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ТИП СТАТЬИ
CASE REPORT

НАЗВАНИЕ СТАТЬИ
Сахарный диабет, хронический панкреатит и первичный гиперпаратиреоз: есть ли связь?

АВТОРЫ
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АННОТАЦИЯ
Гиперпаратиреоз – относительно частое заболевание, характеризующееся гиперпродукцией паратиреоидного гормона. В течении манифестного первичного гиперпаратиреоза (ПГПТ) выделяют несколько клинических форм – костную, висцеральную и костно-висцеральную, или смешанную. В рамках висцеральной формы чаще всего поражаются почки (развиваются нефрокальциноз и нефролитиаз) и возникают пептические язвы желудка и двенадцатиперстной кишки. В то же время, одним из органов-мишеней гиперпаратиреоза может выступать поджелудочная железа. В данной статье описана пациентка с сахарным диабетом, панкреатитом и первичным гиперпаратиреозом в анамнезе, поступившая в связи с неудовлетворительным контролем показателей углеводного обмена. В ходе обследования было предположено, что сахарный диабет развился на фоне частых обострений хронического панкреатита, который, в свою очередь, явился следствием гипертриглицеридемии и первичного гиперпаратиреоза. В отделении было проведено лечение обострения хронического панкреатита, пациентка переведена на инсулинотерапию с достижением целевых показателей гликемии, скорректирована антигиперлипидемическая терапия. Приведенный клинический случай является примером возможного влияния перенесенного ранее первичного гиперпаратиреоза на развитие или усугубление многогранной сопутствующей патологии даже после его радикального лечения с достижением ремиссии ПГПТ.

КЛЮЧЕВЫЕ СЛОВА:
клинический случай; первичный гиперпаратиреоз; хронический панкреатит; сахарный диабет

TITLE
Diabetes mellitus and primary hyperparathyroidism: is there a connection?

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ABSTRACT
Hyperparathyroidism is a relatively frequent condition characterized by hyperproduction of parathyroid hormone. There are several forms of manifest primary hyperparathyroidism. Each form affects its target region. In visceral form nephrocalcinosis, nephrolithiasis and peptic ulcers of stomach and duodenum are
Primary hyperparathyroidism (PHPT) represents a condition characterized by hyperproduction of parathyroid hormone (PTH), most often due to the presence of parathyroid (PT) adenoma. Also, PHPT can be caused by hyperplasia, PT carcinoma, and occur in range of multiple endocrine neoplasia (MEN) syndromes [1]. PHPT is a relatively frequent disease (in Europe, there are 9.9 cases per 100 thousand population, while in the USA, PHPT affects up to 0.86% of the total population) [2, 3].

PTH hyperproduction triggers a complex pathophysiological cascade which causes enhanced bone resorption, increased calcium reabsorption, reduced phosphate reabsorption in the kidneys, and enhanced calcium absorption in the intestine. The processes described are manifested in laboratory-detected hypercalcemia and hypophosphatemia. In addition, there may be a decrease in vitamin D concentration [1, 3].

PHPT manifestations can be different, and they are directly related to the disorder of mineral metabolism and tissue calcification. The most common symptoms include osteopenia or osteoporosis, arrhythmias, nephrocalcinosis or nephrolithiasis, muscle atrophy, and various neurological disorders (insomnia, depression, psychotic disorders). Gastroenterological manifestations (peptic ulcers and pancreatitis) are also relatively common [1], as peptic ulcers of the stomach and/or duodenum are diagnosed in 10–15% of cases, pancreatitis develops in 7–12% of cases, and pancreo-lithiasis and pancreo-calcinosis are less common [4].

According to the major clinical manifestations, several forms of primary hyperparathyroidism are distinguished, namely osseous, with a primary lesion of the internal organs (visceral), and mixed. It is believed that chronic pancreatitis may be one of the manifestations of the visceral form [3]. According to Mayo Clinic, from 40 to 65% of patients with pancreatitis with PHPT also have other pathologies (hypertriglyceridemia, biliary lithiasis, or alcohol abuse), which can lead to the development of pancreatic inflammation with the subsequent development of its fibrosis [2, 5].

What can be the pathophysiological basis of the relationship between PHPT and the development of pancreatitis? Many studies have shown that an increase in PTH concentration alone cannot lead to the development of pancreatitis, while hypercalcemia of any etiology increases the likelihood of pancreatic damage. Thus, PTH leads to the development of pancreatitis indirectly through hypercalcemia [5]. Calcium-sensitive receptors are expressed in various tissues of the body, in particular, they are present on parathyroid cells and all types of pancreatic cells. It has been revealed that the presence of mutations in these receptors increases the likelihood of pancreatitis development. However, in the population of patients with pancreatitis with PHPT, the frequency of receptors mutations to calcium in pancreatic cells was not higher than in the group of patients with PHPT only. Thus, an unambiguous genetic relationship has not yet been found [5, 6].

How is the effect of hypercalcemia on the pancreas implemented? Hypercalcemia leads to an increase in the concentration of calcium in the pancreatic cells cytoplasm. This, in turn, activates the NF-kB-dependent mechanism of inflammation (the nuclear factor that controls the expression of genes of the immune response, apoptosis, and cell cycle) and triggers the tissue damage process. On the other hand, excess calcium is capable of both inhibiting the trypsin autodegradation in intraacinar vesicles and activating calcineurin, leading to the intracinar activation of proteases. Such excessive proteolytic activity in the pancreas itself leads to its inflammation and the development of pancreatitis [6]. Pancreatic calculus, which is a manifestation of the PHPT visceral form, can also affect the development/aggravation of pancreatitis and increase the risk of DM development.

Pancreatogenic DM is a disease rarely diagnosed in clinical practice. In 2012, the PancreasFest working group (scientists of various disciplines with interests in the field of the pancreas) developed a consensus by using the term “type 3c diabetes mellitus”, thereby indicating that carbohydrate metabolism disorders are frequent complications of chronic pancreatitis. This disease was introduced into the American Diabetes Association (ADA) classification only in 2014 as part of “diabetes caused by diseases of the exocrine pancreas”. In 2016, the Consortium for the Study of Chronic Panreatitis, Diabetes, and Pancreas Cancer (CPDPC) also approved the term “type 3c diabetes mellitus” [7, 8].

There is no clear data on the prevalence of pancreatogenic diabetes mellitus (DM). This is due to the difficulty of verifying the disease in routine clinical practice and the insufficient number of studies in this
area. Subclinical cases are particular difficult, when pancreatic tissue damage occurs slowly and detected
cases of DM are more often diagnosed as type 1 or 2 (DM1 or DM2). According to Ewald N. et al., in 1868
patients with newly diagnosed DM, 9.2% of carbohydrate metabolism disorders were associated with non-
autoimmune pancreatic damage. In 78.5% of them, DM was caused by chronic pancreatitis, and 21% was
distributed between pancreatic cancer, cystic fibrosis, hemochromatosis, and conditions after various
surgeries on the pancreas. Thus, DM was a consequence of chronic pancreatitis in 7.2% of cases [9].
According to the literature, with recurrent chronic pancreatitis, up to 30% of patients after 20 years have
impaired glucose tolerance, and DM develops in 40-50% of patients. The CPDPC consortium estimates
currently the prevalence of type 3c DM as about 4-5% and explains that the initial processes of inflammation
and increased cytokines in the pancreatic parenchyma already lead to β-cell dysfunction and, consequently,
to carbohydrate metabolism disorders [7].
As the destruction and sclerosis of the incretory pancreas progresses, stable hyperglycemia may develop
under conditions of insulin deficiency.
As already mentioned, the diagnostic criteria for pancreatogenic DM are quite complex [10-12], the main
ones of them are following:

1) confirmed exocrine pancreatic insufficiency (monoclonal test for fecal elastase-1, direct functional
tests);

2) pathological structural changes in the pancreas using imaging methods (CT, MRI);

3) the absence of autoimmune markers of DM1.

Additional diagnostic criteria showing hormonal disorders include the lack of secretion of the pancreatic
polypeptide, impaired secretion of incretins (e.g. glucagon-like peptide-1), lack of insulin resistance,
impaired β-cell function, low levels of fat-soluble vitamins (A, D, E, K).
Thus, given the possibility of developing pancreatogenic DM in patients with the visceral form of PHPT
described in this article, the clinical case is of interest both for endocrinologists and gastroenterologists, as
well as other medical specialists who can see in their practice the patients with the indicated combination of
pathologies.

CASE DESCRIPTION

Prior to hospitalization at the National Medical Research Center of Endocrinology (October 2017), the
patient was examined and received treatment in a primary care facility. The history was partially compiled
according to the information provided by the patient due to the lack of detailed medical documentation.
Epicrisis were descriptive in nature, and therefore not all of the necessary examinations were available.
The patient’s hereditary history of DM, gastrointestinal diseases, hyperparathyroidism and osteoporosis was
not burdened.
The patient considers herself ill since 2012, when an episode of destructive pancreatic necrosis first
developed (no clear cause was established, the patient did not have significant errors in nutrition, alcohol
abuse, exacerbations of gastrointestinal tract diseases, or toxic effects), which was complicated by the
development of retroperitoneal phlegmon. During hospitalization, hyperglycemia up to 14 mmol/L was first
recorded. A lancing and drainage of the phlegmon was performed; in the postoperative period, according to
the patient, fasting glycemia was 5.6 mmol/L without prescribing sugar-lowering therapy, and therefore no
additional examination was performed. In 2014, a repeated episode of pancreatic necrosis developed.
Antibacterial and antispasmodic therapy was conducted. Further exacerbations of pancreatitis were noted
several times a year.
DM2 was first diagnosed in 2015, when persistent hyperglycemia of 8–14 mmol/l was recorded along with
another exacerbation of pancreatitis. Gliquidone therapy was prescribed (the dose is unknown), and
hypoglycemia was registered 1-2 times a week while taking it. When receiving the therapy and diet, glycated
hemoglobin (HbA1c) was about 7%, the maximum glycemia level in that period was 10 mmol/L. Then
metformin was added to the therapy, and normoglycemia was achieved with this combination (doses are
unknown).
In March 2017, the patient had another exacerbation of chronic pancreatitis; during hospitalization,
gliquidone 15 mg in the morning and evening and metformin 500 mg before bed were recommended. When
receiving this therapy, according to self-monitoring, unstable glycemia indices from 6 to 16 mmol/l were
noted.
In May 2017, when renal colic first occurred, glycemia of up to 20 mmol/L (without acetonuria) was
recorded, and therefore, insulin therapy with Actrapid 4 times per day was initiated (according to the patient,
4-8 Units per injection). In June 2017, the level of HbA1c was 13%. The C-peptide level was 1185 pmol/l
(norm 260–1730). Since insulin and C-peptide in a healthy person are synthesized in equimolar proportions,
the state of glucose-stimulated insulin secretion can be estimated by the concentration of C-peptide. The
administration of exogenous insulin can suppress own secretion and cause a decrease in the C-peptide level. However, in the case described, the C-peptide was closer to the upper limit of the norm, despite the administration of exogenous insulin, which indicates sufficient preserving intrinsic secretion. The determination of the level of antibodies for differential diagnostics of the DM type was not performed. In August 2017, the patient was transferred outpatiently to insulin aspart (NovoRapid) at a dose of 4–6 units before main meals, metformin 500–1000 mg before bed. In September 2017, the HbA1c level was 8.2%. There is no data on the state of calcium metabolism in the provided documentation until 2016. In 2016, during an examination due to exacerbation of pancreatitis, primary hyperparathyroidism was revealed, the level of total calcium was 2.74 mmol/l (2.15–2.58), ionized calcium was 1.45 mmol/l (1.12–1.32), and PTH was 36.4 pmol/L (1.3–6.8). Albumin corrected calcium was not calculated. Scintigraphy of the parathyroid glands was performed, adenoma of the right lower PT gland was revealed. At the time of diagnosis, according to the patient, no bone abnormalities were recorded (X-ray densitometry of the radial bone was not performed, no studies of the lumbar spine and femoral neck were provided), data for visceral manifestations of primary hyperparathyroidism were also not obtained (however, ultrasound or CT of the kidneys were not performed). The presence of chronic pancreatitis was regarded as an independent disease. In February 2017, a parathyroidectomy was performed; histological examination revealed an adenoma of the PT gland from the main dark cells with the formation of microfollicular structures. A dynamic examination in June 2017 revealed total calcium of 2.47 mmol/L (2.15–2.58), ionized calcium of 1.18 mmol/L (1.12–1.32), and parathyroid hormone level of 9.57 pmol/L (1.3–6.8). The level of 25(OH) vitamin D was reduced to 10 ng/ml. Given the lack of visualization of volumetric masses according to expert ultrasound (to exclude recurrence of primary hyperparathyroidism) and a decrease in glomerular filtration rate (GFR) to 45 ml/min/1.73 m², the condition was regarded as secondary hyperparathyroidism with renal failure. In June 2017, a parathyroidectomy was performed; histological examination revealed an adenoma of the PT gland from the main dark cells with the formation of microfollicular structures. A dynamic examination in June 2017 revealed total calcium of 2.47 mmol/L (2.15–2.58), ionized calcium of 1.18 mmol/L (1.12–1.32), and parathyroid hormone level of 9.57 pmol/L (1.3–6.8). The level of 25(OH) vitamin D was reduced to 10 ng/ml. Given the lack of visualization of volumetric masses according to expert ultrasound (to exclude recurrence of primary hyperparathyroidism) and a decrease in glomerular filtration rate (GFR) to 45 ml/min/1.73 m², the condition was regarded as secondary hyperparathyroidism with vitamin D deficiency; colecalciferol of 25,000 IU/week was prescribed (the therapy was prescribed by the endocrinologist in a primary care facility, the recommended dose was 50,000 IU/week). In August 2017, PTH was 6.24 pmol/L (1.3–6.8), total calcium was 2.42 mmol/L (2.15–2.58), ionized calcium was 1.16 mmol/l (1.12–1.32), phosphorus was 1.1 mmol/l (0.78–1.65). According to densitometry, there was no decrease in bone mineral density, in the lumbar spine (0.2 SD according to the T-criterion) and in the femoral neck on the left (−0.4 SD according to the T-criterion), the radial bone was not examined. When colecalciferol therapy, the level of vitamin D was 27 ng/ml by September 2017.

For the first time, an increase in blood creatinine to 109.6 µmol/L and the appearance of protein in the urine (1.35 g/L) was recorded in 2012 during hospitalization due to destructive pancreatitis. At the same time, according to ultrasound and CT, sinus cysts of both kidneys were found. Since 2012, blood creatinine remained within the range of 100.7–117 µmol/L, the specific gravity of urine was within the range of 1005–1012, trace proteinuria (0.05–0.08 g/L) was noted, and the urinary sediment was not changed. In 2016, creatinine was 98 µmol/L, GFR was 69.61 ml/min/1.73 m² (EPI); no daily calciuria was studied. In June 2017, daily albuminuria was 51 mg/day (norm <30), creatinine was 118 µmol/L (norm 50–98), the patient suffered a right-sided renal colic, and nephrolithiasis was diagnosed for the first time (the calculus was independently excreted during the spasmolytic therapy). The increase in BP was noted for the first time in 2005 (up to 140/90 mmHg), since 2008, antihypertensive therapy (including ACE inhibitors) has been conducted. At the time of admission, she received losartan 12.5 mg, amlodipine 5 mg, and bisoprolol 1.25 mg.

The patient had a history of long-term dyslipidemia with an increase in triglycerides to 14 mmol/L (0.1–1.7 mmol/L), and received fenofibrate for 2 weeks before hospitalization. There is no evidence in the history of an increase in uric acid, however, the patient had a dense nodular formation in the area of the first metatarsophalangeal joint on the left, which was regarded as gouty pearl during previous hospitalizations. Complaints of blurred vision first appeared in May 2017 when hyperglycemia was up to 20 mmol/L. The patient was examined by an ophthalmologist; no data were obtained for diabetic retinopathy. The patient was admitted to our institution in accordance with the schedule, for examination and selection of an antihyperglycemic therapy. On the day of admission, she complained of severe girdling abdominal pain, frequent loose stools, an increase in glyceria to 20 mmol/L. At the time of admission, she received the following antihyperglycemic therapy:

1. Insulin therapy: insulin aspart 6 units at lunch time;
2. Gliquidone 15 mg in the morning and evening;
3. Metformin 1000 mg before bed.

The patient took these drugs on her own, without a doctor’s prescription. The combination of sulfonylureas with short-acting insulin is irrational.

The case history is presented schematically in Fig. 1.
Figure 1. Schematic representation of the patient’s history: GFR – glomerular filtration rate; иАПФ – angiotensin-converting enzyme inhibitors; СКД – chronic kidney disease; cr. – chronic, ПТГ – parathyroid hormone; low. right PTG – lower right parathyroid gland; vit. – vitamin; BP – blood pressure.
RESULTS OF PHYSICAL, LABORATORY AND INSTRUMENTAL EXAMINATION

According to the examination upon admission, the general condition was of moderate severity, body temperature was 36.6°C, weight was 65 kg, height was 153 cm, and body mass index was 27.8 kg/m². The skin was clean. There were dense nodular formations in the region of the first metatarsophalangeal joint on the left and the distal interphalangeal joint of the finger III on the right. Pulse was 85 beats/min, rhythmic; heart rate was 85 beats/min. Blood pressure was 150/100 mm Hg. Heart sounds were clear, pure, enhanced. Respiration rate was 17/min, with vesicular breathing over the entire surface of the lungs. In the digestive system, the tongue was moist and clean, the abdomen was moderately painful in the left hypochondrium with superficial palpation, the liver was slightly enlarged (Kurlov’s dimensions were 11×8×7 cm, +2 cm from the costal arch), the symptoms of Korte’s symptom and the Mayo-Robson’s symptom were positive. Symptoms of peritoneal irritation were negative. Bloating was determined. The stool over the past day was repeated, loose. In the urination organs, there was a negative CVAT on the lower back, urination is free and painless.

At the time of admission, decompensation of carbohydrate metabolism was noted, the level of HbA1c was 9% (norm up to 6%), daily fluctuations in glycemia were from 6.2 to 18.8 mmol/l (Table 1). The patient was transferred to intensive insulin aspart therapy with 4–6 units per meal, insulin glargine 6 units at 10:00 p.m., oral antihyperglycemic drugs were withdrawn. Therefore the target values of glycemia were achieved. According to the biochemical analysis of blood, pancreatic amylase was 58.69 U/L (8–53), according to urine analysis, alpha-amylase was 59 U/L (21–447), total bilirubin was 11.6 μmol/L (3.4–20.5), aspartate aminotransferase (AST) was 46.0 U/L (5.0–34), alanine aminotransferase (ALT) was 67.0 U/L (0–55), gamma-glutamyl transferase (GGT) was 50 U/l (9.0–36.0). According to ultrasound of the abdominal organs from 09.10.17, there were echographic signs of diffuse changes in the pancreas, hepatosteatosis, gallbladder deformity, containing hypoechoic suspension. The condition was regarded as an exacerbation of chronic pancreatitis. The patient was consulted by a gastroenterologist, an analysis of feces for pancreatic elastase-1 (on an outpatient basis) was recommended. Diet therapy was conducted (menu No. 5), as well as detoxification and antispasmodic therapy which resulted in a significant improvement in general condition. During hospitalization, a decrease in renal function was confirmed (creatinine level 109.1 μmol/L, GFR by CKD-EPI 48.8 ml/min/1.73 m² (EPI), albumin-to-creatinine ratio in a single portion of urine 9.02 mg/mmol (0–3.5)). The antihypertensive therapy was adjusted, while taking angiotensin receptor blockers and beta-blocker, the target values of blood pressure and heart rate were achieved. The continuous intake of drugs of the group of angiotensin receptor blockers (ARBs) is indicated for nephroprotection. On the part of phosphorus and calcium metabolism, a slight increase in the PTH level to 65.8 pg/ml (15.0–65.0), total calcium of 2.47 mmol/l, albumin-corrected calcium of 2.27 mmol/l, and phosphorus of 1 mmol/L were under notice. It should be noted that earlier, while taking colecalciferol in a saturating dose, a significant decrease in PTH was achieved (in fact, a test with colecalciferol was performed). X-ray densitometry of the radial bone was performed for the first time, osteoporosis was detected in the ultra-distal section (-2.7 according to the T-criterion). Therefore, the condition with an increase in the PTH level after surgical treatment was regarded as secondary hyperparathyroidism, which could be caused, on the one hand, by a deficiency of vitamin D, and on the other hand, by decreased renal function. It was recommended to continue taking native vitamin D preparations in a maintenance dose under the control of calcium, serum phosphorus, and PTH levels and changes in densitometry in time.

Data for the presence of micro-, macrovascular, and neurological complications of DM were not obtained.
In the biochemical analysis of blood, marked dyslipidemia was noted (total cholesterol 10.7 mmol/L, triglycerides 7.2 mmol/L, type III according to Frederickson), the intake of fibrates was continued. Consultation of a specialist in lipid metabolism disorders was recommended. The level of uric acid was within the reference range.

The patient provided the conclusion of an outpatient multispiral computed tomography (MSCT) of the abdominal cavity and retroperitoneal organs, performed 2 weeks before hospitalization, (images, the disc was not provided), which revealed calcifications of up to 1.3 mm in the parenchyma of the pancreatic head and tail and nephrocalcinosis (single microcalcifications in the thinned kidney parenchyma). In addition, calcifications were determined in the soft tissues of the abdomen in the area of postoperative fibrous cords.

Table 1. Diary of glycemia. There was pancreatitis exacerbation from 06.10.10.2017. Improvement of the condition and reduction of pain were noted from 10.10.2017.

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The following diagnosis was made. Primary disease was diabetes mellitus due to chronic pancreatitis; chronic pancreatitis, incomplete remission (ICD-10 code E13.2). Concomitant diseases were primary hyperparathyroidism (osteo-visceral form?), remission after parathyroidectomy of 02.2017; nephropathy of complex origin (hyperparathyroid, hypertonic nephroangiosclerosis, diabetic), CKD C3a A2. Secondary hyperparathyroidism with CKD and vitamin D deficiency, drug compensation. Osteoporosis with a predominant decrease in bone mineral density (BMD) in the radial bone (~2.7 according to the T-criterion). Hypertension 2 deg., normotonia has been achieved with therapy, risk 3. Dyslipidemia type III by Frederickson. Cysts of both kidneys. Chronic gastritis, remission. Biliary dyskinesia along with gallbladder deformity, biliary sludge. Chronic noncalculolus cholecystitis. Nonalcoholic steatohepatitis with signs of intrahepatic cholestasis.

The patient was discharged with significant improvement, namely the exacerbation of chronic pancreatitis was stopped, and the target values of daily glycemia were achieved.

To achieve a stable remission of existing diseases, firstly, glycemic control was recommended to the patient, as given the complex pathogenesis of carbohydrate metabolism disorders, the key to stable glycemia is, in addition to the insulin therapy received, the achievement of a stable remission of pancreatitis. Normalization of lipid metabolism is necessary and the use of fibrates is recommended to reduce the frequency of pancreatitis exacerbations. Compensation and control of calcium and phosphorus metabolism, and normalization of vitamin D levels enable to prevent the progression of osteoporosis. The monitoring of renal function, the constant intake of ARBs or ACE inhibitors (for nephroprotection) under the control of potassium and creatinine levels, and the achievement of the target BP no higher than 140/85 mm Hg have been indicated. Follow-up by an endocrinologist, nephrologist, and gastroenterologist is also recommended.

DISCUSSION

The patient’s DM was regarded as pancreatogenic based on a clearly visible causal relationship between exacerbations of pancreatitis and hyperglycemia. Given the absence of all the necessary diagnostic criteria, the discharge epicrisis contained recommendations for further diagnostic searches, and the need for additional diagnostic tests to clarify the diagnosis, which can be refuted, was clarified. The examination
The presence of various, sequentially developed and, at first glance, unrelated diseases in the patient described made me think about their possible causal relationship. An additional examination is certainly required in order to confirm or refute the diagnosis of pancreatogenic diabetes mellitus, however, the given plan included analysis of feces for pancreatic elastase-1, amylase, a blood lipase test, etc. during the next exacerbation of the disease, which were not available for research in an endocrinological hospital [7]. Given the high level of C-peptide, the absence of acetonuria, the determination of the level of antibodies for differential diagnostics with DM1 was not conducted during that hospitalization. These studies were recommended to perform on an outpatient basis due to the limitation of possible studies within the framework of hospitalization at the expense of compulsory medical insurance.

It should be noted that the presence of intrinsic secretion of insulin does not refute the possibility of pancreatogenic DM development. The special aspect of DM3c pathogenesis at the initial stage is an inflammatory syndrome accompanied by a digestive disorder. Disorders in the digestion processes can lead to a change in the secretion of incretins and reduce glucose tolerance. In turn, fibrosis, β-cell mass loss and insulin deficiency may not develop immediately, but with a longer course of the disease [7, 10]. Despite the absence of insulin resistance in the criteria for the diagnostics of pancreatogenic DM, the question of insulin sensitivity in this disease remains controversial, as a number of authors emphasize its important contribution to the development of pancreatogenic DM, while others note its absence [11]. Thus, an unambiguous understanding of pancreatogenic DM pathogenesis has not yet been developed, and many questions remain open.

The condition of this patient could be aggravated due to the visceral form of primary hyperparathyroidism on history (which is confirmed by the presence of calcifications in the pancreas, detected during MSCT). Nephrocalcinosis, a history of nephrolithiasis, calcifications in the soft tissues of the abdomen in the area of postoperative fibrous cords and dense nodular formations in the region of the first metatarsophalangeal joint on the left and the distal interphalangeal joint of the finger III on the right (regarded during previous hospitalizations as gouty pearl and Heberden’s node, respectively) indicated also the visceral form of hyperparathyroidism, which in the aspect of PHPT can be interpreted as peripheral calcifications. At the same time, it is worth noting that ruling out the gouty nature of nodular formation in the region of the first metatarsophalangeal joint is possible only by puncture of the synovial fluid or the node itself and the absence of sodium monourate crystals in the puncture sample [13], so the question of the nature of this formation remains open. In this case, impaired renal function is complex in nature and is a consequence of arterial hypertension, visceral form of hyperparathyroidism (urolithiasis and nephrocalcinosis according to MSCT) and, possibly, the development of diabetic nephropathy. The exact nature of the lesion can only be established by a kidney biopsy. The patient’s osteoporosis (T-criterion in the radial bone of -2.7 SD) was diagnosed almost two years after PHPT diagnostics and 8 months after successful surgical treatment, while in the onset of the disease, there was no decrease in BMD. Despite the possible pathogenetic relationship, notionally, these data do not allow osteoporosis to be considered a consequence of previous PHPT; therefore, this diagnosis was made separately. However, the absence of a decrease in BMD in the onset of PHPT in the lumbar spine and femur does not exclude the likelihood of a decrease in BMD in the ultra-distal radius, and it can be assumed that, before surgical treatment, the BMD in the radial bone was even lower. Therefore, in this case, bone damage due to PHPT also can not be excluded.

Undoubtedly, in the case described, PHPT is not the only pathogenetic agent for the development of pancreatic lesions and pancreatogenic DM; chronic cholecystitis and hypertriglyceridemia played undoubtedly an important role. It is true that pancreatic calcifications can also be detected in patients without a history of PHPT. However, according to the authors, this case is of interest particularly because of the debatability of the pathogenetic mechanisms of development of the nosologies described and the impossibility of an unambiguous interpretation of some clinical data. Currently, there are no clear recommendations for the treatment of pancreatogenic DM. Therapy is often started with oral antihyperglycemic agents (metformin, secretagogue), taking pancreatogenic DM as type II DM. The therapy with incretin drugs is of particular interest, but this issue currently requires further study. The choice of antihyperglycemic therapy depends largely on the degree of insulin deficiency. When initiating insulin therapy, doses must be chosen with caution, since insulin secretion maintained at certain stages causes a tendency to hypoglycemic conditions. With exacerbations of pancreatitis, it is recommended to avoid the administration of oral antihyperglycemic drugs [11]. Thus, in our case, given the frequent episodes of chronic pancreatitis exacerbations in the patient, leading to pronounced decompensation of carbohydrate metabolism, and the ineffectiveness of oral sugar-lowering therapy, the continuation of intensive insulin therapy was recommended. If frequent episodes of hypoglycemia occurred, the patient was recommended to consult obligatory an endocrinologist to adjust the therapy and prevent the possibility of self-medication.

CONCLUSION

The presence of various, sequentially developed and, at first glance, unrelated diseases in the patient described made me think about their possible causal relationship. An additional examination is certainly required in order to confirm or refute the diagnosis of pancreatogenic diabetes mellitus, however, the given
clinical case is an example of a possible effect of previous PHPT on the development or aggravation of a combined concomitant pathology (in particular, pancreatitis and DM), despite effective surgical treatment with achievement of PHPT remission.

ADDITIONAL INFORMATION

SOURCE OF FINANCING

The patient was hospitalized at the National Medical Research Center of Endocrinology and was examined at the expense of the compulsory medical insurance fund.

PATIENT CONSENT

The patient signed voluntarily an informed consent to the publication of personal health information in anonymized form in the journal Diabetes.

CONFLICT OF INTEREST

The authors declare no apparent or potential conflicts of interest related to the publication of this article.

PARTICIPATION OF AUTHORS

A.M. Gorbacheva organized the examination of the patient, and wrote the text of the manuscript; N.V. Zaitseva performed the supervision of the patient in the hospital, chose the examination and treatment approach, and wrote the text of the manuscript. All authors made a significant contribution to the research and preparation of the article, read and approved its final version before the publication.

REFERENCES
