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Chapter

Up-To-Date View on the Clinical Manifestations and Complications of Chronic Pancreatitis

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Abstract

Chronic pancreatitis is an inflammatory disease that causes irreversible anatomical changes including infiltration of inflammatory cells, fibrosis and pancreatic calcification with destruction of the structure of the gland, leading to abdominal pain, endocrine and exocrine dysfunction. Pancreatic exocrine insufficiency (PEI) prevalence in chronic pancreatitis varies between 40 and 94%. PEI is diagnosed by direct and indirect tests. Nutritional status is assessed by anthropometric indicators; laboratory tests—hemoglobin, plasma proteins (albumin, prealbumin, retinol-binding protein, transferrin), fat-soluble vitamins A, D, E, K; micronutrients. Pancreatic enzyme replacement therapy (PERT) is a fundamental part of PEI treatment. An optimal PERT could prevent serious PEI complications such as metabolic bone disease, adverse cardiovascular events, cachexia, poor quality of life and mortality. A periodic screening for PEI complications with a respect to their primary and secondary prophylaxis is mandatory. Diabetes mellitus secondary to pancreatic disease is defined as pancreatogenic diabetes or type 3c diabetes mellitus. Patients with chronic pancreatitis are at increased risk for pancreatic cancer influenced by smoking, alcohol abuse, chronic inflammation and pancreatic stellate cells over-proliferation. However, chronic pancreatitis could be further complicated with splenic vein thrombosis, pseudocysts, duodenal or biliary obstruction, pseudoaneurysm and pancreatic duct stones which might require endoscopic or surgical treatment.

Keywords: chronic pancreatitis, pancreatic exocrine insufficiency, enzyme replacement therapy, pancreatogenic diabetes, pseudocysts, splenic vein thrombosis, duodenal or biliary obstruction, pseudoaneurysm, pancreatic duct stones

1. Introduction

Chronic pancreatitis (CP) is an inflammatory disease that causes irreversible anatomical changes and damage including infiltration of inflammatory cells, fibrotic processes and calcifications formation with destruction of the gland structure and thus affects normal nutrients digestion and absorption. The clinically early phase is characterized by pain and recurrent acute pancreatitis episodes and complications, and the late phase by exo- and/or endocrine insufficiency. In 2016, a

new definition of CP was proposed, according to which CP is a fibro-inflammatory syndrome, affecting people with genetic, environmental and/or other risk factors, resulting in a persistent pathological response as a result of parenchymal injury or stress. In addition, some of the following features of advanced CP may be present in each patient: pancreatic atrophy, fibrosis, pain syndrome, ductal stricture, calcifications, pancreatic exocrine/endocrine insufficiency and dysplasia. The frequency of CP per year in the European population is 5–10/100,000. Alcohol abuse is the most observed cause. Recurrent episodes of acute pancreatitis and heredity as a contributing factor may result into CP development [1–7].

Pain is the most frequent symptom in CP patients, leading to quality of life impairment. Its pathogenesis is still poorly understood. Multimodal approach, including lifestyle changes, medical therapy, pancreatic endoscopic and surgical procedures, and other non-pharmacological options are recommended [8, 9].

The pancreatic enzymes lipase, amylase, trypsin and chymotrypsin, released predominantly by the duodenal mucosa exposure of nutrients—especially lipids, are of great importance for the macronutrient digestion. Their secretion comprises the following three phases—maximum, stable and basic secretion. Pancreatic enzymes amount and action duration depend on the caloric content maldigestion, the food type and its physical properties [1, 6, 7, 10, 11].

Pancreatic exocrine insufficiency (PEI) due to a progressive loss of acinar cells is a functional limitation of pancreatic enzyme and bicarbonate secretion, regardless its etiology, leading to digestive process deficiency. Main pathological mechanisms in adults are (1) Insufficient pancreatic secretory capacity, (2) Decreased gland stimulation, (3) Impaired enzymes release in the duodenum. The causes are divided into primary (chronic pancreatitis, cystic fibrosis, pancreatic agenesis, congenital pancreatic hypoplasia, Shwachman-Diamond syndrome, Johanson-Blizzard syndrome, pancreatic lipomatosis or atrophy, isolated lipase or co-lipase deficiency, pancreatic carcinoma, pancreatic resection) and secondary (reduced cholecystokinin releasing, somatostatinoma or exogenous administration of somatostatin, gastrinoma, (sub) total gastrectomy, resections and Billroth II anastomosis, periampullary tumors) [11–15].

Although not studied in-depth, the reported prevalence of PEI in patients with CP varies widely between 40 and 94%. The onset of PEI depends on the CP etiology and is about 10–15 years (5–6 years for alcoholic CP) after initiating the pathological CP processes, which is explained by the large functional reserve capacity. Decompensation occurs when the enzyme secretion is reduced by 90–95%. However, in some patients PEI symptoms such as malnutrition and/or abdominal symptoms (diarrhea, flatulence, pain), steatorrhea, body weight loss are first appearance of the disease [1, 7, 16–18].

Although steatorrhea is a typical symptom of a severe PEI, no clinical symptom unambiguously proves or excludes PEI. Steatorrhea may be absent or caused by pancreatic duct obstruction, low duodenal pH, decreased contact time due to increased motility, small intestinal bacterial overgrowth. Fat-soluble vitamin insufficiency, protein malnutrition, increased risk of osteoporosis and fractures, life-threatening complications such as cardiovascular events are further PEI complications [2, 5, 19–22].

An up-to-date assessment of pancreatic exocrine function allows diagnosis of PEI, initiation of pancreatic enzyme replacement therapy (PERT) and its monitoring. Pancreatic exocrine secretion can be assessed by direct and indirect methods. Direct tests are based on determination of volume, bicarbonates and/or enzymes in the stimulated pancreatic gland by intravenous administration of hormones or their peptide analogs. These methods are invasive because duodenal

intubation and a duodenal juice sample are required. Most indirect methods, which evaluate either the digestive ability of the pancreas or the pancreatic secretion by quantification of pancreatic enzymes, are non-invasive, but some require blood sampling and are then considered invasive. The clinical benefit of each method is based on diagnostic accuracy, relevance in clinical practice and cost [20, 23–25].

Pancreatic enzyme replacement therapy is an essential part of PEI treatment. Nowadays a majority of patients with PEI might be asymptomatic, receiving none or suboptimal PERT. They are at increased risk of PEI complications and impaired quality of life. Patients' compliance should be ensured. Periodical monitoring of PERT by nutritional assessment and BMI is mandatory with a respect to primary and secondary prophylaxis of risk factors [1, 6, 18, 26–30].

Pancreatogenic diabetes or type 3c diabetes mellitus develops secondary to pancreatic disease. Recently, DM type 3c is a more recognizable entity due to new proposed criteria. It is a complex disease, further complicated by the presence of comorbidities such as maldigestion and accompanying malnutrition. Metformin is a treatment of choice. Annually screening for type 3c DM by fasting glucose levels and HbA1c is of a great importance in patients with CP regardless the grade of pathological structural changes [17, 18, 20, 31, 32].

Many studies are conducted to demonstrate the association between CP with tropical and hereditary etiology and DM with pancreatic cancer development. The pathogenesis of malignant transformation on the basis of CP remains unclear. Biomarkers and imaging modalities are used to distinguish inflammation from neoplasia [33, 34].

The management of the miscellaneous CP complications pseudocysts, splenic vein thrombosis, duodenal and biliary obstruction, pseudoaneurysm, pancreatic calculi consists of their screening and treating [23].

2. Clinical manifestations of chronic pancreatitis and their management

2.1 Abdominal pain

Abdominal pain is a predominant symptom, affecting 80–90% of patients with CP. Pain significantly reduce quality of life. Pathogenesis is still poorly understood. Multifactorial mechanisms are proposed, including inflammation; duct obstruction followed by hypertension and ischemia; neuronal damage—neuropathic and dysfunctional pain due to hypersensitivity, central and spinal nociceptive neurons alterations. Alcohol and tobacco have contributing role for pain exacerbation. Pancreatic pain covers the characteristics of visceral pain—diffuse severe dull persistent pain, usually with epigastrium location and further radiation to the back, left or right hypochondria. Pain is not necessarily linked to a new acute episode and often worsens with food intake. Pain could be recurrent, during acute episodes and prolonged. Questionnaire scales could be used for pain characterization: Izbicki pain score, brief pain inventory (validated for CP), quantitative sensory testing. According to newest guidelines a multi-modal approach, including lifestyle changes, medical therapy and non-pharmacological approaches, is recommended. Alcohol and tobacco cessation should be advised in all patients. PERT could release pain in patients with ductal obstruction as oral enzymes reduce cholecystokinin levels and therefore decrease pancreatic juice secretion, leading otherwise to duct hypertension. A combination of antioxidants is useful to reduce the oxidative stress and damage. According to the published in 1986 WHO stepwise analgesic's approach is recommended. Simple

analgesics (Paracetamol, NSAIDs, Aspirin) are first-line drugs with Paracetamol being the preferable one. If no pain relief is achieved, weak opioids (Tramadol), strong opioids (Morphine, Oxycodone), gabapentinoids (Pregabalin), antidepressants or *N*-methyl-d-aspartate receptor antagonists (Ketamine) could be used. Endoscopic treatment with or without Extracorporeal Shock Wave Lithotripsy has a beneficial role in cases with duct obstruction (see below). If endoscopic treatment is ineffective, surgery procedures (drainage, partial or total resection) are indicated. Better results are observed, when applied in early stages of CP and in patients with no opioids requirements. Other non-pharmacological options in selected patients include bilateral thoracoscopic splanchnicectomy, celiac plexus blocks and splanchnic nerve ablation, spinal cord stimulation, transcranial magnetic stimulation, psychological therapies [8, 9].

2.2 Pancreatic exocrine insufficiency

2.2.1 Pancreatic exocrine insufficiency assessment by direct functional tests

2.2.1.1 Secretin stimulation test

Hormonal stimulation tests are considered to be the most sensitive and specific tests that investigate pancreatic function, including chronic pancreatitis. The test, introduced by Dreiling in 1948, is based on the physiological pancreatic stimulation by secretin with release of water and bicarbonates from the centroacinar and ductal cells. The volume of the duodenum aspiration and bicarbonate concentration are evaluated after double lumen duodenal tube insertion. Standardized ranges, which exclude pancreatic exocrine insufficiency, are: 80–130 mEq/L for peak bicarbonate concentration; 10.1–37.0 mEq/h bicarbonate output, and volume 1.5–5.7 mL/kg for volume/kg. The patient is most likely to suffer from CP if the peak bicarbonate concentration is less than 80 mEq/L. The sensitivity of the test ranges between 60 and 94% and the specificity between 67 and 95%. In a growing number of publications, the use of secretin in the course of other techniques (secretin-enhanced MRCP or endoscopic secretin testing) demonstrates the ability for evaluation of minimal structural changes in the pancreas, in contrast to standard imaging methods which fail to diagnose them [35–38].

2.2.1.2 Cholecystokinin stimulation testing

The classical cholecystokinin stimulation test was developed and first used in the Mayo Clinic. The test measures the enzyme output. Cholecystokinin is given as a continuous infusion of 40 ng/kg/h, but can also be administered as a bolus. Cholecystokinin increases bile secretion in the duodenum during the first 20–40 min after administration, and as a result, the measurement of pancreatic secretion might be affected. The cholecystokinin test disadvantages are as follows: a need for simultaneous gastric and duodenal juices collection during intubation, duodenal perfusion of mannitol and polyethylene glycol solution, delayed stomach emptying, mediation of pain, symptoms of nausea and vomiting most probably due to blood–brain barrier passage [35, 39–43].

2.2.1.3 Secretin-cholecystokinin testing

The combined secretin-cholecystokinin stimulation testing, also called the secretin-pancreozymin test, allows the simultaneous measurement of secretion of

both bicarbonate and enzyme by the pancreatic gland. However, cholecystokinin may be administered before or after secretion as long as there is no international standard for test performing and it seems to play insignificant role for diagnostic accuracy. Like the classic cholecystokinin test, it increases the secretion of bile in the duodenum [24, 35, 44].

2.2.1.4 Endoscopic testing

After introducing the idea of obtaining pure pancreatic juice during ERCP in 1982, the technique was adopted and modified by the Japanese pancreatic group and the Cleveland Clinic researchers. The pancreatic fluid collected during ERCP has a higher bicarbonate concentration compared with the classic secretin test (130 mEq/L for healthy subjects and less than 105 mEq/L for CP) and is not contaminated with bile and duodenal content. The drawbacks of the method are the potential ERCP complications, the relatively short time for sample collection—15 min and the need for sedation, which can affect pancreatic secretion. Therefore, the collection of duodenal juice after secretin with or without cholecystokinin stimulation during a standard endoscopic procedure with a tube placed in the endoscope biopsy canal was developed as a comparable alternative. The peak of bicarbonate concentration and the lipolytic activity in the duodenal juice are significantly lower in patients with CP. However, experts find bicarbonate and enzyme output to be more reliable markers for exocrine pancreatic function. Due to its nature—invasiveness, labor intensity, length of procedure (endoscope placement in the duodenum for 1 h) and price, the use of endoscopic tests is limited to some specialized centers, so they are not widely used in everyday practice [24, 39, 45].

2.2.1.5 Secretin-enhanced MRCP (s-MRCP)

Secretin-enhanced MRCP becomes more and more interesting as a method of visualization and morphological assessment of the pancreatic structure, as well as for quantitative assessment of various aspects of pancreatic exocrine function. The magnetic resonance technique has a number of advantages: lack of invasiveness, safety, possibility of three-dimensional reconstruction. The method is costly and is currently limited to large centers, where it is often used in combination with other tests. Its sensitivity is about 90% and is a reliable method for diagnosis of CP in an early stage. In CP, fibrous tissue gradually replaces the glandular elements in the pancreas. This process is reflected in the s-MRCP through characteristic changes in the major pancreatic duct (presence or absence of dilated main pancreatic duct >1 mm), peripheral branches (the presence or absence of dilated peripheral branches) and the volume of pancreatic secretion. The method enables the diagnosis of pancreatic divisum, pseudocysts, ductal disruption resulting from pancreatic necrosis or trauma. For the pancreatic functional evaluation a semiquantitative assessment of the duodenal filling with pancreatic juice at 10th min after secretin application is performed by the following criteria: grade 0-missing duodenal filling; grade 1-only bulbus duodeni filling; grade 2-filling up to genu inferior duodeni; grade 3-fluid filling after genu inferior duodeni. Grade 0–2 is assumed to demonstrate reduced exocrine function. During S-MRCP volume of pancreatic output is predominantly measured. That is why sphincter of Oddi spasm or obstructive lesions may lead to false CP diagnosis. Because of the technique performance and duration the sensitivity could be reduced [35, 46–51].

2.2.2 Pancreatic exocrine insufficiency assessment by indirect functional tests

Indirect pancreatic tests are available in clinical practice and are therefore more common. Indirect tests assess pancreatic exocrine function by quantifying pancreatic digestive ability or pancreatic enzyme levels in feces. The sensitivity and specificity of these indirect tests are variable and lower than the direct ones especially in mild and moderate PEI. From a methodological point of view, tests can be classified as oral and fecal tests.

In the oral tests, the substrate is given per os along with test meal. Pancreatic enzymes hydrolyze the substrate in the duodenum, and released metabolites are absorbed from the intestine, metabolized in the liver and therefore they can be measured in serum, urine or exhaled air. Various extrapancreatic causes could limit the accuracy of oral pancreatic tests, mainly by interfering with normal digestion: reduced gastric emptying, biliary secretion and/or intestinal absorption due to intestinal disease. Impaired gastric emptying may be affected by the administration of metoclopramide or another prokinetic (cisapride, domperidone etc.) [24, 35].

2.2.2.1 ^{13}C -mixed triglycerides breath test

The first oral test for fat malabsorption assessment is based on the use of radioactive iodine ^{131}I -triolein as a substrate. Modern oral tests use non-radioactive substrates the mixed triglyceride test ^{13}C -MTG-breath test, cholesteryl ^{13}C -octanoate, ^{13}C -hydrolein and ^{13}C -triolein. Most commonly used and with the most optimal substrate is the only one optimized so far ^{13}C -MTG breath test, which was introduced into clinical practice by Vantrappen et al. in 1989 and develops as a simple alternative to fecal fat quantification. The test directly measures clinically the most significant effect of exocrine pancreatic function: degradation of triglycerides. Following the already explained metabolic pathway of the labeled substrate in oral tests, $^{13}\text{CO}_2$ is released and eliminated together with the exhaled air and measured by near-infrared analysis or mass spectrometry. Patients with PEI have decreased lipase activity, which can be detected by reduced elimination of $^{13}\text{CO}_2$ in the exhaled air. The ^{13}C -MTG breath test sensitivity for PEI verification is higher than 90%. The current mostly adopted and used protocol is the one developed by Domínguez-Muñoz et al. PEI is diagnosed if values are below 29%. The ^{13}C -MTG breath test is an easy, non-invasive and accurate method of PEI diagnosis. The test is easily applicable in clinical practice and can be repeated as often as necessary. It is also used to monitor the enzyme replacement therapy [24, 52–56].

Fecal tests are based on the quantification of pancreatic enzyme concentration (fecal elastase-1) or activity (chymotrypsin) in feces. Enzymes are deactivated and diluted or concentrated during the intestinal passage, which should be taken into account when interpreting the results [24, 35].

2.2.2.2 Fecal chymotrypsin activity

The test is based on the determination of chymotrypsin activity in a single fecal sample. Fecal chymotrypsin activity lower than 3 U/g is indicative of PEI, but the sensitivity of the test is low. The test is normal in cases of mild CP and in about half of cases with moderate or severe pancreatitis. Significant disadvantages of the test are partial enzyme inactivation during gastrointestinal passage; reduced activity in patients with diarrhea. Quantitative determination of chymotrypsin in feces is an accessible way to assess patient complicity according to the taken replacement therapy as fecal chymotrypsin activity should be significantly increased if oral therapy is administered correctly [24, 35, 57].

2.2.2.3 Fecal elastase-1

The protease elastase represents about 6% of the pancreatic enzyme secretion. Determination of Fecal Elastase-1 (FE-1) is the most common PEI screening test as the enzyme is stable during passage through the gastrointestinal tract, its levels correlate with the secreted amount of the pancreas and the direct functional assays. Even though the determination of FE-1 does not offer a significant advantage over other indirect functional tests, its easy conduction makes it a first step pancreatic function screening tool. FE-1 is determined by monoclonal or polyclonal antibodies ELISA tests. The advantage of monoclonal antibody test is its accuracy during enzyme replacement therapy intake. FE-1 concentrations below 200 µg/g feces indicate PEI, and severe PEI is considered if FE-1 is below 100 µg/g (according to some authors below 50 or even 15 µg/g). The specificity of the test is 93%. Diagnostic sensitivity varies between 54 and 63% in mild pancreatic insufficiency and reaches 82–100% in moderate and severe form. Low levels of FE-1 correlate with morphological changes in CP, objectivized by ERCP and MRCP. Determination of FE-1 is very important and useful in children at the age of 2 months with cystic fibrosis. False positive FE-1 results have been reported in the presence of diarrhea, villous atrophy or a strict vegetarian diet prior to testing [24, 35, 57–62].

2.2.2.4 Steatorrhea-based methods

The amount of released fat in the feces indirectly reflects the degree of fat digestion and thus the secretion of pancreatic lipase. The steatorrhea-based methods are divided into: qualitative (direct microscopy of Sudan III stained preparations), semiquantitative (steatocrit and semiquantitative determination by Sudan III staining) and quantitative (coefficient of fat absorption).

A single fecal sample is used for Sudan III staining. The methodology is based on the number and size of fat drops by high-power field (hpf). The accepted normal ranges are the presence of ≤20 fat drops sized 1–4 µm/hpf. Sudan staining has a sensitivity of up to 94% and 95% specificity for the diagnosis of abnormal fat excretion [35, 63].

Steatocrit is a method for semi-quantitative measurement of fats in feces, expressed as a proportion of the fat content of a single centrifuged and homogenized feces sample. The single determination of acid steatocrit (normal values below 10%) has been shown to have 100% sensitivity for steatorrhea detection and 95% specificity when compared to a 72-h quantitative fat assay [64, 65].

The most reliable and recommended steatorrhea detection method is the 72-h chemical analysis using the van de Kamer method. Many technique modifications have been made so far but still the disadvantages to use large amounts of acids and bases, the manual manipulation of the analysis, the need for additional equipment and specially trained staff remain. However, Near-Infrared Reflectance Analysis (NIRA) methodology, based on the relationship between the intensity of the refractive spectrum of the fecal specimen at a specific wave length and the sample composition, is an alternative, that simplifies and aids application of the study in clinical practice [24, 66].

The coefficient of fat absorption (CFA) is used for a better steatorrhea characterization. The CFA is calculated by the following equation: $CFA (\%) = 100 \times [(mean\ fat\ value - mean\ fat\ in\ feces) / average\ fat\ intake]$. In healthy people CFA is usually over 80%. The technique has a number of disadvantages, that reduce its everyday applicability—a standard diet containing 80–120 g of fat daily for five consecutive days, collection of entire amount of feces from the last 3 days of the

diet, inconvenience during feces storing in laboratories, low specificity (any other cause of maldigestion or malabsorption can lead to abnormal fecal fat excretion) [35, 67, 68].

2.2.2.5 Serum trypsin

The trypsin test is the only currently functional diagnostic test that can be performed in serum. Low concentrations of less than 20 ng/mL are specific for CP, but are only sensitive to advanced stage of disease. Levels ranged from 20 to 29 are intermediate, but in some cases may point to an early CP. The sensitivity of the method varies with mild and severe stages of the disease and is between 33 and 65% while the specificity is high. Another advantage of trypsin is that levels above 150 ng/mL are indicative of pancreatic inflammation even in the case of normal amylase and lipase levels [69].

2.2.3 Evaluation of nutritional status as a PEI marker

Malnutrition is a major clinical consequence of PEI. Lindkvist et al. studied 114 patients with CP (EUS, MRCP), 33% suffered from PEI according to ¹³C-MTG breath test. Hemoglobin, albumin, prealbumin and retinol-binding protein (RBP) levels below reference limit, magnesium less than 2.05 mg/dL and HbA1C above the upper reference limit are associated with PEI. A normal panel of these serum nutritional markers excludes PEI with a high negative predictive value. In case of an abnormality, these parameters serve as a marker for initiating PERT. Their follow-up would indicate the need to adjust the dose of PERT [1, 4, 70].

2.2.4 Pancreatic exocrine insufficiency treatment

Fundamental aspects of PEI treatment, ensuring an optimal therapeutic effect, include pancreatic enzyme replacement therapy (PERT), smoking and alcohol consumption cessation, frequent small meals with a normal fats intake, fat-soluble vitamins and a systemic follow-up with respect to BMI and nutritional markers. The main aim of PEI treatment is, while compensating the lack of endogenous enzyme secretion including lipolysis, to avoid malabsorption and steatorrhea, decrease complications severity, and prevent the associated with malnutrition morbidity and mortality as well as disease progression [1, 7, 18, 20, 26, 71, 72].

Pancreatic enzyme preparations are extracts of porcine pancreas (pancrelipase or pancreatin) with main components: lipase, amylase, trypsin and chymotrypsin. Their alternatives are bovine enzymes, lipase of mushroom origin, bacterial lipase and human lipase. The pancreatic digestive enzymes in PERT are administered orally together with the meal to ensure the mixing of pancreatin with the humus [1, 7, 11, 18, 26, 27, 71, 73, 74].

Currently, the main formulations of the enzyme preparations are with immediate release, enteric-coated microspheres and minimicrospheres, enteric-coated microtablets and enteric-coated microspheres with bicarbonate buffer. The most widely used enzyme preparations are administered as acid-resistant enteric-coated minimicrospheres with a pH-related release. Currently, none of the approved enzyme supplements are specifically designed for use through percutaneous gastrostomy. In infants and patients who cannot swallow large capsules, opening the capsules in a small amount of acidic foods is an acceptable way to administer the drug [1, 2, 12, 75–77].

Although not systematically studied in clinical trials, based on recommendations from different national associations the starting dose of PERT ranges between

20,000 to 50,000 IU lipase per main course and half the dose per snacks, which corresponds to about 5–10% of the cumulative lipase activity in the duodenum after normal meal. PERT is well tolerated with no serious adverse events reported. Fibrosing colonopathy is the only serious complication associated with a high PERT dose. Cases of fibrosing colonopathy have been significantly reduced following the recommendation that PERT should not exceed 10,000 IU lipase/kg/day in patients since 1994 [6, 18, 20, 25, 78–82].

Of a great importance is to ensure patient's compliance. If the signs or symptoms of maldigestion persist, the dose of PERT may be increased twice or three times. As the next step for optimal pH release of enzymes and to influence the precipitation of bile acids and prevent lipase degradation, proton pump inhibitors/antacids/H₂ blockers/prostaglandin analogs can be added. If PERT results are still insufficient, diagnosis revision is required in respect to concomitant and/or alternative causes for maldigestion (small intestine bacterial overgrowth, biliary salt deficiency, gastric resection, therapy with certain medications (nonsteroidal anti-inflammatory drugs, antacids). Up to 40% of PEI patients with CP have concomitant small intestinal bacterial overgrowth. Import of 35 kcal/kg/day is required as protein intake of 1.0–1.5 g/kg/day is usually sufficient. Small frequent meals (4–8 times/day) are generally more tolerable than high-calorie meals due to the more effective mixing of the enzyme preparations with the humus. In the modern nutritional concept of PEI no fat restrictions are advisable to reduce the risk of weight loss and deficiency of fat-soluble vitamins. In addition, studies show that corresponding substance presence increases the half-life of the enzyme activity in small intestine [1, 5, 6, 18, 20, 25, 27, 73, 83–87].

Oral, enteral and parenteral nutrition are needed in about 10–15, 5 and 1% of patients respectively, usually in case of disease complications (gastric obstruction) prior to surgery or for a short period of time in patients with advanced exocrine insufficiency [4, 20, 25, 79, 88, 89].

Alcohol and tobacco cessation are of a great importance as they are associated with development of pancreatic cancer, acute and chronic pancreatitis, deterioration of pancreatic exocrine function as shown by endoscopic functional tests in CP cases. Earlier development of calcified pancreatitis and diabetes mellitus are observed in patients with prolonged smoking. Physical activity and a healthy life style along with nutritional therapy should be encouraged for optimal outcome [1, 7, 20, 27, 90].

Most leading researchers recommend a reassessment of symptoms, BMI and serum malnutrition tests with long-term normalization of vitamin status for determining success of PEI treatment. In recent years, studies have shown widespread nutritional deficiencies (fat-soluble vitamins, prealbumin, retinol-binding protein (RBP), and magnesium) in patients with PEI with or without symptoms, which are associated with many risk factors, including malabsorption, diabetes mellitus and alcoholism. Protein markers prealbumin and RBP correlate with age, BMI, morphological changes, fat-soluble vitamins, albumin, hemoglobin, magnesium. According to the United European Gastroenterology evidence based guidelines for the diagnosis and therapy of CP (HaPanEU), PERT should be initiated in patients with PEI in the presence of clinical symptoms or nutritional deficiencies. By PERT optimization in patients with suboptimal dosage an improvement in the nutritional markers is observed [1, 7, 18, 20, 25, 26, 72, 79, 91–95].

Deficiency of vitamins A, D, E, K correlates with the severity of steatorrhea in patients with CP and PEI, but can be caused by various mechanisms, including fat malabsorption, suboptimal nutrition, higher losses or requirements, nutrient depletion, antioxidant activity. Vitamin A, D, E and K deficiency are observed in 3, 53, 10 and 63% of patients (Sikkens et al.) with no clinical manifestations of vitamin E deficiency in up to 75% of CP patients. It has been established that the severity

of CP (according to the Cambridge classification) correlates with the bone mineral density of the spine and the femoral neck. Patients with CP regardless their exocrine status have more often than expected reduced bone mineral density as shown in a recent meta-analysis: 1 in 4 patients were diagnosed with osteoporosis and 2/3 with osteopathy. Risk factors for fractures include female gender, older patients (the relative risk is higher in younger patients), smoking, alcohol consumption (60–150% greater risk than non-alcoholic CP patients), chronic inflammation, low BMI regardless of bone mineral density. The incidence of fractures after minimal trauma among CP patients is comparable and even higher than in patients with high-risk gastrointestinal diseases (Crohn's disease, cirrhosis, celiac disease, after gastrectomy), for which guidelines for osteoporosis screening exists. The treatment of osteopathy should be carried out in accordance with up-to-date guidelines on the treatment of metabolic bone disease in the general population [2, 14, 16, 27, 28, 59, 65, 96–103].

In addition to bone metabolism, vitamin D is a factor in the development of pancreatic fibrosis and atrophy, cardiovascular and autoimmune diseases, type 1 and 2 diabetes mellitus, and contributes to an increased overall mortality [104, 105].

Due to insufficient protease secretion from the pancreas, vitamin B12 deficiency may occur. Micronutrient deficiencies have been reported as well: zinc (especially in diabetes mellitus), calcium (normal levels in patients receiving PERT), magnesium, thiamine and folic acid, riboflavin, choline, manganese, sulfur, copper and others [106–108].

The assessment of fat-soluble vitamins, minerals and trace elements and bone density should be monitored 1–2 times a year [109].

2.2.5 Cardiovascular risk evaluation

A recent study observed increased mortality in patients with PEI. Patients who died used to have a worse nutritional status. However, an optimal PERT is essential to reduce morbidity and mortality associated with CP. Maldigestion is associated with life-threatening complications such as cardiovascular, cachexia, which are related to low plasma levels of the cardioprotective HDL, apolipoprotein (apo) A-I and lipoprotein A (2). In a recent study in patients with CP who had not received PERT, mean triglyceride levels were found to be significantly higher in patients with PEI than those without PEI. According to randomized clinical trials, mean levels of cholesterol, HDL, LDL and triglycerides in patients with CP and PEI receiving PERT have been reported in reference ranges. Based on American, European and Canadian guidelines, a complex approach, including screening systems, lipid profile, apolipoproteins, is needed to properly assess cardiovascular risk. Apolipoprotein B as part of all atherogenic or potentially atherogenic particles including LDL, VLDL, IDL, lipoprotein (a) (each particle contains 1 molecule of apo B) provides direct measurement of all atherogenic lipoprotein particles in the circulation, which makes apo B more reliable indicator of cardiovascular risk than LDL. Clinical and epidemiological studies confirm that apo B and Apo B/Apo A-I ratio are associated with a worse outcome in patients with cardiovascular diseases and are supposed to predict cardiovascular incidents more accurately than the routinely tested cholesterol, LDL, TC/HDL, non-HDL. The proposed cut-off values for Apo B/ApoA-I ratio predicting high cardiovascular risk (acute myocardial infarction) are 0.9 for men and 0.8 for women. In patients with Apo B/ApoA-I ratio higher than 0.9, higher triglyceride levels and plasma atherogenic index and lower apo E were found. A study demonstrates an increased risk of myocardial infarction using Apo B/Apo A-I ratio in patients with CP [1, 5, 7, 79, 89, 110–131].

Apolipoprotein A, which is the main apolipoprotein associated with HDL, has two forms—apo A-I and apo A-II. The levels of apolipoprotein A-I are strongly related to those of HDL and can serve for plasma HDL level determination. In a recent study, an impaired nutritional status with decreased prealbumin, RBP, hemoglobin, magnesium has been found to significantly relate to low apoA-I and apoA-II levels with a tendency of increased apo B/apo A-I ratio, which does not reach a significant value. Apolipoprotein C-III inhibits the lipolysis of triglyceride-rich lipoproteins and complicates their elimination from the bloodstream. High levels of apolipoprotein C-III are associated with an increased risk of cardiovascular events and atherogenesis. Lower apolipoprotein C-III levels are observed by morphological changes worsening in CP. The metabolic and inflammatory status in patients with CP can be traced with great accuracy by examining a protein panel of retinol binding protein, serum amyloid-alpha, Apo A-II, Apo A-I, Apo C-I, Apo C-II, Apo C-III and prealbumin, which are significantly more reduced than the controls (Hartmann et al.). The observed changes may be associated with underlying malnutrition/cachexia, which phenomena are known in the modulation of the synthesis of acute phase proteins in acute or chronic disease [112, 119, 127, 128, 130, 132–137].

2.3 Pancreatic endocrine insufficiency

In respect to its etiology, the diabetes mellitus (DM), which is caused by pancreatic diseases, is defined by the American Diabetes Association (ADA) and World Health Organization as pancreatogenic diabetes or Type 3c DM and is included in “other specific forms of diabetes” (ADA). About 5–10% of all diabetic patients in Western populations fulfill the criteria for pancreatogenic DM, of which circa 80% have underlying CP. The prevalence and clinical significance of DM secondary to CP has been recently underestimated. The median survival is 8.7 years after diagnosing type 3c DM. Chronic pancreatitis and DM are independent risk factors for pancreatic cancer development. While the presence of anti-insulin antibodies and clinical or biochemical data on insulin resistance are associated with type 1 and 2 DM respectively, the pathogenesis of type 3c DM is very complex. According to the recommendations of Rickels MR et al. from the Pancreas Fest 2012, the following criteria for the diagnosis of type 3c DM were proposed. Major criteria (all must be fulfilled): (1) Pancreatic exocrine insufficiency. (2) Pathological pancreas imaging (EUS, MRI, CT). (3) Lack of type 1 DM associated with the presence of autoantibodies. Minor criteria: (1) Impaired beta-cell function (HOMA-B, C-peptide/glucose ratio). (2) Lack of insulin resistance (HOMA-IR). (3) Invasive secretion disorder (GLP-1, pancreatic polypeptide). (4) Low levels of serum fat-soluble vitamins (A, D, E, K). Because of loss of glucagon response to hypoglycemia and low carbohydrate levels (malabsorption; inadequate food intake due to pain, nausea and/or chronic alcohol abuse), patients with type 3c DM may experience frequent episodes of hypoglycemia, making the glucose control challenging. The course of the disease is further complicated by the presence of comorbidities such as maldigestion and accompanying malnutrition. Metformin, which is recommend as first-line treatment for type 2 DM by ADA and EASD, has been shown to reduce the risk of pancreatic cancer by 70% and the associated mortality, making metformin suitable therapeutic option for type 3c DM patients. The associated with an increased risk of developing pancreatitis as well as numerous gastrointestinal side effects (nausea, delayed gastric emptying, weight loss) GLP-1 analogues and DPP4-inhibitors should be avoided as long as their safety and benefits are proven. Impaired incretin hormone secretion can be normalized by supplementation with pancreatic enzymes, which is reflected

in improved insulin secretion and glucose tolerance during meals. Adequate oral enzyme replacement affects steatorrhea, prevents malnutrition and metabolic complications. In patients with severe malnutrition, insulin therapy is a first-line of choice because of the anabolic effect of insulin. The association of low levels of vitamin D and poor glycemic control draws attention to the need to normalize vitamin status in patients with type 3c DM. Diagnosis and monitoring of DM should be consistent with the endocrinology societies guidelines. Annually screening for type 3c DM by fasting glucose and HbA1c is of a great importance in patients with CP regardless the grade of pathological structural changes [18, 20, 25, 31, 32, 122, 138–143].

3. Chronic pancreatitis complications and their management

3.1 Pancreatic cancer

Since the first report by Rocca et al. in 1987 for an increased incidence of pancreatic cancer (PC) in patients with CP, several epidemiological studies have identified that CP, mainly tropical and hereditary pancreatitis, is a major risk factor for pancreatic cancer development. Augustine et al. reported that PC is affecting 8.3% of patients with CP with a roughly 100-fold higher incidence compared to patients without tropical pancreatitis. Younger patients are affected and have a worse outcome. In hereditary CP due to multiple PRSS1 mutations the lifetime risk for PC is 40–55% by the age of 70. Possible explanations for the increased neoplastic transformation risk are the onset of CP at younger age and its long duration. Various risk factors for PC development have been described, of which smoking is the major one. In a recent study, Hao et al. (2017) suggest that age at the onset of CP (hazard ratio, 1.05) and a > 60 pack-year smoking history (hazard ratio, 11.83) are PC risk factors. CP as an inflammatory disease is associated with higher cell turnover with/without DNA damage, progressing to oncogenic mutations in K-ras, p16 and p53 promoting metaplasia and neoplastic degeneration. Another well-known PC risk factor is diabetes mellitus. Ethanol and its metabolites are supposed to activate pancreatic stellate cells over-proliferation. They play a role in tumor progression and chemotherapy resistance. Moreover, cholecystokinin receptors are abnormally over-produced. Clinical features may mimic those of CP in early stages. When symptoms such as obstructive jaundice, pain, weight loss and worsening of diabetes appear, all of which are specific for malignancy, this generally indicates that the disease is at an advanced stage. The most investigated biomarker for malignancy prediction is CA 19–9 with 96.5–100% specificity. Based on metabolic biomarkers, Mayerle et al. (2018) introduce a novel approach for differential diagnose between CP and PC with an accuracy of 90% and a negative predictive value of 99.9%. Other promising markers are plasma micro-RNAs, monoclonal antibody PAM4, CD1D, which require further investigation. For the imaging diagnosis of PC, a CT scan is the technique of choice. Endoscopic ultrasound (EUS) could detect small pancreatic tumors in CP patients at a highest sensitivity compared to the available imaging and has the potential to detect early stage PC. The most appropriate cancer treatment (surgery, chemotherapy, radiation) depends on disease proliferation, defining the cancer as resectable, locally advanced or metastatic [144–149].

3.2 Pseudocysts

Pancreatic pseudocysts are common complication in CP with a frequency of 20–40%. The majority of patients are with alcoholic (70–80%) or idiopathic

etiology of CP (6–16%). The outcome of pseudocysts is assessed 6 weeks after acute episode occurring. In 40% of the pseudocysts there is a spontaneous resolution, another 40% of pseudocysts remain asymptomatic and in 20% of pseudocysts complications are observed (infection, rupture, bleeding, splenic vein thrombosis). Treatment is required if patients are symptomatic, if complications or obstruction of the stomach, duodenum or bile duct occur. Drainage of chronic pseudocysts may be performed by surgical, endoscopic or percutaneous approach. In asymptomatic pseudocysts with size above 5 cm, due to high possibility of complications, an endoscopic or surgical treatment is recommended. Percutaneous drainage should be avoided where possible. In chronic pseudocysts the endoscopic procedure is the treatment of choice due to lower mortality rate, improved quality of life and less length of hospitalization stay. Depending on size and localization, two endoscopic techniques are performed. A transpapillary approach should be considered in small pseudocysts with communication with the main pancreatic duct. The transmural approach (cystogastrostomy) is similar to the management of walled-off necrosis. It is more successful under echoendoscopic guidance. Double-pigtail plastic stents for at least 2 months are used for pseudocyst drainage. If a malignant genesis of the pseudocyst is suspected, surgery should follow [148, 150–156].

3.3 Splenic vein thrombosis

In 1920 Hirschfeldt first reported splenic vein thrombosis (SVT) as a pancreatitis consequence. Secondary involvement of the splenic vein endothelium by a nearby inflammation, compression by a pseudocyst or enlarged retroperitoneal/pancreatic lymph nodes or initial injury could result in a splenic vein thrombosis and obstruction. The incidence of SVT in patients with CP is 1.5–41.6%. Sinistral portal hypertension and collateral development resulting in gastric and/or esophageal varices are major risk factor for bleeding. Splenomegaly is reported in 42–54% of patients. Most patients are asymptomatic. Clinical features include gastrointestinal bleeding in 12.3% of cases and abdominal pain. SVT is diagnosed primary by contrast-enhanced CT scan and/or upper endoscopy. Venous phase angiography is the gold standard confirmatory test, which could verify obstruction and collateral routes. Based on the widely available CT scan most patients nowadays are diagnosed asymptomatic. The SVT management depends on existing symptoms including hypersplenic syndrome and history of variceal bleeding, which might require splenectomy with venous collateral outflow elimination and further variceal decompression. Gastric varices should be treated endoscopically by sclerotherapy, gastric banding [148, 157–162].

3.4 Duodenal obstruction

The duodenal obstruction is a rare complication in CP patients (1%) due to the anatomical relationship between the duodenum and the head of the pancreas. However, when analyzing operated patients with CP, the incidence of duodenal obstruction is higher—12%. Two types of obstruction are observed—transients during acute pancreatitis episodes and fixed by pseudocyst compression (discussed above) or fibrosclerotic process. Paraduodenal or groove pancreatitis is a rare clinic-pathological focal type of CP. The reported incidence of groove pancreatitis in resected CP patients ranges between 2.7 and 24.5%. It was first described by Becker in 1973 as a segmental pancreatitis. In 2004 Adsav and Zamboni unify the previously described terms under paraduodenal pancreatitis. The proposed pathophysiological mechanisms comprise functional/

anatomical obstruction of papilla minor, Brunner's gland hyperplasia around papilla minor, heterotopic intraduodenal pancreatic tissue or ductal variation. Two types paraduodenal pancreatitis are defined—cystic and solid. The cystic type is common with localization in the submucosa or lamina propria. The size may reach 10 cm, resulting in a bile duct obstruction. The solid type is rare and includes sheet-like and mass-like subtypes. According to several retrospective studies, the risk groups for paraduodenal pancreatitis development are middle-aged men with alcohol consumption. Acute manifestation complains include postprandial abdominal pain (90–100%), nausea and vomiting (20%), gastric outlet syndrome. Chronic manifestations are weight loss (90%) and jaundice (20%). Perforation, bleeding, malignant degeneration of heterotopic pancreas are reported rare complications. EUS and MRCP are the preferred imaging methods for diagnostic evaluation. Treatment is based on a stepwise approach: (1) conservative treatment (analgesics, infusions, PPI, PERT, enteral nutrition, somatostatin analogues); (2) endoscopic treatment; (3) surgery (Whipple procedure, pancreaticoduodenectomy, suprapapillar duodenal resection in isolated duodenal dystrophy, palliative gastrojejunostomy) [8, 148, 163–170].

3.5 Biliary obstruction

The incidence of distal common bile duct obstruction in patients with advanced chronic predominantly calcific pancreatitis with frequent acute episodes ranges from 3 to 46%. Pseudocysts are considered more as a risk factor than as a cause. Patients may be asymptomatic or with various spectrum of complains and complications—pain, jaundice (transient or persistent for longer than 1 month), cholangitis and even sepsis, long-term risk of secondary biliary cirrhosis. Hyperbilirubinemia and twofold elevation of alkaline phosphatase levels for more than a month are used as reliable laboratory markers for common bile duct obstruction. CT scan provides information for the structural changes with high specificity and sensitivity. Based on the Caroli and Nora criteria, most patients with common bile duct stricture and CP are classified as type I and III. The treatment of choice depends on presence and severity and duration of symptoms; suspected malignant degeneration. To prevent progression to secondary biliary cirrhosis in patients with progressively increased alkaline phosphatase levels or persistent/with frequent relapses hyperbilirubinemia, endoscopic biliary stenting with self-expanding metal stents or multiple plastic stents or surgical procedures (pancreaticoduodenectomy, choledochojejunostomy, choledochoduodenostomy, hepaticojejunostomy) are required [148, 171–173].

3.6 Pseudoaneurysm

Pancreatic pseudoaneurysm as a rare life-threatening chronic pancreatitis complication occurs in 10% of patients, most often in those with pseudocysts. The pseudoaneurysm represents fibrous tissue containing hematoma and is mainly induced by enzymatic autodigestion or eroding of the nearby vessels, most frequent affecting the splenic artery. Most patients are asymptomatic, however, the first clinical manifestation might be bleeding caused by pseudoaneurysm rupture into gastrointestinal tract or other adjacent anatomic structures—peritoneal cavity, retroperitoneum, biliopancreatic ducts (hemorrhage pancreaticus). Shock and multiorgan failure further complicate the rupture. The mortality rate is about 40% and higher (90–100%) if pseudoaneurysm remains untreated. Worst outcome results have been shown in patients with pseudoaneurysm localization in the pancreas head. Angiography is the diagnostic tool of choice. Patients are nowadays treated

surgical, endovascular, by angioembolization and/or by percutaneous ultrasonographically guided thrombin injection. Treatment in diagnosed asymptomatic patients is recommended [174–179].

3.7 Pancreatic duct stones

In about 50% of patients chronic inflammation, gene predisposition and alcohol intake as a key cause change the pancreatic juice composition with pancreatic stone protein levels reduction, leading to formation of a nucleus with calcium deposition layers and later formation of a stone. The pancreatic duct stones are classified according to their number, localization and density to single or multiple calculi; stones in the pancreatic head, body and/or tail; localized in the main pancreatic duct, side-branches and/or parenchyma; radiopaque positive (the majority of cases), negative or mixed stones. The main pathological consequence is the duct obstruction with upstream dilatation, followed by ductal hypertension, which results in pain episodes, exocrine insufficiency due to reduce pancreatic juice flow into duodenum and impaired quality of life. Pancreatic duct stones are diagnosed by ERCP, CT or MRCP. However, MRCP is superior to ERCP for diagnosis as MRCP is a non-invasive alternative with no complications, providing detailed information about duct system and stone formations. Calculi removal could be performed by extracorporeal shock wave lithotripsy (ESWL), endoscopic techniques and surgery. According to the European Society of Gastrointestinal Endoscopy guidelines, first-line therapy for painful uncomplicated CP is ESWL combined or not with ERCP followed by spontaneous expulsion or endoscopic extraction of less than 3 mm fragments. However, ESWL should be performed in centers with ESWL expertise. Best results from endoscopic techniques are observed in patients with early stages of CP with infrequent pain attacks, when calculi are less than 5 mm and have head localization with upstream main pancreatic duct dilatation. Alcohol and tobacco cessation improve the long-lasting results. Endoscopic techniques include ERCP followed by pancreatic sphincterotomy; stone retrieval with a balloon, Dormia basket and/or forceps; dilatation and stent placement; mechanical lithotripsy. Endoscopy procedures together with ESWL improve the success to up to 90%. Direct visualization by pancreatoscopy followed by intraductal lithotripsy (Spyglass system) might be a future procedure of choice but today its use is limited. Surgery should be performed in patients with large or multiple calculi and strictures, after unsuccessful prior endoscopy or ESWL procedures, as well as in those with no pain relief [8, 180–183].

4. Quality of life

With disease progression, patients with CP report for impaired overall quality of life. Many studies are conducted to investigate the contributing factors, leading to low QoL. Pain significantly correlates with overall health status, physical and mental subscales. Researchers emphasize the role of severity in contrast to pain frequency and pathophysiology. A large study of Machiado et al., including 1024 CP patients, highlights constant pain as well as inability due to pain, smoking status and concomitant co-morbidities to worsen significantly QoL with negative influence on both physical and mental domains, leading to worsened social and family status and health resource utilization. Other assumed factors, which importance differs among the literature data, are disease duration, young age, women, tobacco and alcohol intake, underweight, pancreatic structural changes DM, PEI, prior endoscopic or surgical treatments. Psychologically conditioned disturbances

(depression, anxiety etc.) are linked most often to alcohol abuse and might lead to pain manifestation and impaired QoL. A study, which enrolled non-alcoholic CP patients, significant depressive syndromes were associated with poor QoL. By the newest concepts, the quality of life assessment is an essential part of the monitoring and the outcome in patients with CP. The European Organization for Research and Treatment of Cancer (EORTC QLQ) has developed a quality of life questionnaire, containing 30 questions (EORTC QLQ-C30), including an additional question about steatorrhea. The questionnaire correlates with body weight gain and a reduced number of daily defecations related to malnutrition and maldigestion. The quality of life improved after adequate dosing in both newly diagnosed and patients receiving suboptimal PERT. Later, an additional panel of 26 questions concerning pancreatic cancer patients (PAN26) was developed. In the United European Gastroenterology evidence based guidelines for the diagnosis and therapy of CP (HaPanEU), quality of life including pain should be assessed through validated questionnaires (SF-12, SF-36, EORTC QLQ C-30, GIQLI). However, effort should be point at improvement of variable factors as psychological status, tobacco, alcohol consumption and nutritional deficiencies in respect to improve QoL and further to delay disease progression, using therapeutic education and physical rehabilitation, behavioral support and medication [6, 99, 184–190].

5. Conclusion

Chronic pancreatitis is a progressive fibro-inflammatory syndrome, leading to abdominal pain and later to endocrine and exocrine insufficiency. Patients with CP might suffer a wide variety of complications, including pancreatic cancer, splenic vein thrombosis, pseudocysts, duodenal or biliary obstruction, pancreatic calculi, pseudoaneurysm and cardiovascular events. Proper individual up-to-date approach to diagnosis, treatment and follow-up of patients with CP are of fundamental importance to improve symptoms, detect early risk factors and reduce complications, which are associated with high mortality rate, and ensure better quality of life. Screening strategies development and their introduction into the clinical practice should be encouraged.

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