The other way of pancreatogenic diabetes mellitus: exocrine pancreatic insufficiency upon diabetes mellitus

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Key words: pancreas, exocrine and endocrine functions of the pancreas, interrelations of exocrine and endocrine pancreatic insufficiency, pancreatogenic diabetes mellitus, treatment

The traditional statement, clear to everyone, is that patients with chronic pancreatitis in some cases have secondary, i.e. pancreatogenic diabetes mellitus, which is also called diabetes mellitus type 3. But the statement that in diabetes exocrine pancreatic function may suffer secondarily is less well-known. Let us examine the situation reverse to the pancreatogenic diabetes.

Indeed, a large number of diabetic patients have a significant decrease not only of the endocrine but also exocrine function of the pancreas, which was first shown by H. Pollard et al. in 1943 [42]. Moreover, in patients with diabetes there are quite marked morphological changes of exocrine pancreatic tissue [29]. The pathophysiological mechanisms leading to the development of exocrine pancreatic insufficiency haven’t been fully understood yet, but violations of interaction between endo- and exocrine organ structures underlie this insufficiency.

Most studies have noted that the degree of exocrine pancreatic insufficiency in diabetes is more often mild or moderate, and severe deficiency with steatorrhea is relatively rare. Despite this, shift of the maximum absorption of nutrients in the distal small intestine is proved in diabetic patients, which is typical of exocrine pancreatic insufficiency. Increased nutrient amount in the ileum promotes disruption of its motility and secretion, and causes the symptoms of intestinal dyspepsia (spastic bowel pain, bloating, rumbling, stool disorders) [8, 15, 25, 35, 45]. These symptoms are often mistaken for diabetic gastric, enteric and colonopathy, while in some cases they are associated with exocrine pancreatic insufficiency [2, 43, 44]. It forces to

analyze more carefully the pathogenesis and treatment of exocrine pancreatic insufficiency, which developed as a result of diabetes.

Epidemiology. Most of researches of exocrine pancreatic function in diabetes obtained data on a decline of production of bicarbonates and enzymes. Exocrine pancreatic insufficiency is more evident in insulin-dependent diabetes mellitus (IDDM), and is detected in 40-80% of patients [19, 34, 38, 39, 42]. The degree of reduction of production of various enzymes is different: for example, in IDDM production of proteolytic enzymes suffers the most. Furthermore, the reaction to various stimulators of pancreatic secretion is disturbed [38].

In patients with diabetes type 2 exocrine pancreatic insufficiency is usually expressed less and less common — in 15-73% of patients [33, 39]. However, in examining patients with diabetes type 2 with diarrhea and peripheral neuropathy it was found that a violation of the exocrine pancreatic function occured in all such patients, while amylase and bicarbonates production upon the introduction of various stimulants reached only 40% of normal [27].

The number of studies on exocrine pancreatic function in diabetes has increased in recent years, with the introduction in clinical practice of such tubeless method of studying the pancreatic secretion as determination of fecal pancreatic elastase-1. Such studies are conducted in Ukraine too. So, V. G. Perederiy et al. (2004) [4] studied 35 patients with IDDM and 92 patients with diabetes type 2. The decrease in the elastase-1, i.e. the presence of pancreatic insufficiency was found respectively in 57.1% and 53.3% of cases, i.e. in 54.3% of all examined patients with diabetes. In the same clinic V. Gdal et al. (2001) studied 18 patients with diabetes type 1 and type 2, who underwent evaluation of the pancreatic lipase production by ^{13}C-triglyceride breath test. In 16 of 18 patients breath test parameters were reduced, while in patients with severe diabetes and an average degree of severity of the disease a significant decrease in the results of the breath test was showed in all cases.

A number of epidemiological studies on the frequency of exocrine pancreatic insufficiency in diabetes has been conducted both with a use of the "gold standard" — a direct probe method (secretin-pancreozymin test — SPT), and by a variety of

tubeless methods (fecal elastase-1, breath tests, etc.). The results are shown in Table 1.

Table 1

Rate of the exocrine pancreatic insufficiency in diabetes (according to J. E. Dominguez-Munoz, 2005, with amendments)

Study	Number of patients	Rate of the pancreatic insufficiency, %	Used method of research
IDDM			
B. M. Frier et al., 1976 [20]	20	80	SPT
P. G. Lankisch et al., 1982 [19]	53	43	SPT
P. D. Hardt et al., 1999 [23]	128*	74	elastase-1, chemotrypsin in the feces
P. D. Hardt et al., 2000 [39]	114*	57	elastase-1
W. Rathmann et al., 2001 [33]	112	26	elastase-1
V. G. Perederiy et al., 2004 [4]	35	57	elastase-1
A. S. Larin et al., 2006 [4]	74	51	elastase-1
Diabetes type 2			
P. D. Hardt et al., 1999 [23]	128*	36	elastase-1, chemotrypsin in the feces
P. D. Hardt et al., 2000 [39]	114*	35	elastase-1
A. Icks et al., 2001 [34]	544	12	elastase-1
V. G. Perederiy et al., 2004 [4]	92	53	elastase-1
A. S. Larin et al., 2006 [4]	82	56	elastase-1

Note: * — patients with diabetes type 1 and 2 are examined.

Data on the incidence of pancreatic insufficiency in patients with diabetes are rather contradictory, depending on the patient's body weight, sex, age, duration of diabetes. Thus, according to some researchers, the "older" diabetes age, the greater a likelihood of pancreatic insufficiency, reduced fecal elastase-1 is often find in a duration of diabetes history for more than 10 years [2, 4]; Other authors point out that there is no relationship between the duration of diabetes and the degree of pancreatic insufficiency [19, 20]. Some authors believe that the exocrine pancreatic function more often suffers in adults with diabetes [9], while others point to the possibility of pancreatic insufficiency in young patients with diabetes.

Morphological changes of exocrine pancreatic tissue in diabetes. Pancreas in diabetic patients is smaller in comparison with healthy, due to exocrine tissue involution [32]. More evident atrophy in the body of the pancreas often appears in patients with IDDM than in patients with diabetes type 2 [14]. There are no convincing data on the relationship between the morphological changes of the pancreas and the duration of diabetes, as well as the patient's age [32]. However, the proven is a link between the presence of islet cell antibodies (ICA) and the development of changes in the ductal system of the pancreas in the blood of diabetic patients. For example, changes in endoscopic retrograde pancreatography are detected in 40% of patients with IDDM and 59% of patients with diabetes type 2 who have ICA in the blood, but only in 9% of patients with diabetes type 2 without ICA [18]. In addition to changes in the ducts of the pancreas, patients with IDDM in the morphological study have fibrosis, fatty infiltration of the pancreas [22, 29].

A morphological study of the pancreas in IDDM revealed that acinar cells located around the islets, atrophy, which can be explained by the loss of trophic effect of insulin and loss of halo phenomenon [21].

It is shown that a degeneration of glandular tissue in the connective one can develop in IDDM after manifestation in the pancreas, which leads to exocrine pancreatic insufficiency [2].

Pathogenesis. As mentioned above, the pathogenesis of exocrine pancreatic insufficiency in diabetes is not completely understood. The following hypotheses are put forward:

- imbalance of hormones stimulating and inhibiting pancreatic secretion (insulin, ↓, glucagon ↑, somatostatin ↑);
- pancreatic fibrosis as a result of angiopathy;
- autoimmune mechanisms;
- autonomic neuropathy;
- violation of regulatory mediators gastrointestinal excretion;
- inhibitory effect of diabetic acidosis on pancreatic exocrine.

We have already dealt with the trophic influence of insulin on exocrine pancreatic tissue and the halo phenomenon. It is proved that an increased level of hormones contra-insular pancreatic islets (glucagon, somatostatin) can also contribute to the development of pancreatic exocrine insufficiency in diabetes. In particular, glucagon at low doses resulted in a reduced production of trypsin and lipase, while in large doses — amylase also increased in experimental animals and diabetic patients [17, 28]. Moreover, it has been hypothesized that glucagon may contribute to pancreatic atrophy [30]. Somatostatin reduces basal pancreatic secretion by 50% and clearly suppresses stimulated secretion of the pancreas [46, 47]. It is believed that this occurs both as a result of direct inhibitory action of somatostatin, and due to lower production of cholecystokinin influenced by somatostatin [46].

These data suggest that an imbalance between the hormones of pancreatic islets is one of the main causes of pancreatic insufficiency in diabetes (Fig. 1). However, this hypothesis contradicts that the exocrine pancreatic function is reduced although in most, but not all the patients with IDDM.

Data on the role of diabetic angiopathy in the pathogenesis of exocrine pancreatic function reduction are scarce. This hypothesis seems quite reasonable, especially since most of the authors find a link between diabetes duration and the rate of pancreatic insufficiency [29].

Certain importance is given to the autoimmune mechanisms, in particular ICA, which may affect not only the islet, but also the endocrine tissue of the pancreas [26]. It is interesting that 75% of IDDM patients have blood antibodies to pancreatic lipase. 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 [11]. Pathogenetic significance of anticytokeratin autoantibodies is also suggested in the development of pancreatic insufficiency [24, 37].

In our opinion, the most important data are obtained by C. Semakula et al. (1996) [6], who showed that 10% of IDDM patients are recorded to have elevated levels of lipase or amylase in the blood with simultaneous detection of high titer autoantibodies to islet cells. In 20% of patients lipase activity or blood amylase were

reduced. The authors suggest that increased rates of blood enzymes may indicate damage of acinar cells, whereas lower enzyme levels can occur due to a decrease of expression of the halo effect.

It should be noted that the role of autoimmune mechanisms in the development of pancreatic insufficiency in diabetes hasn’t been fully understood. It may be that autoimmune mechanisms cause a simultaneous reduction in exo- and endocrine functions of the pancreas. It is possible that the autoimmune process involves first exocrine parenchyma with subsequent spread to the endocrine tissue or vice versa. The role of viruses in the formation of functional pancreatic insufficiency (exo- and endocrine) is not clarified; viruses are likely to act as trigger factors of autoimmune process, or directly affect the pancreatic tissue.

Autonomic neuropathy is a common complication of diabetes, which explains, for example, the development of gastroparesis, intestinal dysmotility in IDDM. Production of human pancreatic enzymes is strongly dependent on cholinergic tone, which in its turn is modulated by the influence of cholecystokinin receptors located in the parasympathetic nerves. That is why patients with autonomic neuropathy have disrupted pancreatic secretion response to cholecystokinin and its analogs. For example, patients with diabetes type 2 have reduced production of pancreatic enzymes in response to stimulation by cholecystokinin and the introduction of amino acids [27]. Consequently, autonomic neuropathy violates enteropancreatic reflexes [13].

Violations of production of the pancreatic polypeptide, intestinal hormones (motilin), having a potential impact on the exocrine pancreatic function, are observed in patients with diabetes. It is also presupposed that decrease in production of intestinal peptides — peptide YY and glucagon-like peptide-1 — is significant in the formation of pancreatic insufficiency in diabetes [7, 41].

The role of diabetic acidosis, which can provoke the development of pancreatitis, is suggested in the pathogenesis of pancreatic insufficiency in diabetes [48].

Not only the diabetes is very important in the development of exocrine pancreatic insufficiency, but also the metabolic syndrome, including diabetes type 2 as a component. Details of such a concept were firstly developed by professor H. W. Claire (Germany) in his lecture at the 5th National School of gastroenterologists, hepatologists of Ukraine (Kiev, 2003) [3] (Fig. 2).

First of all, development of metabolic syndrome and both acute and chronic pancreatitis is promoted by excessive fat intake, alcohol. Modern "American" food style in McDonald’s and others fast-foods also contributes to this. Upon the development of metabolic syndrome, hormonal profile is impaired with an increase in blood levels of estrogen and androgen. With an increase in the blood content of estrogens, antiatherogenic blood lipid profile is formed, and dietary cholesterol is mostly secreted into the bile. Consequently, bile is supersaturated by cholesterol, microlits and then concrements are formed therein. With long-term injury of the major duodenal papilla by microlites papillostenosis is formed, which, in its turn, promotes pancreatic ductal hypertension, chronic obstructive pancreatitis. It is clear that functional pancreatic insufficiency (including endocrine one) progresses in pancreatitis. It is included in the pathogenesis of the metabolic syndrome, worsening diabetes symptoms. Thus, a first pathogenetic circle is closed. In higher levels of androgens in the blood, an atherogenic lipid profile is formed, contributing to the progression of atherosclerosis. Violation of the pancreatic trophism, as well as other organs of the abdominal cavity, accelerates fibrosis and progression of pancreatic insufficiency. In this case, the newly formed pancreatogenic diabetes exacerbates the symptoms of metabolic syndrome (second pathogenetic circle). Generally, obesity as a component of the metabolic syndrome and itself promotes the reduction of the exocrine pancreatic function, probably due to fatty degeneration of acinar cells and/or lipoidosis of the organ. Exocrine pancreatic insufficiency occurs in approximately a third of cases in the obese patients [1]. Except for papillostenosis, which was mentioned above, cholelithiasis promotes the development of pancreatitis, which is a recognized etiological factor of acute and chronic pancreatitis [12]. This hypothesis,

mostly confirmed by the results of scientific research, should be taken into account in a practice, in the planning of examination and treatment of patients.

Diabetes type 2 is involved in the development of exocrine pancreatic insufficiency not only itself, but also as part of the metabolic syndrome, but not so much by an imbalance of insulin and contra-insular hormones, diabetic angiopathy, etc., but through the formation of chronic pancreatitis. In general, we believe that a large proportion of cases of exocrine pancreatic insufficiency in patients with diabetes is caused by chronic pancreatitis, i.e. these patients initially suffer from pancreatitis, resulting in a reduction of both exo- and endocrine pancreatic function, i.e. diabetes type 3. Maybe that's why evident morphological changes of the parenchyma of the pancreas and its duct system are often found in diabetic patients. Such a hypothesis is expressed by other authors [4, 10].

The pathogenesis of clinical manifestations developing in diabetes as a result of diabetic autonomic neuropathy, and as a result of exocrine pancreatic insufficiency, is shown in Fig. 3. This figure shows that exocrine pancreatic insufficiency has a great and almost decisive importance in the development of pain, dyspepsia, defecation disorders in diabetic patients.

It is logical that these clinical symptoms can be eliminated by treatment with enzyme preparations [8, 31]. It is important that the enzyme preparation and, first of all Creon is prescribed not only for compensation of pancreatic insufficiency in diabetes, but also for elimination of pain syndrome. It is explained as follows. We have already told that even in a small decrease in pancreatic secretion (without steatorrhea) there is a shifting of the most intense digestive processes in the distal small intestine. Production of intestinal neurotransmitters (mainly inhibiting) also increases in response to receipt of more nutrients in the distal ileum [8]. The result is a disturbance of the secretion and motility of the small intestine, which in turn is realized in the development of intestinal dyspepsia in patients with diabetes. Prescription of Creon helps to eliminate these violations and therefore leads to a pain relief [29]. Consequently, Creon is prescribed in diabetes and in terms of eliminating manifestations of pancreatic insufficiency, i.e. as a preparation of replacement

therapy, and as a pathogenetically substantiated drug for pain elimination in the stomach and upon intestinal dyspepsia. Confirmation of Creon's reasonability for the pain relief and intestinal dyspepsia is its high efficiency in this regard in healthy that eat a large amount of fats [40]. The effectiveness of Creon as a preparation of replacement therapy for exocrine pancreatic insufficiency of any origin has been proved by a lot of studies, corresponding to the A level of evidence. The results of these studies have been published in academic pancreatic guidelines [12, 16], and are so convincing that Creon is an undisputed leader in enzyme preparations around the world. Unfortunately, there are no studies on the impact of Creon treatment on abdominal symptoms of diabetes, although such studies are very necessary and promising.

References

1. Внешнесекреторная недостаточность поджелудочной железы. Что это такое? Как часто встречается? Как диагностируется и лечится? В вопросах и ответах гастроэнтеролога врачам и пациентам / В. Г. Передерий, С. М. Ткач, А. С. Ларин, С. В. Скопиченко. — Киев : Твиса, 2005. — 193 с.
2. Едва ли не каждый второй больной диабетом имеет недостаточную секрецию поджелудочной железы : обзор / Под ред. Б. Н. Маньковского // Діабет і життя. — 2002. — № 3. Репринт. — С. 1–4.
3. Клер Х. У. Хронический панкреатит: современные аспекты патофизиологии и лечения / Х. У. Клер // Материалы V Национальной Школы гастроэнтерологов, гепатологов Украины. — Киев, 2003. — С. 64–66.
4. Ларин А. С. Диагностика и коррекция экзокринной недостаточности поджелудочной железы у больных сахарным диабетом / А. С. Ларин, С. М. Ткач, Т. Ю. Юзвенко // Сучасна гастроентерологія. — 2006. — № 3. — С. 42–45.
5. Передерий В. Г. Частота и возможные причины экзокринной недостаточности поджелудочной железы при сахарном диабете / В. Г. Передерий, С. М. Ткач, Л. М. Парунян // Укр. терапевт. журнал. — 2004. — № 2. — С. 12–16.
6. Abnormal circulating pancreatic enzyme activities in more than twenty-five percent of recent-onset insulin-dependent diabetic patients: association of hyperlipasemia with high-titer islet cell antibodies. Belgian Diabetes Registry / C. Semakula, C. L. Vandewalle, C. F. Van Schravendijk [et al.] // Pancreas. — 1996. — Vol. 12. — P. 321–333.
7. Alterations of plasma immunoreactive glucagons-like peptide-1 behavior in non-insulin-dependent diabetics / M. Hirota, M. Hashimoto, M. Hiratsuka [et al.] // Diabetes. Res. Clin. Pract. — 1990. — Vol. 9. — P. 179–185.

8. Altered postprandial motility in chronic pancreatitis: role of malabsorption / P. Layer, M. R. von der Ohe, J. J. Holst [et al.] // Gastroenterology. — 1997. — Vol. 112. — P. 1624–1634.
9. Bennett P. H. Diabetes in the elderly: diagnosis and epidemiology / P. H. Bennett // Geriatrics. — 1984. — Vol. 39. — P. 37–41.
10. Chey W. Y. External pancreatic secretion in diabetes mellitus / W. Y. Chey, H. Shay, C. R. Shuman // Ann. Intern. Med. — 1963. — Vol. 59. — P. 812–821.
11. Circulating antibodies against an exocrine pancreatic enzyme in type 1 diabetes / L. Panicot, E. Mas, C. Thivolet [et al.] // Diabetes. — 1999. — Vol. 48. — P. 2316–2323.
12. Clinical Pancreatology for practicing gastroenterologists and surgeons / Ed. J. E. Dominguez-Munoz. — Magdeburg : A Blackwell Publ. Co, 2005. — 535 p.
13. A comparatives study of diabetic complications in patients with pancreatic diabetes mellitus and chronic pancreatitis / E. Schäfer, Á. Fekete, R. Gasparics [et al.] // Pancreatology. — 2006. — Vol. 6. — P. 375.
14. The density, contour, and thickness of the pancreas in diabetics: CT findings in 57 patients / J. P. Gilbeau, V. Poncelet, E. Libon [et al.] // Am. J. Roentgenol. — 1992. — Vol. 159. — P. 527–531.
15. Differential responses of human pancreatic and biliary secretion to graded ileal lipid perfusion / J. Keller, H. Conrads, H. Goebell [et al.] // Digestion. — 1998. — Vol. 59. — P. 206.
16. Diseases of the pancreas / M. W. Büchler, W. Uhl, P. Malfertheiner, M. G. Sarr. — Basel ; Freiburg ; Paris [et al.] : Karger, 2004. — 212 p.
17. Effect of exogenous insulin and glucagon on exocrine pancreatic secretion in rats in vivo / R. Ferrer, J. Medrano, M. Diego [et al.] // Int. J. Pancreatol. — 2000. — Vol. 28. — P. 67–75.
18. Exocrine pancreatic ductograms in insulin-dependent diabetes mellitus / K. Nakanishi, T. Kobayashi, H. Miyashita [et al.] // Am. J. Gastroenterol. — 1994. — Vol. 89. — P. 762–766.

19. Exocrine pancreatic function in insulin-dependent diabetes mellitus / P. G. Lankisch, G. Manthey, J. Otto [et al.] // Digestion. — 1982. — Vol. 25. — P. 210–216.
20. Exocrine pancreatic function in juvenile-onset diabetes mellitus / B. M. Frier, J. H. B. Saunders, K. G. Wormsley, I. A. D. Bouchier // Gut. — 1976. — Vol. 17. — P. 685–691.
21. Foulis A. K. Histology of the islet in insulin-dependent diabetes mellitus: a positive sequence of events / A. K. Foulis // Textbook of diabetes / Ed. J. C. Pickup, G. Williams. — 2nd ed. — Oxford, 1997. — Vol. 15. — P. 24–29.
22. Gepts W. Pathology of the pancreas in juvenile diabetes / W. Gepts // Diabetes. — 1965. — Vol. 14. — P. 619–633.
23. Hardt P. Diabetes mellitus and exocrine pancreatic disease / P. Hardt, H. Kloer // Pancreatic disease: towards the year 2000 / Ed. C. D. Johnson, C. W. Imrie. — London et al., 1999. — P. 33–39.
24. Histopathological changes of the pancreas in islet cell antibodies (ICA)-positive subjects before and after the clinical onset of insulin-dependent diabetes mellitus / T. Kobayashi, K. Nakanishi, T. Sugimoto [et al.] // Diabetes. — 1988. — Vol. 37. — P. 24A.
25. Human pancreatic secretion and intestinal motility: effects of ileal nutrient perfusion / P. Layer, S. Peschel, T. Schlesinger [et al.] // Am. J. Physiol. — 1990. — Vol. 258. — P. G196–G201.
26. ICA 69 is expressed equally in the human endocrine and exocrine pancreas / I. M. Mally, V. Cirulli, A. Hayek, T. Otonkosky // Diabetologica. — 1996. — Vol. 39. — P. 474–480.
27. Impaired exocrine pancreatic function in diabetes with diarrhea and peripheral neuropathy / H. El Newihi, C. P. Dooley, C. Saad [et al.] // Dig. Dis. Sci. — 1988. — Vol. 33. — P. 705–710.
28. Influence of glucagons on pancreatic exocrine secretion in man / W. P. Dyck, E. C. J. Texter, J. M. Lasater [et al.] // Gastroenterology. — 1970. — Vol. 58. — P. 532–539.

29. Keller J. Acinar-islet interactions: pancreatic exocrine insufficiency in diabetes mellitus / J. Keller, P. Layer // Pancreatic disease: basic science and clinical management / Ed. C. D. Johnson, C. W. Imrie. — London [et al.], 2004. — Vol. 21. — P. 267–278.
30. Konturek S. J. Characteristics of inhibition of pancreatic secretion by glucagons / S. J. Konturek, J. Tasler, W. Obulowicz // Digestion. — 1974. — Vol. 10. — P. 138–149.
31. Layer P. Pancreatic enzymes: secretion and luminal nutrient digestion in health and disease / P. Layer, J. Keller // J. Clin. Gastroenterol. — 1999. — Vol. 28. — P. 3–10.
32. Löhr M. Residual insulin positivity and pancreatic atrophy in relation to duration of chronic type 1 (insulin-dependent) diabetes mellitus and microangiopathy / M. Löhr, G. Kloppel // Diabetologia. — 1987. — Vol. 30. — P. 757–762.
33. Low fecal elastase 1 concentration in type 2 diabetes mellitus / W. Rathmann, B. Haastert, A. Icks [et al.] // Scand. J. Gastroenterol. — 2001. — Vol. 36. — P. 1056–1061.
34. Low fecal elastase-1 in type 1 diabetes mellitus / A. Icks, B. Haastert, G. Giani, W. Rathmann // Z. Gastroenterol. — 2001. — Vol. 39. — P. 823–830.
35. Luminal availability and digestive efficacy of substituted enzymes in pancreatic insufficiency / P. Layer, M. Ohe, G. Groeger [et al.] // Pancreas. — 1992. — Vol. 7. — P. 745.
36. Morgenroth K. Pancreatitis / K. Morgenroth, W. Kozuschek. — Berlin ; New York : Walter de Gruyter, 1991. — 120 p.
37. Pancreatic cytoceratin: an antigen of pancreatic exocrine cell autoantibodies in type-1 (insulin-dependent) diabetes mellitus / T. Kobayashi, K. Nakanishi, H. Kajio [et al.] // Diabetologia. — 1990. — Vol. 33. — P. 363–370.
38. Pancreatic enzyme responses are altered in patients with insulin dependent diabetes mellitus / G. Gröger, J. Keller, C. Bertram [et al.] // Digestion. — 1999. — Vol. 60. — P. 378.

39. Pancreatic exocrine function in patients with type 1 and type 2 diabetes mellitus / P. D. Hardt, A. Krauss, L. Bretz [et al.] // Acta Diabetol. — 2000. — Vol. 37. — P. 105–110.
40. Pancreatic supplements reduce symptomatic response of healthy subjects to a high fat meal / F. Suarez, M. D. Fevitt, J. Adshead [et al.] // Dig. Dis. Sci. — 1999. — Vol. 44. — P. 1317–1321.
41. Peptide YY inhibits interdigestive pancreatic enzyme secretion in humans / D. Grandt, S. Bein, C. Beglinger [et al.] // Pancreas. — 1995. — Vol. 11. — P. 430.
42. Pollard H. External secretion of the pancreas and diabetes (study of secretin test) / H. Pollard, L. Miller, W. Brewer // Am. J. Dig. Dis. — 1943. — Vol. 10. — P. 20.
43. Prevalence of the gastrointestinal symptoms associated with diabetes mellitus : a population-based survey of 15,000 adults / P. Bytzer, N. J. Talley, M. Leemon [et al.] // Arch. Intern Med. — 2001. — Vol. 161. — P. 1989–1996.
44. Psychological distress is linked to gastrointestinal symptoms in diabetes mellitus / S. J. Talley, P. Bytzer, J. Hammer [et al.] // Am. J. Gastroenterol. — 2001. — Vol. 96. — P. 1033–1038.
45. The ratios between pancreatic secretory enzymes are modulated by physiologic ileal lipid concentrations / J. Keller, H. Conrads, J. J. Holst [et al.] // Pancreas. — 1998. — Vol. 17. — P. 442.
46. Simultaneous observation of endocrine and exocrine functions of the pancreas responding to somatostatin in man / T. Emoto, M Miyata, M. Izukura [et al.] // Regul. Pept. — 1997. — Vol. 68. — P. 1–8.
47. Somatostatin 28 and coupling of human interdigestive intestinal motility and pancreatic secretion / M. von der Ohe, P. Layer, C. Wollny [et al.] // Gastroenterology. — 1992. — Vol. 103. — P. 974–982.
48. Tully G. T. The diabetic coma of acute pancreatitis / G. T. Tully, J. J. Lowenthal // Ann. Intern. Med. — 1958. — Vol. 48. — P. 310.

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The article represents a detailed literature review, which analyses normal physiological interrelations of exocrine and endocrine pancreatic parenchyma. Literature data are elucidated regarding pathogenesis, clinical peculiarities, treatment of pancreatogenic diabetes mellitus and exocrine pancreatic insufficiency secondary to the diabetes mellitus. A pathogenetic substantiation of reasonability of Creon's indication in type 3 diabetes mellitus and for treatment of exocrine pancreatic insufficiency in patients with diabetes mellitus is conducted.

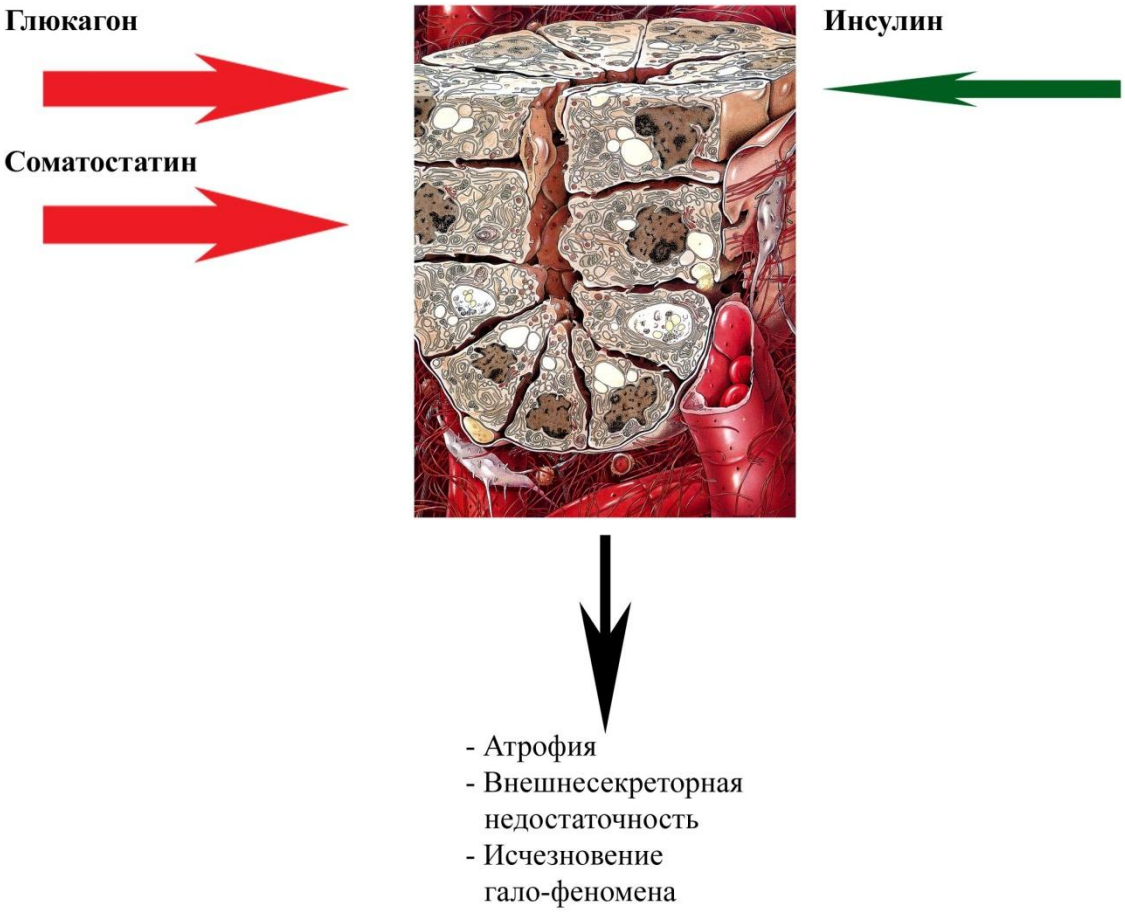

Fig. 1. The imbalance between the hormones that stimulate (green arrow) and inhibit (red arrows) the pancreatic secretion in diabetes (by J. Keller et al., 2004 [29]). Acinar cells are reduced in size, with the decreased number of zymogen granules (acinus image — by K. Morgenroth et al., 1991 [36]).

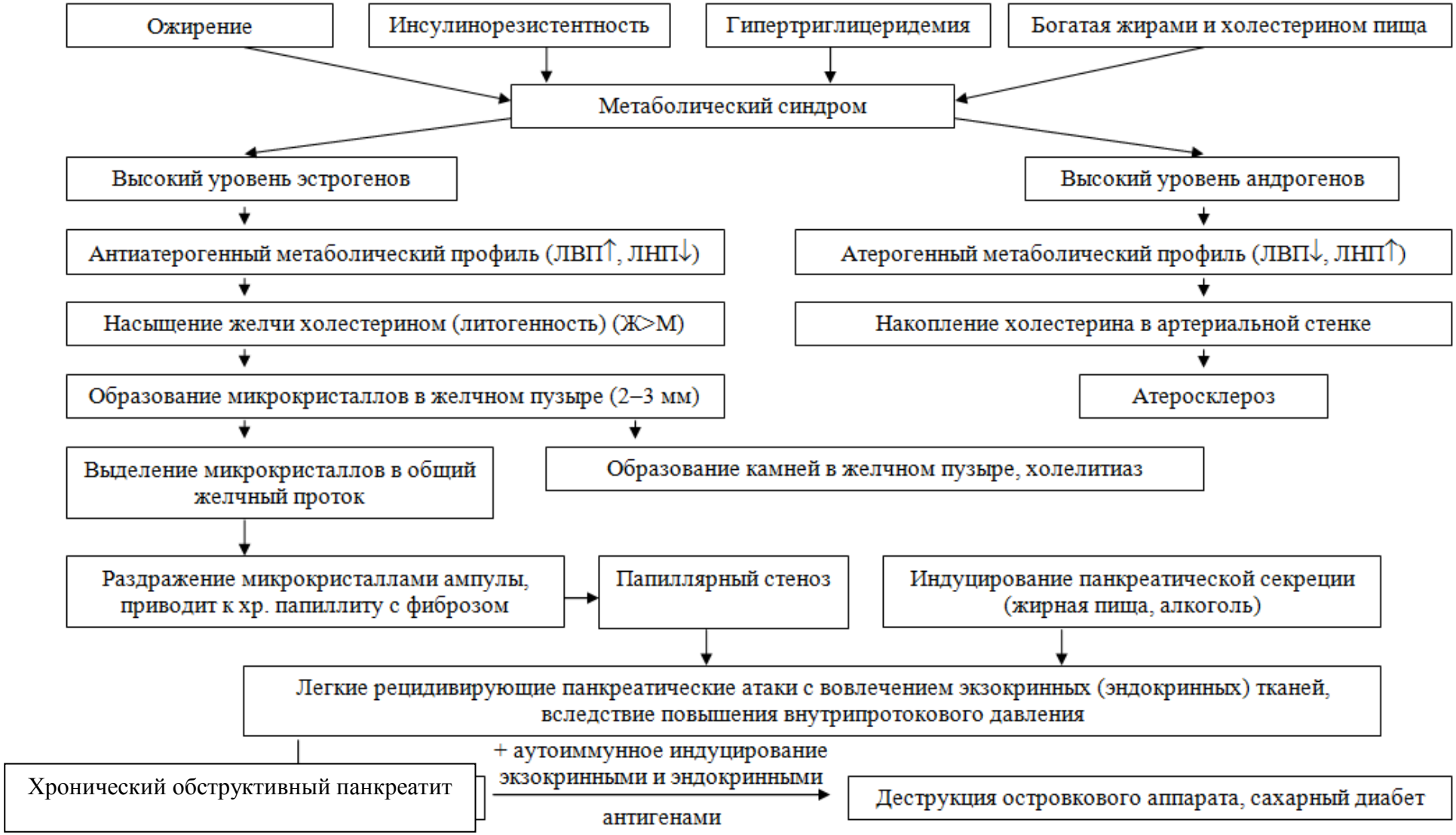

Fig. 2. Pathogenesis of clinical manifestations of the digestive system in diabetes (by J. Keller et al., 2004 [29]).

Fig. 3. Correlation of metabolic syndrome and pancreatitis (according to H. W. Clair, 2003 [3]).