased TG ≥1.7 mmol/L and reduction in HDL cholesterol <1.29 mg/L in women and <1.03 mmol/L in men. The level of LDL cholesterol in MS usually normal or only slightly elevated [17]. Predictive factors of MS are overloading the diet of carbohydrates and fats. A special role is played by frequent carbohydrate intake against the backdrop of reduced physical activity, reducing the translocation of glucose transporters in muscle. The well-known fact that muscle glycogen is consumed only during exercise. Increased flow of carbohydrates from food, amid falling energy costs and depletion of glycogen-depositing liver function result in liver and muscle incapability to deposit glucose in the form of glycogen. This causes hyperglycemia and stimulating the formation of fat (of glucose in the liver is converted into fatty acids, TG, HDL, which are part of LPN into the blood). Excessive fat intake leads to inactivity background to increase the total body fat mass which modifies the hormonal balance in the body, which in turn contribute to the progression IR and disorders of glucose and lipid metabolism [6, 10 15]. If obesity is an external sign of abuse weight gain, hyperglycemia and dyslipidemia then are the main biochemical criteria for MS [14].

Study on pathogenesis of MS has been allocated its main criteria: IR, hyperinsulinemia (compensatory), impaired glucose tolerance (later hyperglycemia — glucose in plasma glucose >6.1 mmol/L), abdominal obesity (waist circumference (OT) >80 cm in women and >94 cm in men, BMI more than 25 kg/m^2 in women over 27 kg/m^2 in men), hypertriglyceridemia, low total cholesterol, hypertension, coronary heart disease, microalbuminuria, hyperuricemia, decrease in blood fibrinolytic activity, hiperleptynemiya and resistance to leptin. Population studies conducted in Italy showed that IR is observed in 84% of patients with

hypertriglyceridemia, 42% — from hypercholesterolemia, 95% — from MS. It is important that hyperinsulinemia in MS suppresses the breakdown of fats, contributing to the progression of obesity [11]. Many researchers believe that the development of MS disrupted hormonal homeostasis with a tendency to increased levels of estrogens and androgens in the blood. Upon the increased level of estrogen atherogeniclipid profile is formed in the blood. Bile with which exogenous cholesterol is released, leads to cholesterol supersaturation, which leads to the formation of microlites, and later concretions, and due to constant trauma zone major duodenal papilla develops stenosis. Stenosis is the cause of pancreatic intraductal hypertension and obstructive of CP. And at the prevalence of high levels of androgens in the blood, atherogenic lipid profile is created. Obesity as a component of the metabolic syndrome reduces exocrine pancreatic secretion through fatty acinar cells or organ lipidosis [5].

It should be noted that researchers often use term dysmetabolic forms of CP, which are often observed in diabetes, hyperlipidemia, hemochromatosis, hyperparathyroidism and others. These CP forms are ignored by practitioners and therefore are diagnosed at later stages of the disease [16].

Based on the above it can be argued that the study of the nature and depth of the lipid metabolism in patients with CP and their pa poured upon further progression in the pancreas torpid inflammation, fibrosis of tissue and functional organ failure is very important and requires in-depth study. This prompted us to a more detailed study of this problem.

Therefore, a set of measures for diagnosis CP regardless of etiology should include determination of lipid homeostasis. For this purpose, determine the content of total cholesterol plasma TG, HDL and LDL cholesterol, atherogenic factor, as the level of serum enzymes, glucose and glycated hemoglobin. A comprehensive treatment of CP different genesis, because of pathological amendments in lipid homeostasis, which are often important for the future nature of the disease, should also include the correction of lipid metabolism.

It is known that atherosclerosis essential with modified LDL, the seizure of which monocytes and macrophages via receptors leads to the formation of foam cells and is the basis for the formation of atherosclerotic plaque. Pathomorphological changes that occur in the pancreas on LDS background, are similar to those in atherosclerosis. That is, given the data, we can talk about the unity of the pathogenesis of metabolic links of CP and atherosclerosis, so the approach to treatment may have common links.

Inhibitors of HMG-Co reductase or statins are considered the most effective treatment for hyper- and dyslipidemia nowadays. Given the rapid progress in the pharmaceutical industry, many manufacturers improve chemical formula of this group of drugs, which increases their safety profile, eliminating the side effects that limit their use still in wide practice. The richest base from clinical trials with good results and convincing efficacy and safety belongs to rozuvastatin and atorvastatin, which are essential tools in the LDS with proven clinical efficacy.

The use of statins in CP of lipid metabolism is poorly understood, and forecasting the impact of such therapy on the further course of CP certainly important.

Analyzing all the above-mentioned, we can conclude that the pathogenetic approach to CP therapy should be based on a deeper understanding of the pathogenetic role of metabolic changes in the body, including the LDS. Complex treatment of CP should include means to correct metabolic disorders that should help not only change the course of the disease, but also to prevent related functional and organic changes, both in pancreas and in other organs.

The study of statins in the treatment of CP with LDS will enable to take many challenges — this is an opportunity of optimizing the diagnostic algorithms and integrated treatment programs of CP combined with LDS, development of system of effective control of the such a treatment, which should consist of two stages — correction of lipid homeostasis and treatment of damaged and target organs — namely the pancreas. This approach, in our view, could contribute to halting the pancreatic tissue destruction, reduce depth of inflammatory changes and

fibrosis in it, reduce the frequency of CP exacerbations, would allow to monitor the severity of clinical manifestations of CP and comorbidity, improve the quality of life of patients, reduce the incidence of complications and cases of disability in CP.

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The basic aspects of lipid metabolism and influence of lipid disbalance on development of morphological and functional changes in pancreas in patient with chronic pancreatitis is described. The new approaches in the complex treatment of chronic pancreatitis with correction of lipid homeostasis were offered basing on the pathogenetic mechanisms of different pathologies, developed due to metabolic imbalance including dislipidemias.