Exocrine pancreatic insufficiency in diabetes mellitus: frequency, pathogenesis, diagnosis, treatment

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The pancreas is a unique organ with an extremely complex anatomical and physiological organization. The simultaneous existence of tissues with endocrine and exocrine activity required years of research to study the functional relationships between these two parts of the organ. Both from a physiological and clinical point of view, it is much easier to study the external and intrasecretory functions separately. Therefore, for many years the exocrine part of the pancreas (acini) was studied by gastroenterologists, whereas the functional activity of the endocrine regions (islets) was an area of keen interest of diabetologists. However, at the present stage of development of medical science comes the understanding that these different departments of the pancreas are part of one body, therefore, the violation of the exo-and endocrine function should be considered holistically, within the so-called "acinar-islet-acinar" (AIA) axis [56, 57].

At present, all scientists and doctors perfectly understand the mechanisms of the occurrence of the secondary, i.e. pancreatic diabetes mellitus (DM) in patients with chronic pancreatitis, also called type 3 diabetes. But the position that the exogenous function of the pancreas may suffer for the second time in diabetes is less known. Let us examine the situation, the reverse pancreatogenic diabetes.

Indeed, a large number of patients with diabetes have a significant decrease in not only the endocrine, but also the exocrine function of the pancreas, which was first shown by H. Pollard et al. back in 1943 [58]. Moreover, patients with diabetes have rather pronounced morphological changes in the exocrine pancreatic tissue [34]. The pathophysiological mechanisms leading to the development of exocrine pancreatic insufficiency have not yet been fully studied, but nevertheless, the basis of this deficiency is mainly a violation of the interaction between the endo- and exocrine structures of the organ.

In most studies, it is noted that the degree of exocrine pancreatic insufficiency in diabetes is more often mild or moderate, and severe insufficiency with steatorrhea is relatively rare. Despite this, in patients with diabetes, a shift in the maximum absorption of nutrients into the distal small intestine has been proven, which is typical of EPI. The increase in the volume of nutrients entering the ileum, contributes to the violation of its motility and secretion, and, consequently, the appearance of symptoms of intestinal dyspepsia (spastic intestinal pain, flatulence, rumbling, impaired stool) [32, 33, 40, 43, 44]. These symptoms are often mistaken for diabetic gastro-, entero- and colopathy, while in some cases they are associated with exocrine pancreatic insufficiency [3, 11, 65]. This forces us to more carefully analyze the pathogenesis and means of treatment of exocrine pancreatic insufficiency, which has developed as a result of diabetes.

Features of the structure and normal physiology of the pancreas

The functionally active parenchyma of the pancreas, represented by acini and islets, synthesizes a large number of various hormones. It is known that a healthy adult pancreas contains about 1 million islets scattered throughout the body. One islet contains, on average, about 5,000 endocrine cells, including cells that synthesize and secrete insulin, amylin (β-cells), glucagon (α-cells), somatostatin (δ-cells), pancreatic polypeptide (PP) and adrenomedullin (PP / F-cells). Their number in the pancreatic islets is, respectively, 68%, 20%, 1% and 2%. Recently ε-cells producing ghrelin have also been discovered. Each hormone produced by the pancreas is of great importance for the body. Thus, insulin secreted by β-cells is involved in the regulation of exocrine secretion of the pancreas: it stimulates the basal secretion of amylase and potentiates secretagog-stimulated secretion of amylase [67]. In vivo, the inhibitory effect of glucagon on

pancreatic secretion has been proven; it is assumed that this effect may be mediated by stimulation of the release of somatostatin. Somatostatin is found in the pancreatic δ-cells, small intestine and nerve terminals. It inhibits exocrine secretion of the pancreas in the islet-acinar axis, but the mechanism of this inhibitory effect is still being studied [67]. According to one theory, the paracrine messenger somatostatin directly inhibits the function of acinar cells by binding to somatostatin receptors on their surface; according to another version, this hormone has an indirect effect, inhibiting the release of secretin, cholecystokinin and insulin [67]. Pancreatic polypeptide (PP) enters the bloodstream only after eating. On an empty stomach, endogenous PP is released cyclically and its release into the blood is closely related to the activity of the cyclic migrating motor complex in the duodenum (duodenum). Intravenous administration of PP leads to the suppression of basal and stimulated pancreatic secretion of amylase and bicarbonates. Currently, ghrelin is recognized as a strong inhibitor of pancreatic amylase secretion, it also has the ability to inhibit the release of insulin. Amylin, synthesized in β-cells in response to food intake, is considered a potent inhibitor of stimulated pancreatic enzyme secretion. Pancreastatin, found in the α-, β- and δ-cells of the islets, inhibits the release of insulin induced by various physiological and hormonal stimuli. Several more inhibitory hormones are known: peptide YY suppresses secretin- and cholecystokinin-stimulated pancreatic secretion, and adrenomedullin inhibits insulin secretion. Cholecystokinin, which stimulates insulin secretion, is able to regulate the contractility of the gallbladder and exocrine secretion of the pancreas, and as a neuropeptide, it affects the level of anxiety, satiety and other behavioral responses [67].

An important feature that ensures the harmonious functioning of the exo- and endocrine parenchyma of the pancreas is the unique blood supply system of the organ, which allowed scientists to declare the existence of the so-called insulo-acinar vascular system (Fig. 1).

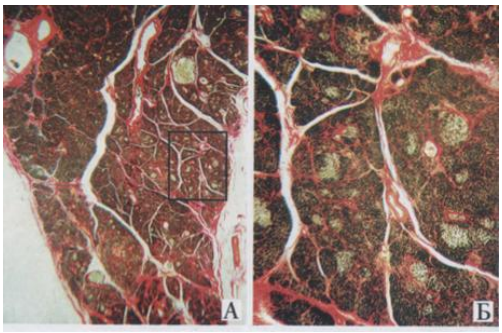


Fig. 1. The site of accumulation of pancreatic islets in the rear-lower part of the gland head (according to I. I. Kagan et al., 2004 [4]). Photo of the sagittal histogram of the head. Coloring according to Van Gieson. A — overview image, B — the area of the back-bottom of the head.

According to currently available data, it is believed that blood flow in the pancreas is directed from the islets to the acini. The insulo-acinar system is represented by afferent vessels, which first go to the islets, forming in them the islet glomeruli, and then leave the pancreatic islets in the form of efferent capillaries supplying the exocrine organ with blood (Fig. 2).

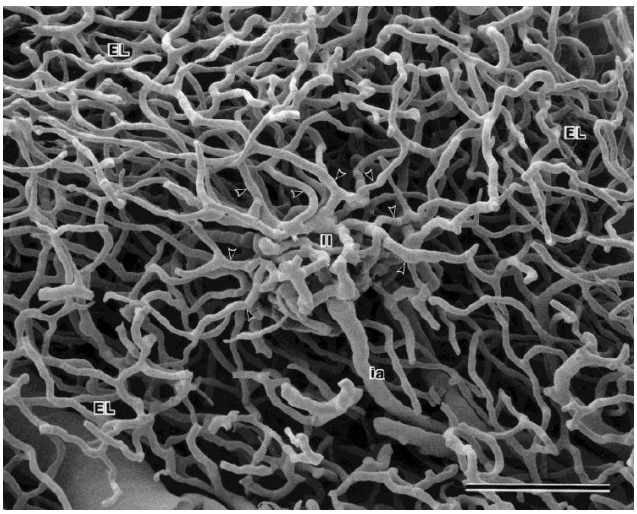


Fig. 2. Human intralobular islet (II), located deep in the exocrine lobe (EL) of the pancreas (according to T. Murakami et al., 1997 [52]). A deeply located islet has many insulo-acinar portal vessels (arrowhead), which extend into lobular capillaries (EL). Note: ia — afferent vessels of the islets.

This feature of the blood supply leads to the creation of a high concentration of hormones (including insulin) in the exocrine part of the pancreas compared with the general circulation. It is assumed that the above-described feature explains the close intra-pancreatic interactions between the endo- and exocrine part of the pancreas: the ability of pancreatic hormones to influence the external secretion of the organ. Currently, the exact mechanisms of the effect of endocrine islets on the exocrine parenchyma of the pancreas have not yet been determined, but it is possible that this effect is mediated through the membrane contacts of neighboring cells, through paracrine interactions of non-contacting cells, as well as through microvascular portal relationships [7]. Other authors cite data demonstrating the existence of special signaling pathways between pancreatic cells that carry out a functional relationship between them through extracellular fluid; The importance of local interactions of end products of metabolism of both endo- and exocrine parts of the pancreas is also emphasized [56]. Therefore, describing the close intra-pancreatic relationship of the exo-and endocrine parenchyma of the pancreas, some researchers talk about the existence of the so-called AIA axis, providing glucose utilization through insulin-dependent (in muscle, adipose tissue) and amylase-dependent (in the intestine with the mandatory participation of its microflora) mechanisms [56]. This theory of the AIA axis explains the ability of pancreatic enzymes to affect glucose homeostasis at the intestinal level and systemic circulation, and also describes additional out-of-digest properties of pancreatic enzymes.

The current literature provides strong evidence for the existence of JSC Axis, which demonstrate the ability of insulin and other hormones synthesized by the islets of the pancreas (glucagon, somatostatin, etc.) to have a significant impact on the function of acinar cells, in particular, in relation to the synthesis of amylase (a feature that has received a wide fame under the name "Halo-phenomenon").

Epidemiology

According to N. Ewald et al., Who reviewed the literature over the past 10 years on the problem of pancreatogenic diabetes, type 3 diabetes is much more common than type 1 diabetes and is often incorrectly interpreted [19]. Pancreatogenic diabetes should be suspected in each case of newly diagnosed diabetes. Researchers insist on the mandatory determination of the degree of EPI, clarification of the level of glycemia, C-peptide, HbA1c, PP, autoimmune markers (antibodies to islets and insulin), vitamin D.

In most of the studies of the exocrine function of the pancreas in diabetes, data on the reduction of bicarbonate and enzyme production were obtained. Exocrine pancreatic insufficiency is more pronounced in insulin-dependent diabetes mellitus (IDDM) and is detected in 40–80% of such patients [26, 28, 30, 39, 58]. Nevertheless, the degree of reduction in the production of various enzymes is different: for example, in IDDM, the production of proteolytic enzymes is more affected. In addition, the reaction to various stimulants of pancreatic secretion is disturbed [26].

In patients with type 2 diabetes, exocrine pancreatic insufficiency is usually less pronounced and less common in 15–73% of patients [28, 60]. However, when examining patients with type 2 diabetes with diarrhea and peripheral neuropathy, it was found that impaired pancreatic exocrine function occurs in all such patients, and production of amylase and bicarbonate with the introduction of various stimulants reached only 40% of the norm [15].

In recent years, the introduction of pancreatic fecal elastase-1 (FE-1) determination of pancreatic fecal elastase-1 (FE-1) to the widespread clinical practice of pancreatic secretion has increased the number of studies on the exocrine function of the pancreas in diabetes. Such studies are conducted in Ukraine. So, V.G. Peredery et al. (2004) [8] examined 35 patients with IDDM and 92 patients with type 2 diabetes. Reducing the performance of PV-1, i.e. the presence of pancreatic insufficiency was found respectively in 57.1% and 53.3% of cases, i.e. 54.3% of all examined patients with diabetes. In the same clinic V. Gdal et al. (2001) [2] examined 18 patients with type 1 and 2 diabetes who were evaluated for pancreatic lipase production using a 13C-triglyceride breath test. In 16 of 18 patients, the respiratory test performance was reduced, and in patients with severe diabetes and moderate disease, a significant decrease in the results of the respiratory test was found in all cases.

Currently, a sufficiently large number of epidemiological studies have been carried out to study the frequency of exocrine pancreatic insufficiency in diabetes using both the “gold standard” — the direct probe method (secretin-pancreozyme test — SPT) and various probe-free methods (FE-1, respiratory tests, etc.). The results are presented in Table 1.

Table 1

The frequency of exocrine pancreatic insufficiency in diabetes (according to JE Dominguez-Munoz, 2005, with additions)

Study	Number of patients	Frequency of pancreatic insufficiency,%	Methods used
IDDM			
B.M. Frier et al., 1976 [22]	20	80	CST
P.G. Lankisch et al., 1982 [39]	53	43	CST
P.D. Hardt et al., 1999 [27]	128 *	74	Elastase-1, x andmotrypsin in feces
P.D. Hardt et al., 2000, 28]	114 *	57	Elastase-1
W. Rathmann e t al., 2001 [60]	112	26	Elastase-1
V.G. Peredery et al., 2004 [8]	35	57	Elastase-1
A.S. Larin et al., 2006 [6]	74	51	Elastase-1
N. Ewald et al., 2007 [18]	546	21.1 severe	Elastase-1
Type 2 DM			
P. D. Hardt et al., 1999 [27]	128 *	36	Elastase-1, x andmotrypsin in feces

P. D. Hardt et al., 2000 [28]	114 *	35	Elastase-1
A. Icks et al., 2001 [30]	544	12	Elastase-1
V.G. Peredery et al., 2004 [8]	92	53	Elastase-1
A.S. Larin et al., 2006 [6]	82	56	Elastase-1
R. Kangrga et al., 2016 [31]	48 *	33, 3	Elastase-1
V. Lindkvist et al., 2018 [45]	3 09	mild — 5, 2 %, moderate — 4, 9 %	Elastase-1
N. R. P rasanna Kumar et al., 2018 [59]	88	moderate — 47.7 %, heavy — 34.1 %	Elastase-1

Note: * — patients with both the 1st and 2nd type of diabetes were examined.

Extremely controversial data on the incidence of pancreatic insufficiency in patients with diabetes, depending on the body weight of patients, their sex, age, age of diabetes. So, according to some researchers, the "older" the age of diabetes, the greater the likelihood of pancreatic insufficiency, reduced PE-1 rates are more often detected with a diabetic history of more than 10 years [3, 6]; other authors indicate that there is no relationship between the duration of diabetes and the degree of pancreatic insufficiency [22, 39]. Some authors believe that the pancreatic insufficiency of the pancreatic function is more common in patients with diabetes mellitus [9], others indicate the possibility of pancreatic insufficiency in young patients with diabetes [3].

Morphological changes in exocrine pancreatic tissue in diabetes

The pancreas in patients with diabetes has a smaller size compared with healthy individuals, which is explained by the involution of exocrine gland tissue [46]. Often more pronounced atrophy is in the area of the body of the pancreas in patients with IDDM than in patients with type 2 diabetes [24]. There is no convincing data on the relationship between the morphological changes in the pancreas and the duration of diabetes, as well as the age of the patient [46]. However, the link between the presence of islet cell antibodies (ICA) and the development of changes in the ductal system of the pancreas has been proven in the blood of patients with diabetes. For example, changes in endoscopic retrograde pancreatography are found in 40% of patients with IDDM and in 59% of patients with type 2 diabetes who have ICA in their blood, but only 9% of patients with type 2 diabetes without ICA [53]. In addition to changes in the pancreatic ducts in patients with IDDM, morphological examination reveals fibrosis and fatty infiltration of the pancreas [23, 34].

A morphological study of the pancreas during IDDM revealed that the acinar cells located around the islets atrophy, which can be explained by the loss of the trophic effect of insulin and the loss of the halo phenomenon [21]. It was shown that at IDDM after the manifestation in the pancreas, the process of degeneration of glandular tissue into the connective tissue can develop, which leads to pancreatic insufficiency [3].

Analysis of autopsy material obtained from patients suffering from EPPZH and IDDM, stated a significant decrease in the number of islets and β-cell zones, an unreliable decrease in the number of zones containing α-cells, while maintaining the number of islets [70]. In addition to fibrosis, atrophy and fatty degeneration, a pronounced lymphatic infiltration (46.8%) was found in the exocrine part of the pancreas, with T-lymphocytes and macrophages predominantly dominating infiltrate. This fact was explained by researchers by the occurrence of immune responses in IDDM in relation to exocrine pancreatic tissue and, in particular, β-cells.

A recently published review by S. Mohapatra et al. Summarized current data on the structural and functional changes that occur in the exocrine pancreatic parenchyma [50]. The authors of this work provided convincing data on the reduction in the mass and volume of the pancreas in patients with type 1 diabetes ($p < 0.005$) and type 2 compared with control persons comparable in age, sex, body mass index (BMI). Analysis of autopsy data ($n = 1272$) confirmed that significant diabetes occurs in the pancreas tissue against the background of diabetes: intraacinologic fibrosis of varying severity develops, minor inflammatory infiltration occurs with

hyalinization of the arteries without significant changes in the pancreatic duct. Based on the data obtained, scientists believe that moderate / severe subclinical pancreatic fibrosis, developing on the background of diabetes of both type 1 and type 2, causes the development and occurrence of moderate exogenous pancreatic dysfunction even in the absence of clinical or histological signs of chronic pancreatitis. The identified phenomenon of S. Mohapatra et al. described as "diabetic exocrine pancreatopathy".

Pathogenesis

As mentioned above, the pathogenesis of exocrine pancreatic insufficiency in diabetes has not been fully elucidated, however, the multifactorial nature of the mechanisms that determine the occurrence of ENPs against diabetes is emphasized [73]. Atrophies of the pancreas give one of the main roles in the development of EPI. Considering the trophic effect of insulin on the acinar tissue of the pancreas through the insulin-acinar portal system, scientists suggest that a local decrease in insulin intake can lead to pancreatic atrophy [73]. It has been established that a decrease in pancreas in the volume is associated with the occurrence of EPI in diabetes. On the other hand, there is evidence of inhibition of basal and cholecystics-stimulated secretion of pancreatic enzymes under conditions of acute hyperglycemia. Under conditions of hyperglycemia, proliferation and activation of pancreatic stellate cells also occurs, leading to the formation of collagen and pancreatic fibrosis.

At present, the following hypotheses have been put forward, explaining the formation of EPI in diabetes:

- imbalance of hormone stimulating and inhibiting pancreatic secretion (insulin ↓, glucagon, somatostatin (Fig. 3));
- pancreatic fibrosis as a result of angiopathy;
- autoimmune mechanisms;
- autonomic neuropathy;
- impaired excretion of gastrointestinal regulatory mediators;
- inhibitory effect on pancreatic external secretion of diabetic acidosis.

Thus, in particular, in experimental animals and in patients with diabetes, glucagon in small doses led to a decrease in the production of trypsin and lipase, and in large doses, amylase [14, 20]. Moreover, it was hypothesized that glucagon could contribute to the development of atrophy of the pancreas [39]. Somatostatin reduces basal pancreatic secretion by 50% and clearly suppresses stimulated secretion of the pancreas [16, 69]. It is believed that this occurs as a result of the direct inhibitory effect of somatostatin, and due to a decrease in the production of cholecystokinin under the influence of somatostatin [16]. On the other hand, it is likely that in conditions of prolonged hyperinsulinemia (occurring in obesity, type 2 diabetes) and hyperstimulation of pancreatic acinar cells, the hormones produced by the islets come into contact with acini, weakening the synthesis of pancreatic enzymes. These data suggest that the imbalance between hormones of the islets of the pancreas is one of the main causes of pancreatic insufficiency in diabetes (Fig. 3). However, this hypothesis contradicts the fact that the exocrine function of the pancreas decreases, although in most, but not in all patients with IDDM.

Data on the role of diabetic angiopathy in the pathogenesis of a decrease in external secretion of the pancreas are few. This hypothesis seems to be quite reasonable, especially since most authors find a link between prescription diabetes and the frequency of pancreatic insufficiency [34].

Certain importance is attached to autoimmune mechanisms, in particular ICA, which, possibly, affect not only insular, but also endocrine pancreatic tissue [47]. Interestingly, in 75% of patients with IDDM in the blood antibodies to pancreatic lipase are detected. The same antibodies are detected in 30% of first-degree relatives of patients with IDDM, but only in 10% of healthy, non-relatives of IDDM patients [54]. In the development of pancreatic insufficiency, the pathogenetic significance of anticytokeratin autoantibodies is also suggested [36, 37].

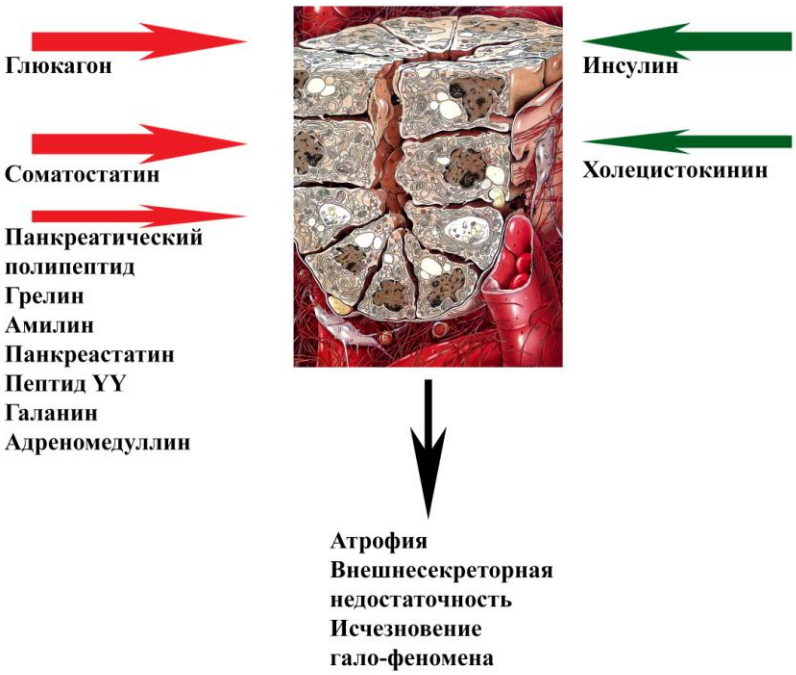


Fig. 3. The imbalance between hormones stimulating the secretion of the pancreas (green arrow) and inhibiting it (red arrows) in diabetes (by J. Keller et al., 2004 [34]; N. Beger [67]. Acinar cells are reduced in size, they are reduced number of zymogen granules (image of the acini according to K. Morgenroth et al., 1991 [51]).

In our opinion, important data were obtained by C. Semakula et al. (1996) [63], who showed that with IDDM in 10% of patients an elevated level of lipase or amylase in the blood is recorded with simultaneous detection of a high titer of autoantibodies to islet cells. In 20% of patients, the activity of blood lipase or amylase was reduced. The authors suggest that elevated levels of blood enzymes may indicate damage to acinar cells, while lower levels of enzymes may occur due to a decrease in the severity of the halo effect.

It should be noted that the role of autoimmune mechanisms in the development of pancreatic insufficiency in diabetes is not fully understood. Perhaps autoimmune mechanisms lead to a simultaneous decrease in the exo- and endocrine functions of the pancreas. It is not excluded that the autoimmune process initially affects the exocrine parenchyma with the subsequent spread of the process to the endocrine tissue or vice versa. In support of this fact, mention should be made of the work of J. Ross et al. [61]. Having examined patients with type 1 diabetes with a disease duration of <3 months (n = 70), patients with type 1 diabetes with an experience of the disease for> 3 months. (n = 57), as well as persons without diabetes, but with autoantibodies characteristic of type 1 diabetes (n = 56) and healthy volunteers (n = 110), the researchers recorded an interesting fact [61]. It turned out that the minimum level of blood amylase and lipase activity was recorded in patients with type 1 diabetes, incl. with a short duration of the disease compared with participants who had autoantibodies, but not suffering from diabetes. Based on the data obtained, the researchers suggested that a decrease in the production of pancreatic enzymes may be a predictor of the development and progression of type 1 diabetes.

Similar data were obtained in children suffering from diabetes: the content of FE-1 in young patients with type 1 diabetes was significantly lower compared with the control group who did not have this metabolic pathology [38]. The authors suggested that the EPPZH will be aggravated as the production of autoantibodies specific for type 1 diabetes increases.

The role of viruses in the formation of functional insufficiency of the pancreas (both exo- and endocrine) is not clarified; viruses are likely to act as trigger factors for the autoimmune process or directly affect the pancreas tissue.

Autonomic neuropathy is a fairly frequent complication of diabetes, which, for example, explains the development of gastroparesis, impaired intestinal motility in IDDM. The production of pancreatic enzymes in humans is highly dependent on cholinergic tone, which, in turn, is modulated by the effect on cholecystokinin receptors located in the parasympathetic nerves. That is why, in patients with autonomous neuropathy, the reaction of pancreatic secretion to cholecystokinin and its analogues is impaired. For example, in patients with type 2 diabetes, the production of pancreatic enzymes is reduced in response to cholecystokinin stimulation and the introduction of amino acids [15]. Therefore, autonomic neuropathy disrupts the enteropancreatic reflexes [61].

Patients with diabetes have impaired production of pancreatic polypeptide, intestinal hormones (motilin), which have a potential effect on the exocrine function of the pancreas. It is also assumed that in the formation of pancreatic insufficiency in diabetes it is important to reduce the production of intestinal peptides — YY peptide and glucagon-like peptide-1 [25, 29]. In the pathogenesis of pancreatic insufficiency in diabetes, the role of diabetic acidosis, which can provoke the development of pancreatitis, is also suggested [68].

According to R. Talukdar et al. [66], who tried to summarize all this information, schematically the pathogenesis of EPI in diabetes is as follows (Fig. 4).

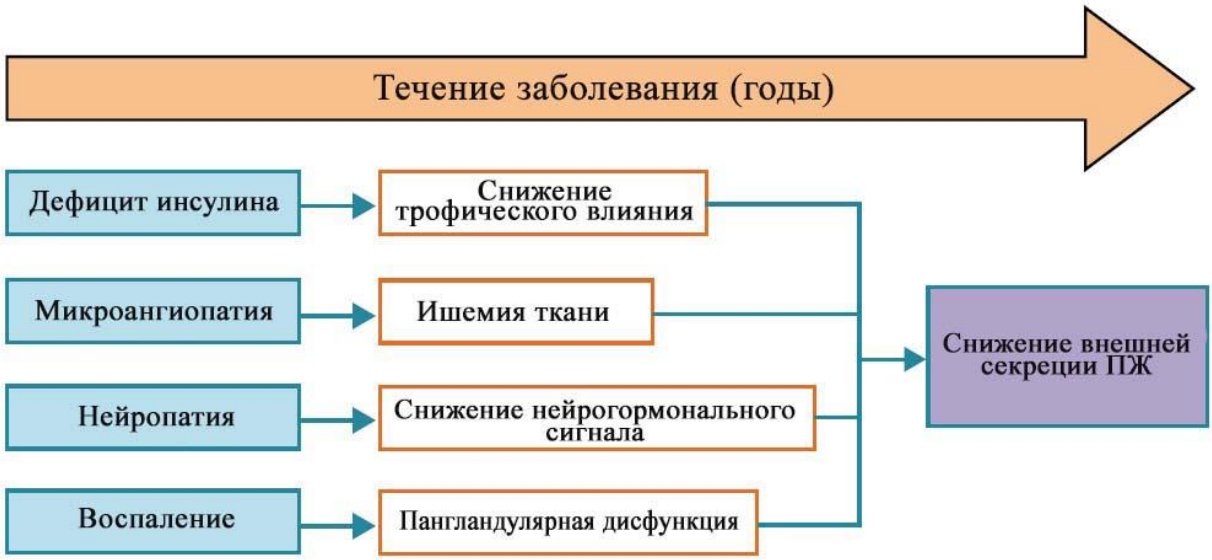


Fig. 4. The pathogenesis of EPI in diabetes (according to R. Talukdar et al., 2017 [66]).

In the development of exocrine insufficiency, prostate is of great importance not only diabetes itself, but also metabolic syndrome (MS), including as a component of diabetes type 2 This concept was developed in detail by Professor H.U. Claire (Germany) in his lecture at the V National School of Gastroenterology, Hepatology of Ukraine (Kiev, 2003) [5] (Fig. 5).

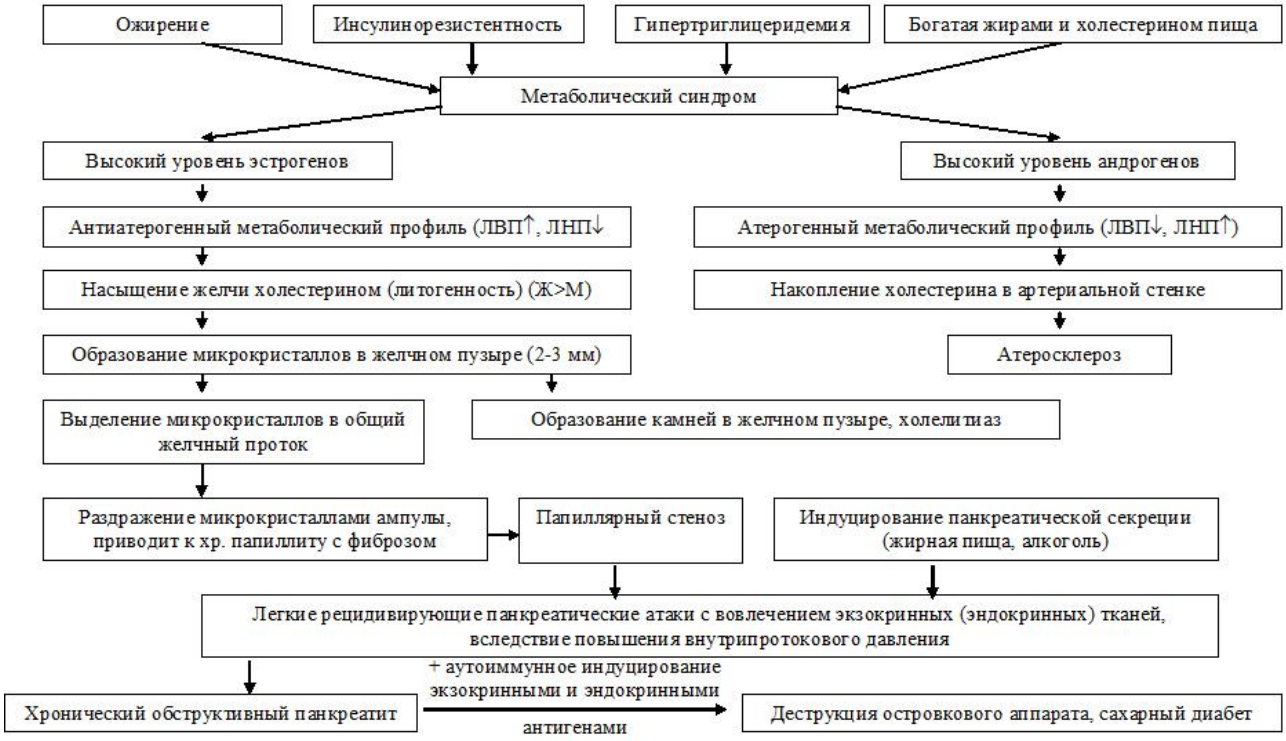


Fig. 5. Pathogenesis of clinical manifestations on the part of the digestive organs in diabetes (by J. Keller et al., 2004 [34]).

First of all, the development of both MS and pancreatitis, both acute and chronic, contributes to the excessive consumption of fatty foods and alcohol. This also contributes to the modern "American" style of food in a bistro such as McDonald's and others. With the development of MS, the hormonal profile is disturbed with an increase in the level of estrogen or androgen in the blood. With an increase in the content of estrogen in the blood, an anti-atherogenic lipid profile of the blood is formed, and cholesterol from food is mainly excreted into bile. As a result, bile is saturated with cholesterol, microliths are formed in it, and then concrements. With long-term injury by microliths of the Vater papilla area, papilostenosis is formed. He, in turn, contributes to the development of intraductal pancreatic hypertension, chronic obstructive pancreatitis. It is clear that pancreatitis progresses functional insufficiency of the pancreas, including endocrine. It is included in the pathogenesis of MS, exacerbating the manifestations of diabetes. Thus, the first closed pathogenetic ring is formed. With the predominant increase in the level of androgens in the blood, an atherogenic lipid profile is created, contributing to the progression of atherosclerosis. Violation of the trophism of the pancreas, as well as other abdominal organs, accelerates its fibrosis and progression of pancreatic insufficiency. In this case, newly formed pancreatic diabetes exacerbates the manifestations of MS (second pathogenetic ring). In general, obesity as a component of MS and by itself contributes to a decrease in the external secretion of the pancreas, probably due to fatty degeneration of acinar cells and / or lipidosis of the organ. Excessive pancreatic insufficiency develops in approximately one third of cases in obese patients [1]. In addition to papillostenosis, which was mentioned above, the development of pancreatitis is also promoted by cholelithiasis, which is a recognized etiological factor for acute and chronic pancreatitis [13]. This hypothesis, largely confirmed by the results of scientific research, should be taken into account in practice when drawing up a plan for the examination and treatment of patients.

Thus, type 2 DM not only independently, but also as part of the MS, participates in the development of exocrine pancreatic insufficiency. But not so much through an imbalance of

insulin and contra-insular hormones, diabetic angiopathy, etc., but rather through the formation of chronic pancreatitis. In general, we believe that a considerable part of cases of EPI in patients with diabetes is caused by chronic pancreatitis, i.e. these patients initially suffer from pancreatitis, and the result is a decrease in both exo- and endocrine functions of the pancreas, i.e. Type 3 diabetes. Perhaps that is why, when diabetes is so frequent, pronounced morphological changes in the parenchyma of the pancreas and its ductal system occur. A similar hypothesis is expressed by other authors [6, 12].

The pathogenesis of clinical manifestations that develop in diabetes, both as a result of diabetic autonomic neuropathy, and as a result of exocrine pancreatic insufficiency, is presented in Fig. 6. From this figure it is clear that exocrine pancreatic insufficiency is of great, if not decisive, importance in the development of pain, dyspepsia, and stool disorders in patients with diabetes.

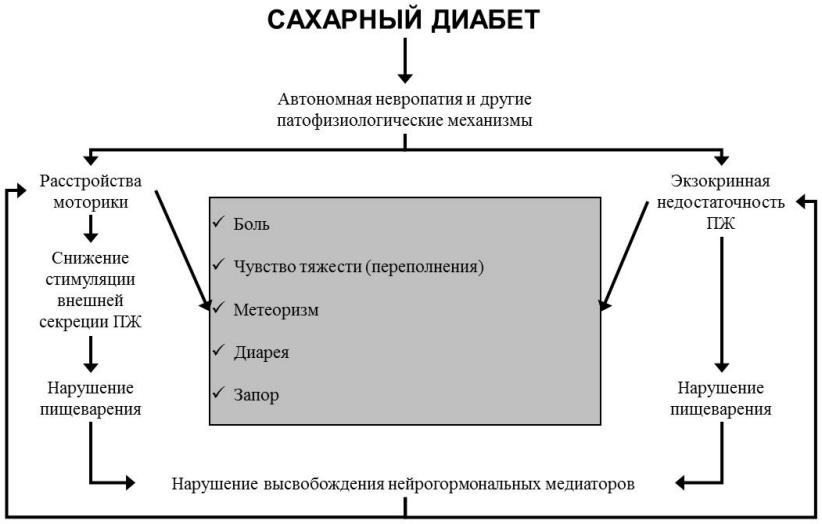


Fig. 6. Interrelation of MS and pancreatitis (after HU Claire, 2003 [5]).

Optimal diagnosis of EPI in diabetes

Determination of FE-1 allows to measure the levels of elastase-1, a proteolytic enzyme produced by pancreatic acinar cells, in feces. It has been proven that the content of FE-1 correlates with the production of other pancreatic enzymes, the feces elastase is very stable and is easily measured [73]. FE-1 demonstrated good sensitivity and specificity in the diagnosis of moderate and severe EFL. That is why the measurement of the level of FE-1 is recognized as a "screening tool for EPPZH", which can also be used in diabetes.

According to the results of various studies, there are strong interrelations between the content of FE-1 and various indicators of carbohydrate metabolism compensation, the concentration of pancreatic enzymes. For example, R. Kangrga et al., Conducting screening of EPPZH in patients with diabetes by determining the level of FE-1, stated a sharp decrease in the level of FE-1 in patients with DM ($p = 0.001$), as well as the concentration of C-peptide ($p = 0$, 03), amylase ($p = 0.02$) compared with healthy volunteers (Fig. 7) [31]. The content of C-reactive protein (PSA, $p = 0.004$) and triglycerides ($p = 0.02$) was significantly higher than in the control group. It is noteworthy that in patients with diabetes, the content of vitamin D was very different from that in healthy volunteers, being much lower than the standard values ($p = 0.001$). Researchers recorded a positive correlation in patients with diabetes between PE and C-peptide levels ($p = 0.04$), lipases ($p = 0.009$), PSA ($p = 0.04$), BMI ($p = 0.02$), sex ($p = 0.03$).

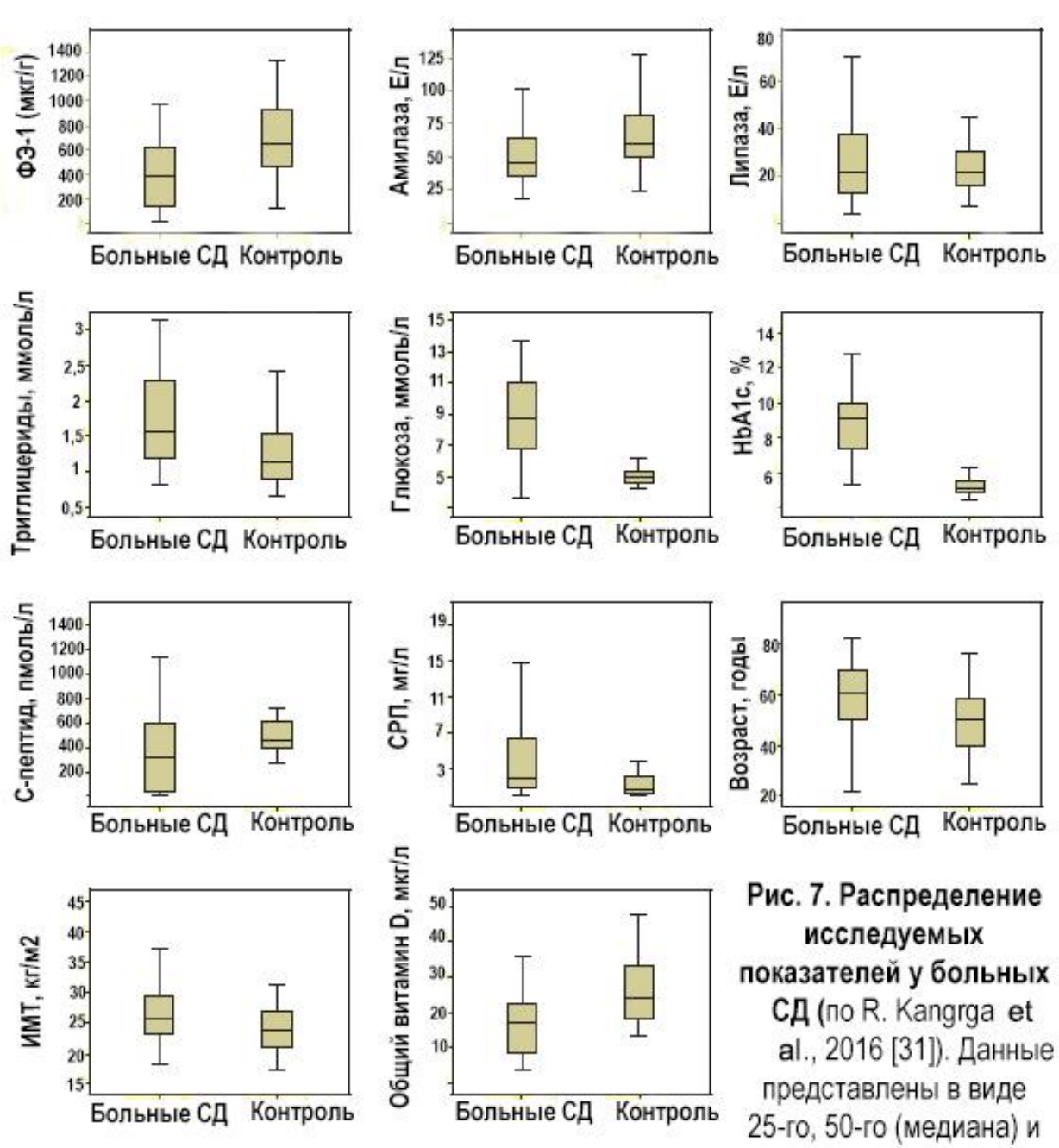


Рис. 7. Распределение исследуемых показателей у больных СД (по R. Kangrga et al., 2016 [31]). Данные представлены в виде 25-го, 50-го (медиана) и 75-го перцентиля.

In another paper, an inverse correlation relationship was recorded between the values of FE-1 and the duration of diabetes ($p = 0.004$), the level of HbA1c ($p = 0.031$) [17]. The content of C-peptide positively correlated with the indications of FE-1 ($p < 0.001$); there is also a significant correlation between the values of BMI and FEL-1 ($p = 0.042$; Fig. 8).

A prospective comparative study, in which patients with type 2 diabetes and healthy volunteers took part, analyzed the prevalence of EPI and the relationship between FE-1 content and the degree of hyperglycemia [59]. The authors recorded a statistically significant relationship between the level of FE-1 and HbA1c ($p = 0.003$), as well as between the content of FE-1 and the development of retinopathy ($p = 0.001$), the state of the peripheral arteries ($p = 0.001$). Scientists believe that early diagnosis of EPPZH and the timely appointment of pancreatic enzymes can improve the quality of life of patients with severe pancreatic insufficiency.

The relationship between FE-1 and lipid absorption was analyzed in an open, randomized, crossover study by B. Lindkvist et al. [45]. According to the study design, patients with type 2

diabetes who took oral hypoglycemic drugs for 18-70 years (n = 315) took part in it. Although the prevalence of mild and moderate EPI was relatively small (5.2% and 4.9%, respectively), the researchers found a correlation between the decrease in FE-1 and low serum levels of vitamin D, eiczopentaenoic acid.

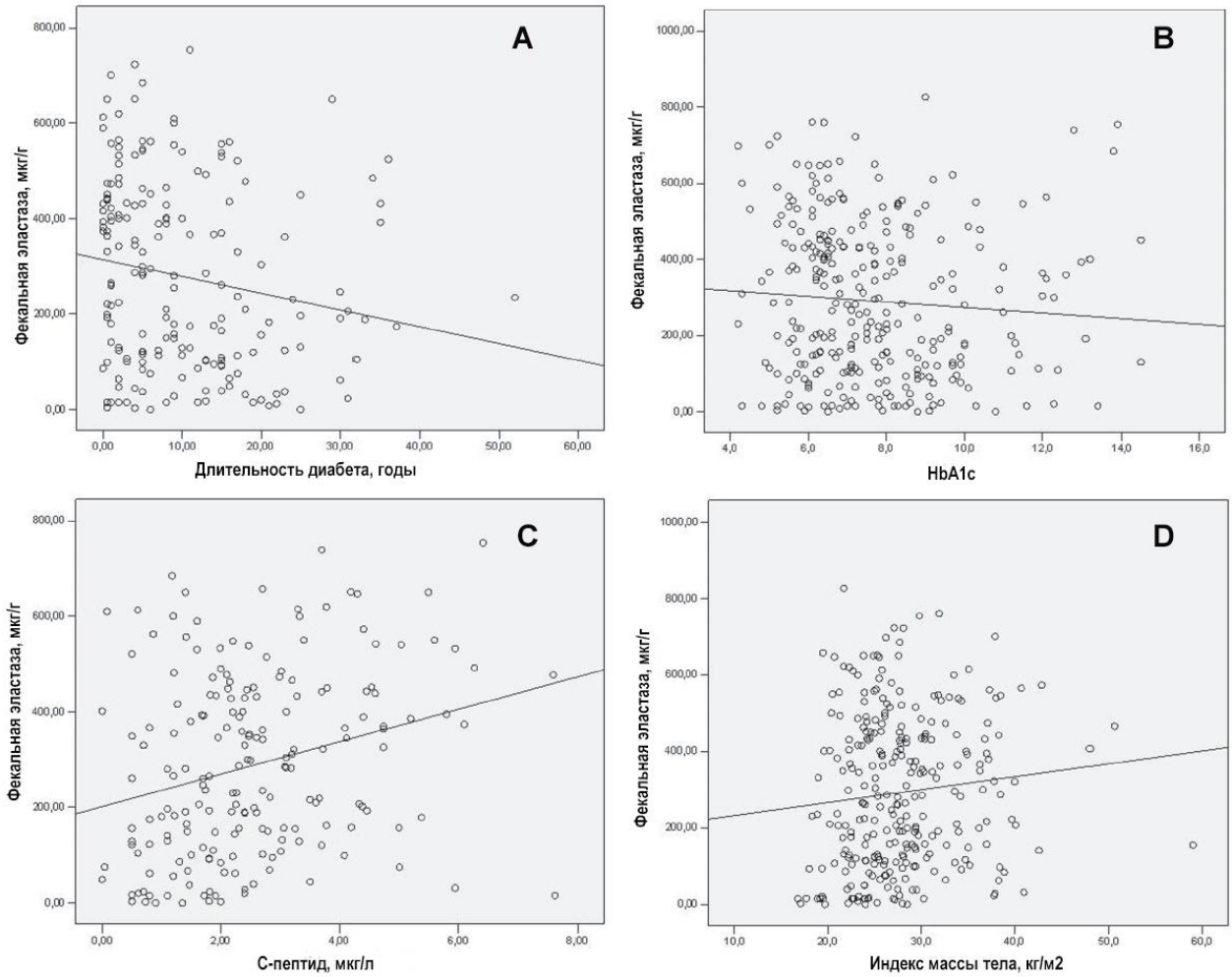


Рис. 8. Факторы, влияющие на формирование экзокринной недостаточности ПЖ у больных СД (по N. Ewald et al., 2009 [17]). Корреляционная зависимость между уровнем ФЭ-1 и длительностью СД **(A),** уровнем HbA1c **(B),** С-пептида **(C)** и индексом массы тела **(D).**

Pancreatic enzymes and glycemic control

The fact that insulin, synthesized in the β-cells of the pancreas, affects the production of enzymes in acini, has been known for many years; however, there are a large number of works (although some of them did not find broad support) describing the ability of pancreatic enzymes to take part in controlling glycemia. For example, L. Lozinska et al. It has been proven that enteral administration of acinar enzymes helps control the production and / or release of insulin in response to changes in glycemia [47].

In the experimental work of S. Pierzynowski et al. have demonstrated extra-digestive properties of pancreatic enzymes at the intestinal level and their ability to influence glucose absorption and its metabolism [57]. Scientists have shown that oral ingestion of pancreatic enzymes 1 hour before the glucose-peroral test is associated with a decrease in blood glucose levels, whereas after intravenous glucose, glucose elimination slows down along with a decrease in insulin. The researchers explained this feature by the action of amylase or peptides formed during its decomposition: "... We assume that the mechanism underlying this phenomenon is based on a specific transduction signal from enteral / parenteral amylase or its components /

peptides interacting with glycoconjugates probably receptors on the apical or basolateral surface of the enterocyte ”[57].

It is believed that pancreatic amylase binds to N-glycans in the brush border located on the enterocyte membrane and inhibits intestinal absorption of glucose via sodium-dependent glucose transporters (SGLT) -1. In addition, amylase and / or its derivatives can alter the flow of glucose into insulin-dependent tissues (for example, enterocytes) by GLUT1 or GLUT2; This feature is considered as a protective mechanism that prevents the development of hyperglycemia. Scientists suggest that amylase limits insulin secretion, directing glucose from the systemic bloodstream to the intestine, and intestinal amylase reduces glucose absorption and decreases insulin release [56]. Thus, glucose utilization by the enterocytes during its first entry into the bloodstream or depletion of the glucose level in the bloodstream can be considered as one of the likely insulin-independent mechanisms of glucose metabolism controlled by amylase. These data reveal the qualitatively new role of amylase in glycemic control.

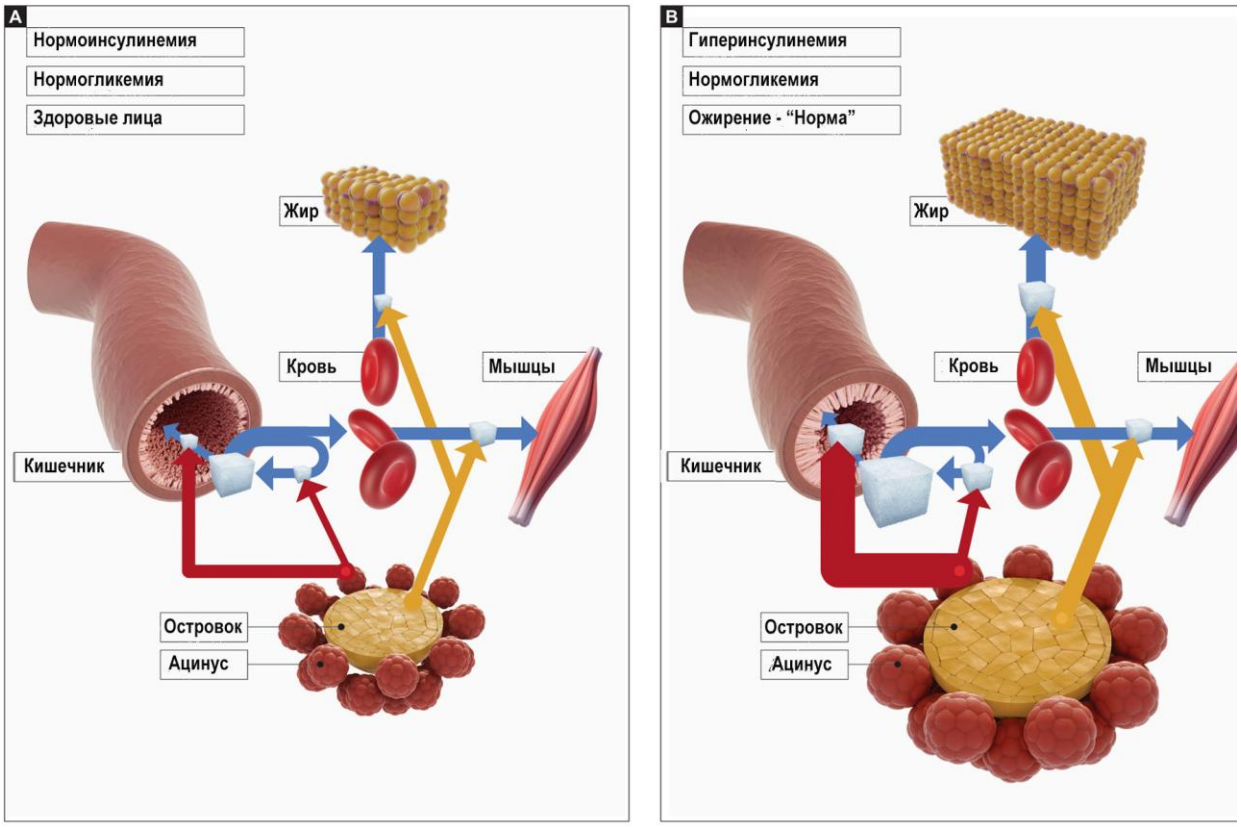
A.L. Mandel and P.A. Breslin (2012) demonstrated that high endogenous amylase activity in the blood is associated with improved glucose homeostasis [49], while low serum amylase concentration is associated with an increased risk of MS prevalence, increased body mass index and insulin resistance (IR) [53].

Based on the above data, S. Pierzynowski et al. (2018) consider the role of the AIA axis in the regulation of glucose homeostasis to be scientifically substantiated and convincingly proven [56]. A high concentration of alpha-amylase in the intestine (blood) may be a factor regulating the absorption of glucose and utilization in the intestine, and determining its subsequent transmission along the insulin-dependent pathway throughout the body. Therefore, scientists say: "The production of pancreatic enzymes and the" healthy state "of pancreatic acini is a fundamental factor determining the release of insulin and hormones involved in the regulation of insulin production, and are also necessary conditions for glucose metabolism" [56].

The above authors propose the following explanation for the normal functioning and pathological changes in the activity of the AIA axis, leading to a violation of glycemic control (Fig. 9). Normally, with moderate consumption of carbohydrates, both parts of the parenchyma (both endo- and exocrine) pancreas work at an optimal level. The activity of the AIA axis is fully balanced, which ensures adequate glucose absorption, redistribution and metabolism. At the same time, a relatively small part of food glucose is used by intestinal cells (including enterocytes) or goes to the synthesis of glycogen by the intestinal microflora.

If more glucose / carbohydrate is ingested with food, the functional activity of the exo- and endocrine portions of the pancreas increases to maintain an adequate level of digestion and the deposition of glucose in the depot. At this transient stage, glucose uptake in the intestine may also increase (Fig. 9B). Excessive consumption of sugars can stimulate a further increase in the level of amylase and an increase in insulin production, which may contribute to the resolution of the emerging postprandial hyperglycemia. However, in obesity, excessive consumption of simple sugars that stimulate insulin secretion, leads to hyperinsulinemia and subsequent hypersecretion of pancreatic enzymes. Presumably, amylase through its non-digestive properties, is involved in the assimilation of glucose in insulin-dependent tissues (for example, in the intestinal mucosa). But the presence of “free” insulin in the blood causes the development of IR, which is exacerbated by the presence of pancreatic proteinases in the blood [56].

Further hyperstimulation of the pancreas leads to the development of MS and DM (Fig. 9c). Against the background of the continuing significant consumption of carbohydrates, the depletion of the AIA axis develops, which is accompanied by a sharp drop in the production of pancreatic enzymes or a lack of acini reaction, which are in a state of IL, for insulin. There are signs of functional EPPZH — so the overproduction of insulin can deplete the ability of acini to synthesize pancreatic enzymes. All these changes can provoke an involution of the pancreas and disrupt the functioning of the acini, which affects insulin susceptibility and leads to the development of exo- and endocrine pancreatic insufficiency due to impaired pancreatic enzyme secretion [56].



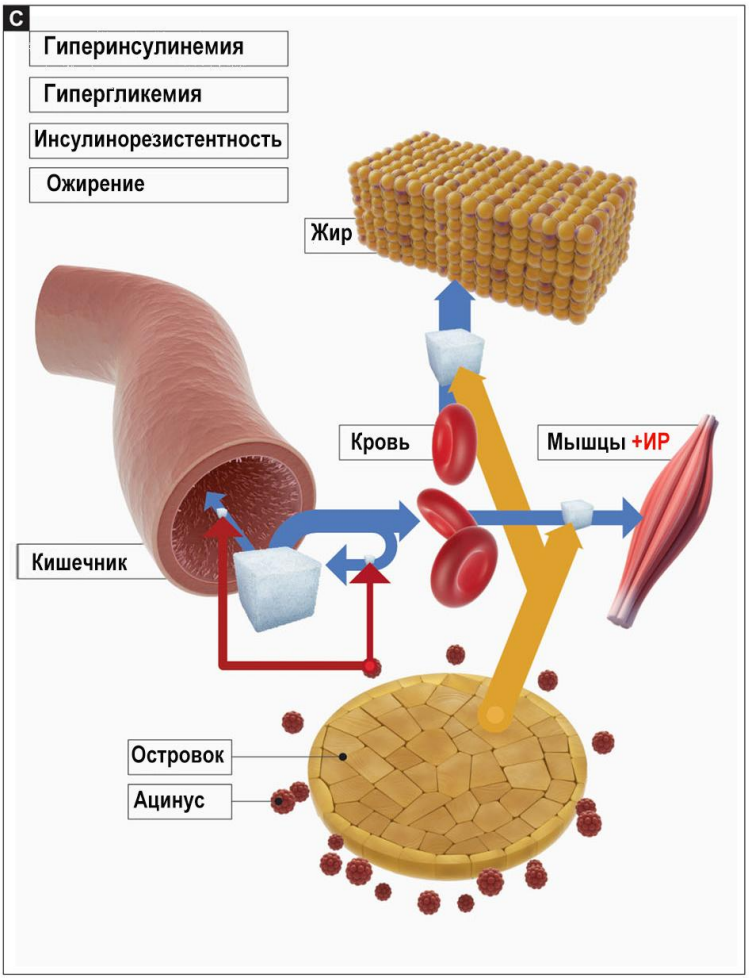


Рис. 9. Роль АОА в развитии ожирения и СД (по S. Pierzynowski et al., 2018 [56]).

А – сбалансированная ацинарно-островково-ацинарная (АОА) обратная взаимосвязь обеспечивает устойчивую утилизацию глюкозы посредством инсулин-зависимого (мышечная, жировая ткань и т.д.) и амилазо-зависимого механизмов усвоения глюкозы (кишечник, микрофлора кишечника).

В – чрезмерная стимуляция ПЖ усиливает защитный механизм АОА от гипергликемии.

С – истощение ацинарных клеток приводит к развитию функциональной экзокринной панкреатической недостаточности и, как следствие, гипергликемии.

The natural course of type 2 diabetes involves the use of insulin preparations in its treatment, which is a consequence of the functional insufficiency of β-cells of the islets preceding the appearance of peripheral IR (Fig. 10a). It is likely that oral administration of amylase at this stage can support the effectiveness of insulin therapy, having a direct effect on glucose metabolism in the intestine (Fig. 10B), as well as contributing to a decrease in the amount of insulin required for parenteral administration. Some authors even suggest that oral administration of amylase in the hypoinsulinemia and hyperglycemia stages (Fig. 9c) may delay / prevent the transformation of diabetes into an insulin-dependent disease.

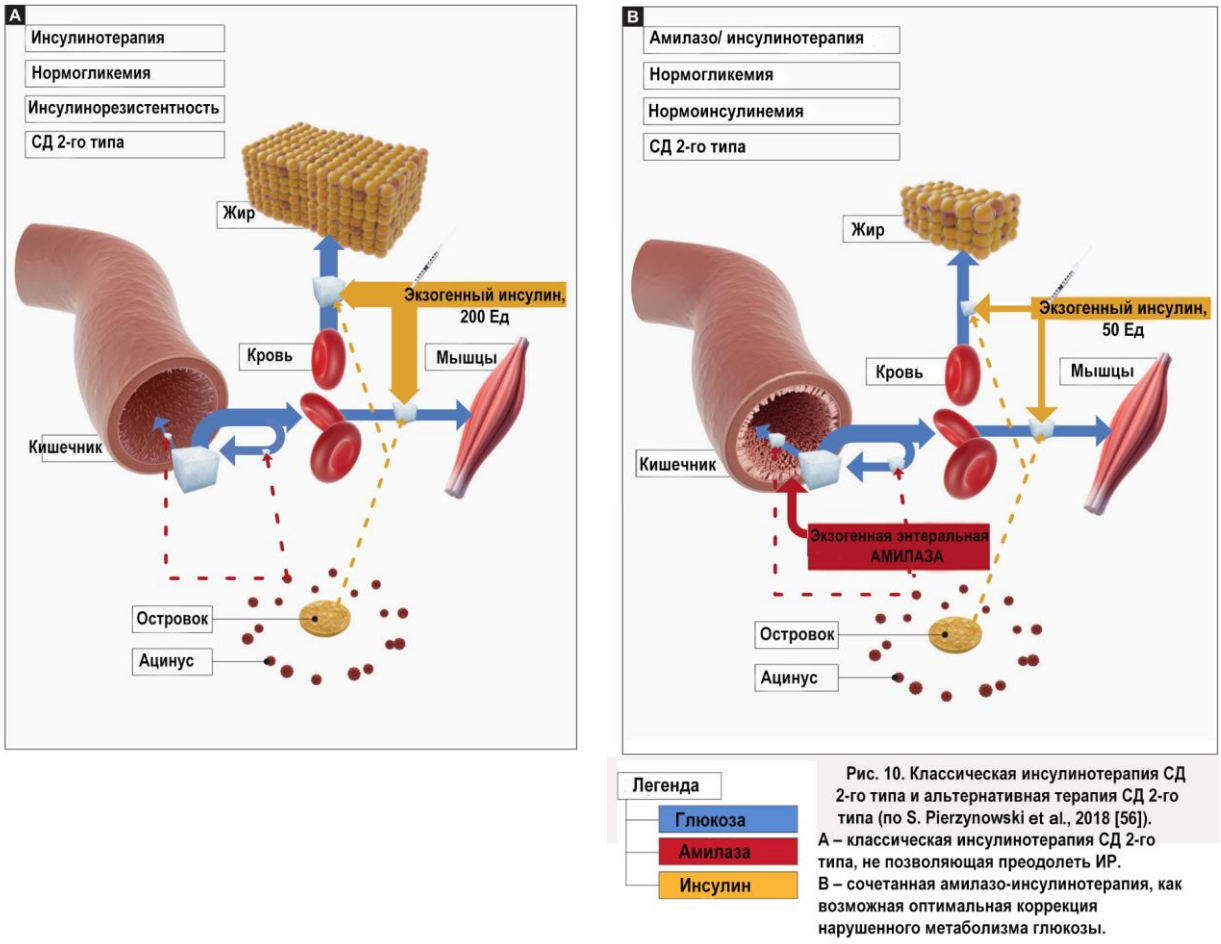


Рис. 10. Классическая инсулинотерапия СД 2-го типа и альтернативная терапия СД 2-го типа (по S. Pierzynowski et al., 2018 [56]).
А – классическая инсулинотерапия СД 2-го типа, не позволяющая преодолеть ИР.
В – сочетанная амилазо-инсулинотерапия, как возможная оптимальная коррекция нарушенного метаболизма глюкозы.

Substitution enzyme therapy for diabetes

It is quite logical that the above described clinical manifestations can be eliminated during treatment with enzyme preparations (AF) [40, 42]. However, some authors emphasize that the choice of AF may affect the effectiveness of treatment. According to R. Talukdar et al., It is necessary to use optimal OP: protected from the effects of the acidic contents of the stomach (having an enteric coating), enter the duodenum simultaneously with the chyme (having a minimum size <2 mm, produced in the form of minimicrospheres), contain an adequate amount of lipase (not less than 20 000 U) — Creon [66].

It is important that AF and, above all, Creon are shown not only to compensate for pancreatic insufficiency in diabetes, but also to eliminate pain. This is explained as follows. We have already written that even with a slight decrease in pancreatic secretion (without steatorrhea), the most intense digestion processes shift to the distal small intestine. In response to the entry of more nutrients into the ileum, the production of distal intestinal mediators (mainly inhibitory) also increases [40]. The result is a violation of motility and secretion of the small

intestine, which, in turn, is implemented in the development of intestinal dyspepsia in patients with diabetes. The purpose of Creon contributes to the elimination of these disorders and, accordingly, to the relief of pain [34]. Therefore, Creon is shown in diabetes and in terms of eliminating the manifestations of pancreatic insufficiency, i.e. as a means of substitution therapy, and as a pathogenetically based drug to eliminate abdominal pain and intestinal dyspepsia. Confirmation of the appropriateness of the use of Creon for the relief of intestinal pain and dyspepsia is its high efficiency in this regard in healthy, eating large amounts of fat [64]. The effectiveness of Creon as a means of FPT in exocrine insufficiency of the pancreas of any origin has been proven by many studies that correspond to the level of evidence A. The results of these studies were published in academic guidelines on pancreatology [10, 13, etc.] and so convincing that Creon is the undisputed leader among AF the whole world.

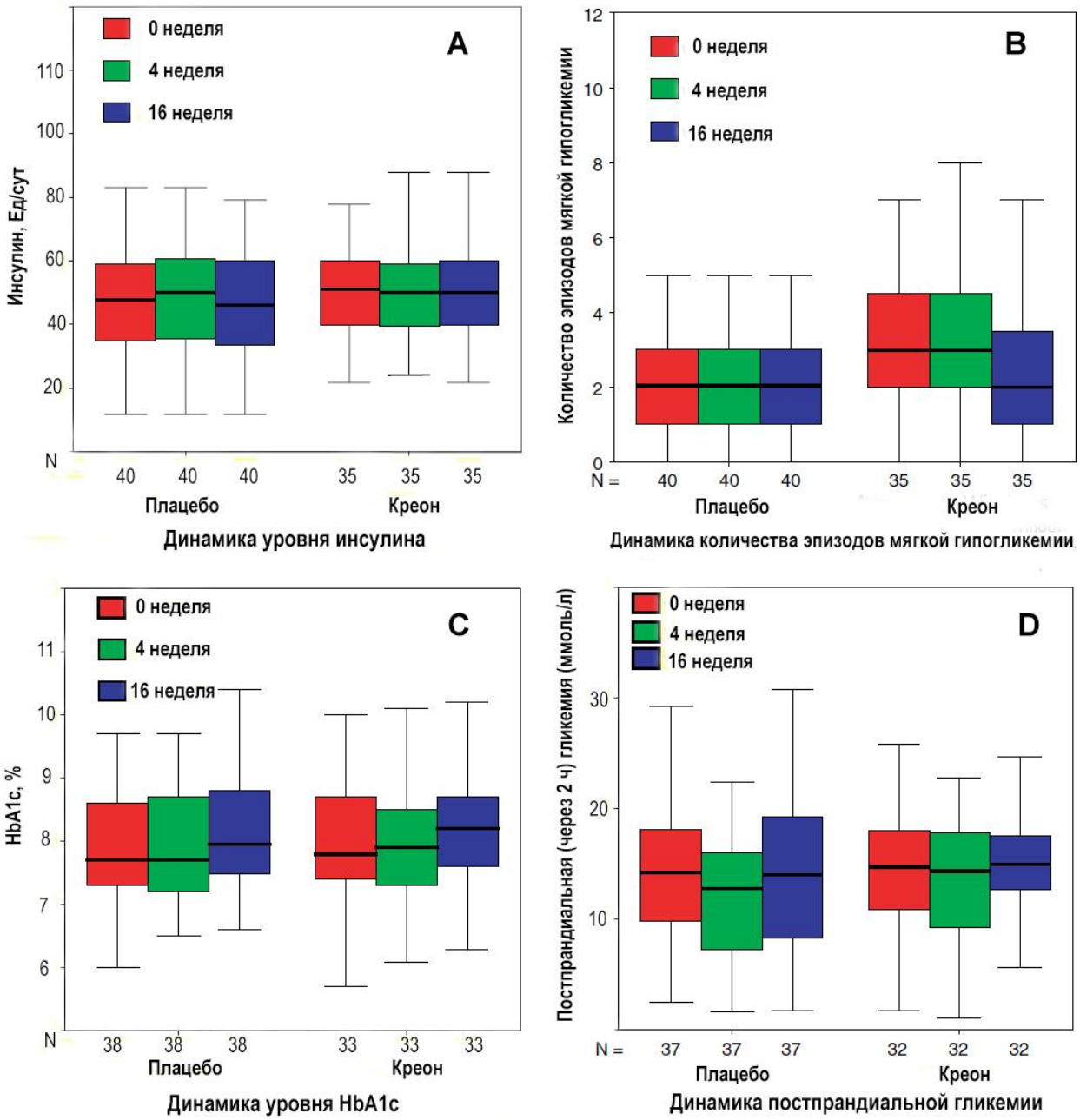


Рис. 11. ЗФТ Креоном у больных СД, получающих инсулин (по N. Ewald et al., 2007 [18]).
Влияние Креона на суточную дозу инсулина **(A)**, уровень HbA1c **(C)**, постпрандиальной гликемии **(D)** и количество эпизодов мягкой гипогликемии **(B)**.

One of the first works that proved the efficacy and safety of Creon in the treatment of EPI in diabetes is a study done by N. Ewald et al. (2007) [18]. The authors of this multicentre, randomized, double-blind, placebo-controlled study screened EPI in patients with diabetes who needed insulin replacement therapy (n = 546), determining the level of FE-1. Patients diagnosed with EPPZH (n = 115; FE-1 <100 μg / g) were invited to participate in the study; they were then randomized into two groups for Creon (n = 39) or placebo (n = 41) for 16 weeks. Participants in the Creon group were advised to take the drug at a dose of 40,000 U with basic meals, as well as 20,000 U with additional (2–3 times) snacks. Researchers analyzed HbA1c levels, fasting glucose levels, postprandial glycemia, as well as vitamin A, D, and E levels over the course of treatment. It turned out that the use of Creon had no significant effect on the insulin dose, HbA1c level and postprandial blood glucose (Fig. 11). The researchers found a significant increase in the level of vitamin D and E in patients treated with Creon. An interesting fact was the statement of a decrease in the number of episodes of mild and moderate hypoglycemia in the Creon group by the 16th week of therapy (Fig. 11). This study convincingly demonstrated that Creon ZFP is safe in patients with diabetes, it does not adversely affect the compensation of diabetes. A decrease in the amount of mild / moderate hypoglycemia, on the contrary, indicates a more stable control over the level of insulin when taking Creon [18].

In addition to this study, the effectiveness and safety of Creon has been demonstrated in other studies (Table 2). Analyzing the results of these categories, it is necessary to emphasize a particularly important conclusion: the result of therapy is not only compensation for a decrease in pancreatic secretion, but also an improvement in the course of diabetes.

Table 2

The efficacy and safety of Creon in the treatment of diabetes disorders in diabetes mellitus (according to R. Talukdar et al., 2017 [66])

The authors	Study design	Treatment	Efficiency	Side effects
N. Ewald et al., 2007 [18]	Prospective multicenter	Creon / placebo	Increased vitamin D levels in the Creon group and increased levels of vitamin E in the blood in both groups during the observation period. Reduced frequency l e mild or moderate hypoglycemia Kreona group at week 16	Similar in both groups (headache, infections, diarrhea, dyspepsia)
F.K. Knop et al., 2007 [35]	Open	Creon / standard nutrition	Total glucogon-like peptide-1 (7.8 ± 1.2 vs. 5.3 ± 1.6 nM, P = 0.01) and total insulinotropic polypeptide (375 ± 77 vs. 270 ± 84 nM, P = 0.04) increased after the appointment of Creon as blood insulin levels increase and total insulin secretion increases	No indication of side effects.
D.C. Whitcomb et al., 2016 [71]	Analysis after the end of a randomized clinical trial	Creon / placebo	The increase in fat absorption index from the start of the study with diabetes was 36% (18.6%) in the Creon group and 7.5% (12.3%) in the placebo group (P <0.0001). The change in nitrogen absorption coefficient from the start of the study with diabetes was 33.4% (30.5%) in the Creon	Most patients with diabetes had no side effects. However, in one patient with diabetes in the Creon group, the chair changed and became more

			group and 3.7% (29%) in the placebo group (P <0.0002). The mean change in both coefficients in the Creon group was significantly higher than in the placebo group (P <0.0001)	frequent, and glycemic control became inadequate. Episodes of hyper- and hypoglycemia were recorded in one patient with diabetes.

Thus, the course of diabetes is associated with a significant decrease in the level of FE-1, which is a manifestation of EPI; the correction of EPI in patients with diabetes by means of FPT can not only level adominal manifestations, normalize the level of vitamin D, but also have a beneficial effect on the degree of compensation of diabetes.

In conclusion, we present the fundamental data for the successful correction of EPPZH, which arose against the background of diabetes (Table 3).

Table 3

Key points in the treatment of diabetes-related erectile dysfunction (by R. Talukdar et al., 2017 [66])
• Patients with diabetes are characterized by a high risk of developing EPI due to atrophy of the acini pancreas. • Symptoms of EPI are not clinically manifested until the duodenal lipase decreases 5-10% below the normal postprandial level. • The clinical significance of EPI is a violation of fat absorption, which leads to steatorrhea and weight loss. • If there is a clinical suspicion of EPI, it should determine the function of the pancreas for the diagnosis of subclinical EPI • ERT is the main method of correction of EPI. The best drug is CREON. • The minimum recommended dose of PEL is 25 000 — 40 000 IU of lipase per meal; Subsequently, the dose is titrated depending on the clinical response. The maximum recommended dose in adults ERT — 75 000-80 000 units of lipase at each meal. In children and adolescents, the maximum recommended dose is 10,000 IU of lipase / kg / day. For light snacks, the dose of AF may be reduced by 2 times. • AF is most effective if taken at the same time with food, and not before or after meals. • FPT helps stabilize body weight and improve the quality of life of patients with diabetes. • Additional intake of fat-soluble vitamins is desirable.

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Exocrine pancreatic insufficiency in diabetes mellitus: frequency, pathogenesis, diagnosis, treatment

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Key words: pancreas, exocrine and endocrine functions of the pancreas, interrelations of exocrine and endocrine pancreatic insufficiency, treatment, replacement therapy

The article represents a detailed literature review, which analyses normal physiological interrelations of exocrine and endocrine pancreatic parenchyma. Literature data regarding

pathogenesis, clinical peculiarities, treatment of pancreatogenic diabetes mellitus (DM) and exocrine pancreatic insufficiency secondary to the DM are highlighted. Fecal elastase- 1 (FE- 1) is found to be a perfect biomarker to reflect the exocrine pancreatic insufficiency in patients with DM type 2. We demonstrate study results which highlighted a strong association of diabetes with low FE- 1 levels and positive correlation FE- 1 with C-peptide levels, lipase, C-reactive protein, body mass index, total 25-(OH)-vitamin D. Results of the studies which reveal the existence of two intra-pancreatic axes of communication are presented: one involved in the regulation of enzyme production by insulin via the insular-acinar axis; another involved in the regulation of insulin release by pancreatic enzymes via the acini-insular axis. The concept of acini-islet-acinar axis is introduced. Exocrine pancreatic insufficiency might be explained as a DM complication. A pathogenetic substantiation of reasonability of Creon indication in DM type 3 and for treatment of exocrine pancreatic insufficiency in patients with DM is presented. Pancreatin therapy can be used safely in patients with DM and exocrine pancreatic dysfunction.