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Pancreas in a Patient with Diabetes Mellitus the Current State of the Issue

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Abstract: To date, DM is one of the most common non-communicable human diseases after cardiovascular and oncological pathology, leading to disability and, often, fatal outcomes. Exocrine pancreatic insufficiency (ENPJ) is a common name for the malabsorption process caused by inadequate production and reduced activation of enzymes of pancreatic acinar cells, such as amylase, lipase and protease, necessary for digestion. According to numerous studies, up to 14% of the adult population in European countries has a violation of glucose tolerance, 7% of the surveyed revealed violations of fasting glucose levels, and 3-4% found a combination of these violations. The prevalence of ENP in patients with type 1 diabetes mellitus (DM1), according to many authors, varies from 25 to 59%, which is determined by the data of pancreatic elastase-1 (PE-1).

Keywords: exocrine pancreatic insufficiency, metabolic syndrome, type 1 diabetes mellitus, pancreatic elastase-1, glucose.

Introduction

The problem of combating diabetes mellitus (DM) is becoming more and more urgent for modern medicine from year to year, due to the rampant increase in morbidity worldwide. Features of the conditions and lifestyle of people in the XXI century associated with hypokinesia; the use of foods high in carbohydrates, salt, fats, synthetic additives; frequent stressful situations caused by the acceleration of the pace of life; bad habits and many other factors underlie weight gain, the development of metabolic syndrome (MS) and type II diabetes (SD II)[1,7]. In DM, there are several possible causes that can explain the occurrence of ENPJ — the absence of trophic action of insulin and, possibly, glucagon, as well as somatostatin on acinar cells, autoimmune damage to islet cells, causing destruction of both endocrine and exocrine tissue, fatty infiltration of pancreatic tissue or a decrease in exocrine secretion as a complication of diabetic neuropathy (DN)[13,4]. All the main pathogenetic mechanisms of the development of DM II include IR, secretory defect of β-cells and hyperproduction of glucose by the liver. The level of glycemia is influenced by numerous factors that determine the functional activity and the amount of glucose released into the blood during the day. The daily fluctuations of glucose, i.e. circadian regulation of glycemic homeostasis, are determined by the degree of physical activity, eating habits, the state of the psycho-emotional sphere, etc[2,19]. The development of diabetogenesis is also promoted by an increase in the tone of the sympathetic part of the ANS, increasing the so-called contrainsular effect of hormones [13]. The detection of early disorders of carbohydrate metabolism in diabetes, according to WHO, includes the determination of impaired glucose tolerance, impaired fasting glycemia and their combinations. According to numerous studies, up to 14% of the adult population in European countries has a violation of glucose tolerance, 7% of the surveyed revealed violations of fasting glucose levels, and 3-4% found a

combination of these violations. Early disorders of carbohydrate metabolism today are increasingly inclined to call the condition "prediabetes". In most studies, the concentration of pancreatic, or fecal elastase-1 (PE-1) was used to assess ENPJ[6,19]. The prevalence of ENP in patients with type 1 diabetes (DM1), according to many authors, varies from 25 to 59%, which is determined by the data of the PE-1 level, The consequences of ENP are a violation of the absorption of fat-soluble vitamins (A, D, E and K), deficiency of calcium, folic acid, magnesium, thiamine and zinc, as well as a higher frequency of episodes of postprandial hypoglycemia in comparison with patients without ENPJ. At the same time, it is necessary to take into account the fact that many patients with DM1 are not examined to assess the exocrine function of the pancreas, and perhaps their number is much higher, especially in the cohort of patients with a long history of DM disease. We present a clinical case of confirmed BPH in a patient with a 6-year history of DM1, which became the main cause of the development of episodes of postprandial hypoglycemia[11,17].

Material and methods. During this period, there was a decrease in body weight to 7 kg for 2 months. Glycemia in the debut was 19.0 mmol/l. At the place of residence, due to obesity of the 1st degree (at that time, the body mass index (BMI) was 33.9 kg/m2), a diagnosis of DM2 was established. In connection with the revealed ketonuria, insulin therapy was initiated in the basic bolus mode with glargine 100 units / ml at a dose of 20 units at 22:00 and glulisine 4-12 units before the main meals in a fixed mode. In the future, metformin 1000 mg per day was added to the therapy. During the next 5 years, there were no changes in the ongoing hypoglycemic therapy. During the entire period of the disease until 2019, there was no compensation for carbohydrate metabolism, the level of glycated hemoglobin (HbA1c) varied between 7.9–10.2% against the background of frequent episodes of hypoglycemia (7-9 times a week). In winter 2022 The patient applied on an outpatient basis to the senter of Endocrinology", where the level of autoantibodies (AT) to the components of islet cells — AT to the zinc transporter 8 (ZnT8), tyrosine phosphatase (IA-2), glutamate decarboxylase (GAD), surface antigens (ICA) and C-peptide was determined (Table 1). AT to ICA, IA-2 were within the reference values, the level of C-peptide was below normal, a positive level of AT to GAD, ZnT8 was detected, on the basis of which it was decided to change the diagnosis to DM1. Metformin was canceled. The patient was trained in self-control of glycemia and counting bread units with titration of insulin dose.Результаты. The department carried out correction of the dose of ultrashort insulin (UCD) and prolonged action, postponement of the injection time of UCD to a later time (5-15 minutes after the end of the meal), however, all the measures carried out did not give the expected result, and the cancellation of the injection of UCD for the main meals led to persistent hyperglycemia 1.5–2 hours after it. Of the accompanying complaints, episodes of flatulence and heaviness after eating, frequent and unformed stools were noted. The patient was examined by a gastroenterologist. Of the complaints characteristic of the gastrointestinal form of diabetic autonomous polyneuropathy, only a feeling of fullness of the stomach after meals was noted, but dysphagia, abdominal pain, nausea, alternation of diarrhea and constipation, nocturnal diarrhea, pain and heaviness in the right hypochondrium were not detected, and therefore it was decided to search for other causes of this problem. An ultrasound examination (ultrasound) of the pancreas, a study of the clinical analysis of feces, the level of pancreatic enzymes: pancreatic amylase, lipase, alpha-amylase, and PE-1 were performed. After receiving laboratory data, a decrease in the level of PE-1 to 101 mcg/g of feces (norm >200 mcg/g, severe ENPJ — less than 100 mcg/g) was revealed at normal levels (within the reference values) of other enzymes studied — lipase, pancreatic amylase, alpha-amylase. According to the results of a clinical analysis of feces, a violation of the shape and structure of feces, the presence of a small amount of neutral fat, fiber and starch in it was revealed. According to the ultrasound of the pancreas, diffuse changes of the organ were determined, but there were no signs characteristic of the manifestations of chronic pancreatitis. Based on the data obtained, the gastroenterologist established ENPJ, and it was decided to prescribe enzyme replacement therapy (pancreatin) for each main meal: immediately before meals — 10,000 meals and immediately after meals — 25,000 meals. Intestinal

decontamination was also performed using topical intestinal antiseptics in order to eliminate a possible "enzyme escape syndrome", which had a favorable result — a pronounced reduction in hypoglycemia episodes. In the future, the long-term use of pancreatin replacement therapy in the amount of 25,000-40,000 units for main meals and 10,000-25,000 units for snacks was recommended. In September 2019, additional examination methods were carried out — MRI of the pancreas, determination of AT detected in autoimmune exocrinopathy and autoimmune pancreatitis — to lactoferrin (A-LF), IgG4, as well as pancreatic enzymes not used in routine practice — alpha-amylase-2 (A-A-2), bile salt-dependent lipase (LCL), carbonic anhydrase-2 (KA-2), vitamin D — 25(OH)D, AT to the parietal cells of the stomach. The volume of the pancreas (OPJ) according to MRI was 37.1 ml with a BMI of 29.4 kg/m2 and a body surface area (BPT) of 1.94 m2, OPJ, adjusted for BPT (OPJ/PPT) and BMI (OPJ/BMI), — 19.07 ml/m2 and 1.26 ml/kg/m2, respectively. The patient was found to have a slightly elevated level of A-LF. AT to IgG4 — within normal values. There was a decrease in the level of enzymes ZHSL and KA-2, the level of A-A-2 was within normal values. In December 2020 against the background of the constant intake of pancreatin for 6 months, the patient was recommended to take enzymes in a maintenance mode — 10,000 - 25,000 units, provided abundant meals rich in fats. Against the background of satisfactory compensation of carbohydrate metabolism (HbA1c 6.9%), primarily due to the reduction of episodes of hypoglycemia, repeated monitoring of the level of PE-1 was carried out, which amounted to 216 mcg/ g of feces. The accompanying symptoms have almost completely disappeared.

Discussion. The patient was found to have a slightly elevated level of A-LF. AT to IgG4 — within normal values. Violation of exocrine secretion of pancreas is often associated with the presence of DM, and in particular DM1. PE-1 is a marker of pancreatic enzyme secretion, and not ENPJ as such. It does not allow differentiating the primary ENPJ from the secondary one. However, the PE-1 level can be used to set the degree of ENPJ. Currently, diagnostic reference values for PE-1 are used — 15, 50, 100 and 200 micrograms/g [5]. Diagnostic testing using PE-1 has some advantages over other tests due to the absence of the need to maintain a special diet, as well as the high sensitivity of this analysis for asymptomatic manifestations of ENPJ. However, there are also disadvantages of this method of studying ENPJ, characterized by low sensitivity in determining from mild to moderate degree of insufficiency. The presence of ENF is determined at an enzyme level of less than 200 mcg/g, and a PE-1 level of less than 100 mcg/g requires special attention. The result may be false positive when analyzing a watery stool, so the measurement should be carried out on a sample of a solid or semi-solid stool [6, 7]. Some scientists note that the prevalence of ENPJ, determined by studying the level of PE-1 in patients with DM1 and DM2, is not so pronounced and is 13%. However, more often ENPJ was determined either in people with DM1 or with a long history of DM [5]. The progression of ENPJ often leads to structural and functional atrophy of the pancreas, manifested by enzymatic insufficiency and a decrease in OPJ. Since the islets make up only 1-2% of the total OPJ, the decrease in this parameter is due to a significant loss of the exocrine gland tissue. In addition to the direct examination of the pancreatic material, the decrease in OPG was confirmed by a variety of non—invasive imaging methods - ultrasound, computed tomography and MRI in adults and children. According to the results of these research methods, the decrease in OPH is 35-45% in the population of patients with a long history of DM1 and about 20-25% during the first year of the disease [8-10]. In the case described by us, the level of PE-1 in combination with a decrease in the level of pancreatic enzymes — KA-2 and ZHSL and a reduced OPF, which normally amounts to more than 50 ml in the general population [11], indicates the presence of EPF in a patient with DM1. The reasons for this decline are unknown, and probably some of them originate months or even years before the manifestation of SD. A possible explanation for the decrease in the size and volume of the pancreas in DM1 includes the loss of insulin-trophic effects by acinar cells as a result of endogenous insulin deficiency, as well as the destruction of the exocrine tissue of the pancreas as a result of autoimmune exocrinopathy (AE) [12]. AE, according to the authors, is manifested by diffuse lymphocytic infiltration of the exocrine part of

the pancreas, which is most common in patients with recently developed DM1. AT, determined with AE, to lactoferrin and IgG4, were found in 66 and 53% of patients with autoimmune pancreatitis (AIP), respectively. They are also found in 20-65% and 7-67% of adult patients with DM1, respectively, but are quite rare in children, patients with DM2 or in control subjects [13, 14]. In our case, only a slight increase in the level of AT-LF was detected with a normal level of AT to IgG4, which cannot fully reflect the presence of AE or AIP in the patient. A number of symptoms of BPH are similar to manifestations of the gastrointestinal form of autonomic neuropathy. Symptoms such as a feeling of full stomach after meals, nausea, alternation of diarrhea and constipation, night diarrhea, can often be diagnosed with ENPJ. ENPJ can be both a cause and a consequence of diabetic neuropathy [15, 16]. In the examined patient, the gastrointestinal form of autonomic neuropathy was excluded based on a survey and examination by a gastroenterologist, and a decrease in the level of PE-1 to less than 200 mcg/g, as well as the volume and size of the pancreas in comparison with the data in the general population testified in favor of the presence of ENPJ [17-19]. The same decrease in the volume and size of the organ occurs with CP. Among the signs characteristic of the manifestations of CP, there is an increase in the echogenicity of the organ, an uneven expansion of the main pancreatic duct, calcifications in the parenchyma, stones in the pancreatic duct, an uneven ("jagged") contour of the pancreas, pain during palpation and pressure in the area of the projection of the pancreas by an ultrasound sensor, compression of large vessels or choledochus, the presence of retention cysts or pseudocysts it was not revealed [20]. In our case, according to ultrasound data, only diffuse changes in the pancreas were noted, no other signs were detected. Given the absence of a previously diagnosed history of CP, the presence of this disease in the patient is unlikely. Enzyme replacement therapy is indicated in the presence of ENPJ, generally improving the quality of life and favorably affecting the course of other diseases, possibly related to each other. Similarly, in our case, a violation of the digestive process caused by ENP in the patient led to episodes of hypoglycemia. When prescribing enzymatic therapy with pancreatin, compensation of carbohydrate metabolism is noted in the outcome, due to a decrease in the frequency of hypoglycemia episodes, as well as the absence of unpleasant sensations after eating. The relationship between the exocrine function of the pancreas and DM1 remains currently unclear to the end. Nevertheless, changes in the exocrine function of the pancreas may precede the occurrence of DM1, which suggests that exocrine and endocrine dysfunction may have a similar pathogenesis. CONCLUSION ENPJ was detected in a patient with DM1 during examination and identification of the causes of persistent hypoglycemia. The study of generally accepted enzymes, such as pancreatic amylase, lipase, alpha-amylase, cannot fully reflect the presence and development of ENPJ in the early stages, and the definition of OPJ, PE-1, ZHSL, KA-2, A-A-2 is not included in routine practice. If such episodes of hypoglycemia occur without an established cause in patients with DM1, we recommend an examination of the exocrine function of the pancreas.

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