

# CLINICAL AND FUNCTIONAL STATE OF THE PANCREAS IN PATIENTS WITH METABOLIC SYNDROME (LITERATURE REVIEW)

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**Key words:** metabolic syndrome, atherogenic dyslipidemia, pancreatic steatosis, insulin resistance, functional state of the pancreas

Diseases of the digestive organs upon the metabolic syndrome (MS), such as non-alcoholic fatty liver disease (NAFLD), cholesterosis of the gall bladder gastroesophageal reflux diseases and other dedicated are described in numerous exploring the pathophysiological mechanisms of their development, clinical and diagnostic criteria, presenting approaches to therapy [1, 3, 19, 22]. However, clinical and functional state of the pancreas in MS has been insufficiently studied. The literature presents a small number of works, mostly review articles or experimental work, in which little attention is paid to the clinical and functional state of the pancreas in MS [2, 5, 35]. Thus, the data of the research presented in the works are controversial.

Functional state of the pancreas has a significant share in the development of the basic components of MS (hyperinsulinemia, insulin resistance (IR), impaired glucose tolerance) and, vice versa, the existing metabolic changes (obesity, atherogenic dyslipidemia) contribute to disruption of the endocrine and exocrine pancreatic functions.

## **Etiology and pathogenesis**

In most papers devoted to MS obesity is considered as its main pathogenetic factor [3, 13, 35]. Obesity, especially visceral (or central), is important for the development of many components of MS. This is due to the fact that it is visceral adipose tissue is richer supplied with blood and innervated unlike subcutaneous one. Adipocytes of visceral adipose tissue, having a high sensitivity to catecholamines lipolytic action and low one to antilipolytic effects of insulin, secrete free fatty acid (FFA) directly into the portal vein. High concentrations of free fatty acids on the one

hand, become a substrate for the formation of atherogenic lipoproteins, on the other hand — interfere with the binding of insulin to the hepatocyte, which leads to hyperinsulinemia and potentiates IR [3, 6, 7].

However, in clinical practice, there are cases when the obvious normotrophic ( $\text{BMI} < 27 \text{ kg/m}^2$ ) has high amount of abdominal fat and the risk factors for cardiovascular disease are present [26, 34]. In contrast, patients with increased nutrition ( $\text{BMI} > 27 \text{ kg/m}^2$ ) have normal amount of abdominal fat and there are no [44, 51] metabolic risk factors for cardiovascular disease and diabetes, i.e. there is a "metabolically normal" obesity. This proves polyetiology of MS and its components, respectively, including the clinical and functional state of the pancreas, which underscores the relevance of the above-described problems.

According to some researchers [10, 37], there is a clear relationship between excessive consumption of high-calorie foods containing fats and steatosis of the pancreas. This is the so called external factors that lead to obesity. Along with this, there is a genetic predisposition to the development of obesity or IR. In the literature, there is still no consensus about the root cause of the cascade of metabolic disorders. So, according to some authors, the primary is a genetic predisposition to obesity and IR, which is implemented in low physical activity and excess nutrition, and leads to compensatory hyperinsulinemia [21]. In turn, hyperinsulinemia blocks insulin receptors resulting in exogenous carbohydrates and fats being increasingly deposited by adipose tissue, and lipolytic processes are slowed down. Obesity progresses, and a vicious circle is closed. Permanent hyperinsulinemia drains  $\beta$ -cells of the pancreas, which sooner or later leads to impaired glucose tolerance (IGT), and then to the development of diabetes mellitus (DM).

Lipid metabolism disorder appears in atherogenic dyslipidemia, in which there is a significant increase in the concentration of FFA in the parenchyma of the pancreas, which in turn leads to both reduced activity of insulin and dysfunction of  $\beta$ -cells and mainly to their apoptosis as evidenced by the number of studies [3, 17]. Furthermore, high blood levels of free fatty acids contribute to an increased formation of nitrogen oxide, which in turn leads to apoptosis of  $\beta$ -cells. The increased activity

of the free radical oxidation of lipids (lipid peroxidation), which are also toxic to cells of the pancreas, leads to the progression of pancreatic lesion with violation of its endo- and exocrine functions. It should be noted that the amplification of degree of pancreatic obesity is associated not only with an increase in free fatty acids, but also with other cytokines, such as interleukin-6, leptin, adiponectin, and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ). Moreover, the latter has a direct cytotoxic effect on  $\beta$ -cells, especially in combination with other cytotoxins. [17] Along with this, atherogenic dyslipidemia is also a cause of hyperlipidemic pancreatitis, based on the fat embolism in conjunction with a massive FFA influence on tissue, but usually it is an acute pancreatitis.

Research results of morphological changes of functional state of the pancreas are in many experimental studies [9, 31, 35]. One of the postulates of these theories is that the hydrolysis of triglycerides of pancreatic lipase and the accumulation FFA in the pancreas take place. In its turn, FFA both affect cells of the pancreas, and damage the capillaries of the pancreas. As a result of ischemia, an acidic environment (acidosis) is created which enhances the toxicity of FFA. The authors also detect another important point — it is increased blood viscosity due to high levels of chylomicrons, which may cause a violation of the microcirculation in the pancreas and its ischemia. In these experimental studies, in experimental animals (mice, rats) receiving a special diet rich in fat, a significant association between diet and steatosis of the pancreas was shown, with subsequent development of  $\beta$ -cell dysfunction and the formation of type 2 diabetes [15, 35]. In the experimental animals suffering from obesity, pancreas contained more total pancreatic fat, triglycerides, FFA, but significantly less the phospholipid and cholesterol as compared to mice with unchanged body weight. In view of the fact that FFA are peroxidation substrates, thus contributing to the violation of the integrity cell membranes of cells of the pancreas, while increasing the production of proinflammatory cytokines (TNF- $\alpha$ , IL-6, IL-8), researchers assumed that the identified differences could be related to pro-inflammatory activity of adipose tissue.

In a research on the genetic study of fatty degeneration of the pancreas, Y. T. Chang et al. [12] provides data on the presence of specific genes associated with hypertriglyceridemia. It is also noted that the mutation of these genes along with polymorphism of TNF- $\alpha$  are independent markers of risk for hyperlipidemic pancreatitis in Chinese population. According to some reports, only in rare cases, a genetic mutation of lipoprotein lipase is revealed [43].

Therefore, we can assume a completely different way of development of fatty degeneration (steatosis) of the pancreas, which in turn proves its polyetiology (from the banal excess nutrition associated with the eating behavior of the patient to prior violations at the gene level) [1, 3, 14].

### **Clinic and diagnostics**

Changes in the pancreas in MS, basically, are diffusive. Steatosis of the pancreas is usually combined with subacute inflammation of organ under the influence of various pancreatogenic factors (such as alcohol, medications, gallstone disease in a history). It should be noted that the development of steatosis in the pancreas most often occurs on the background of MS presence [16].

In the clinic steatosis of the pancreas is often associated with steatosis of the liver (NAFLD), gastroesophageal reflux disease, gall bladder cholesterosis, chronic ischemic disease of the digestive organs, cardio-vascular diseases.

In rare cases, patients with steatosis of the pancreas do not complain. In most cases, patients complain of epigastric pain associated with the intake of fatty foods, bloating, diarrhea. Pain occurs in 30-40 minutes after eating, and radiates to the back. These patients are characterized by abdominal type of obesity [3, 7]. While skin examining, xanthomas can be found, especially on the upper eyelids, elbows folds. Optometrist may reveal characteristic changes of the retina and corneal, inducing thinking about long-term lipid metabolism disorder [47].

In the biochemical analysis of the blood dyslipidemia is revealed, mainly due to hypertriglyceridemia, and low level of amylasemia. According to the literature, patients are at risk of acute hyperlipidemic pancreatitis, if triglyceride concentration of serum is greater than 1000 mg/dL [25].

Laboratory signs of the exocrine pancreatic insufficiency include steatorrhea and decreased fecal elastase activity. Clinical and laboratory evidence of endocrine disease are impaired carbohydrate tolerance, diabetes, frequent infections.

With the advent of high technology diagnostic methods, namely, computed tomography (CT) [42, 48], magnetic resonance imaging (MRI) [32, 36] and ultrasound [50], it became apparent that the increase in abdominal fat was a prerequisite for the development of MS, and, in retrospect, showed its connection with the initial manifestations of MS (IR, carbohydrate metabolism disorders, hypertension) [20 29].

According to the literature, there was a high correlation between steatosis of the pancreas, age of the patient, the development of subcutaneous fat and body weight of the patient [40, 52].

Diagnostic criteria of lesions of the pancreas in MS, according to radiological methods of study, are: increase in the size of the pancreas, dilatation of the main pancreatic duct greater than 2 mm, increased echogenicity of the pancreatic duct wall, uneven contours of the pancreas, pancreatic parenchyma heterogeneity, retention cysts and pseudocysts, focal acute pancreatitis, intraductal filling defects, stones and pancreatic calcifications, obstructions and strictures of the pancreatic duct.

Upon ultrasonography (US) of the pancreas for its steatosis, some researchers compared its echogenicity with the liver echogenicity [23, 52]. Others compared the echogenicity of the pancreas with the kidney, as considered kidney metabolically less active than the liver, which in addition had a different echogenicity [18, 41]. Ultrasound reveals steatosis of the pancreas as uneven increased echogenicity combined with some indistinct internal structure of the body (reducing internal granularity) and blur contours. Interpretation of the above ultrasound criteria of steatosis contains an element of doctor's subjectivism compared to the method of calculation of densitometric parameters obtained in the CT study.

Assessing the state of the pancreas in MS during CT of the abdomen, a decrease of densitometric indices of its tissue is defined (below 30 units Hounsfield), as well as the presence of characteristic fatty layers in the structure of organ [7].

More common is a prevalent steatosis of the pancreas. On the scans it looks like weakening of the signal. "Local forms" are less commonly observed that requires differential diagnostics with focal lesions of the pancreas. Usually they occur in the body and tail of the pancreas, rarely — in the head. Difficulties of differential diagnostics of pancreatic steatosis from focal lesions of the pancreas are detected in mild steatosis. In this regard, CT is not regarded as the only one reliable method of research. In such cases, to clarify the diagnosis of steatosis of the pancreas, MRI is used, allowing more accurate confirmation of the presumed pathology.

Nowadays computer-based assessment (CT and MRI) of abdominal fat is popular and the most accurate. Methodology for quantifying abdominal fat is to measure the fat layer at the level of the umbilicus (4-5 lumbar vertebrae). However, some authors present a high correlation between the number of abdominal fat and steatosis of the pancreas as compared to BMI [1, 11, 38, 49].

It should also be noted that in more than 2/3 of the clinical cases combined lesion of the liver and pancreas occurs, which is an early marker of MS detection and IR development [16].

### **Approaches to the treatment**

Therapy of the pancreatic steatosis in MS is presented by many authors [28, 54]. They are mostly connected with correction of dyslipidemia by diet, drugs, or by the use of plasmapheresis.

The diet consists of full exclusion of animal fats, limitation of vegetable fats and carbohydrates, increasing foods rich in fiber.

Among the preparations, lipid-lowering drugs are used, such as statins and fibrates. These drugs reduce the level of triglycerides by 40-60% and increase the concentration of high density lipoprotein [4, 33, 53].

Some studies suggested using the insulin and heparin to enhance lipase activity [24, 27]. Insulin activates proteinlipase, while heparin enhances the release of endothelial lipase, thereby strengthening mutual observed effects of both components on lipid metabolism. It is primarily used by intravenous or subcutaneous

administration of heparin at a dose of 5000 Units twice daily on the background of intravenous insulin on the basis of hyperglycemia indices.

Example of conducting the procedures of plasmapheresis to reduce hypertriglyceridemia was first reported by D. J. Betteridge et al. in 1978 [46]. In that case, in 35-year-old woman with diabetes and TG=7120 mg/dL, the used method provided the normalization of TG levels in 2.5 hours. Many applications of plasmapheresis in hyperlipidemia have been described since that time [28, 30, 45]. Except reduced hyperlipidemia, restoration of insulin sensitivity and normalization of carbohydrate metabolism as MS component were observed during plasmapheresis [39]. Reduction of hyperlipidemia or its normalization leads to the removal of the potential damage to the trigger of the pancreatic lesion — low density lipids. Regular use of "prophylactic" plasmapheresis in 4 weekly intervals, the simultaneous use of lipid-lowering therapy and diet can reduce the risk of developing complications of MS, and sometimes prevent the further development of fatty degeneration of the pancreas.

### **Conclusion**

The above-stated indicates MS contingency with steatosis of the pancreas. On the one hand, fatty disease of the pancreas plays a crucial role in the development of metabolic disorders with the formation of the insulin resistance syndrome, on the other hand, hyperinsulinemia, hyperglycemia, and dyslipidemia, as well as microcirculatory disturbances, aggravate the state of the pancreas. Inflammation is a trigger of progression of the pancreatic pathology in metabolic syndrome, closely accompanied with fatty infiltration of the organ upon obesity. Changes in the pancreas, that are typical of metabolic syndrome, are not only secondary on its background, but also contribute to the progression of this syndrome and the development of complications, thus closing a pathogenetic circle.

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