Chapter

Current Approaches in Chronic Pancreatitis

Didem Saka, Can Boynukara, Elif Reyyan Çadırcıbaşı and Gürhan Şişman

Abstract

Chronic pancreatitis is a fibroinflammatory syndrome of the pancreas that results in exocrine and endocrine pancreatic insufficiency and chronic pain. It can be seen in all age groups depending on the etiologic factors. It is believed that alcohol is one of the major etiologic factors of chronic pancreatitis, but it is now recognized that alcohol is responsible for 50% of the cases. Mutations in many genes such as PRSS1, SPINK1, CTRC, CFTR are identified as causative or predisposing factors for CP. Early diagnosis and staging of CP are still a challenge in clinic. Although the chief complaint of patients with CP is abdominal pain, CP can cause many disorders such as diabetes or metabolic bone diseases. The treatment of CP mainly depends on the severity of the disease and morphology of the pancreas. Medical therapy, endoscopy and surgery are all used for the treatment of CP and its complications.

Keywords: pancreas, chronic pancreatitis, endoscopy, gastroenterology, endosonography

1. Introduction

Chronic pancreatitis (CP) is characterized by fibroinflammatory inflammation of pancreatic tissue that causes progressive and irreversible destruction of the exocrine pancreas and loss of islets of Langerhans. The cause of the chronic pancreatitis is often multifactorial, involving chronic alcohol usage, recurrent acute pancreatitis attacks, structural or genetic anomalies.

2. Epidemiology

CP can be seen in all age groups depending on the etiologic factors. Although true prevalence is approximately < 50 per 100,000 adults, peaking in patients aged 46–55 years, the determination of its prevalence is difficult because of local standards and reporting bias. The incidence is predicted to be 4 to 5 new diagnoses per 100,000 yearly [1]. Data from Italian, Spanish, Chinese and Japanese surveys have the similar results as mentioned above [2].

CP is a slightly male predominant disease due to more alcohol and tobacco usage. Recently, several studies aimed to explain male sex predominance with the changes of the Claudin (CLDN)2 locus on the X chromosome in alcohol-induced chronic pancreatitis [3, 4].

Hospital admission for acute and chronic pancreatitis are increasing in the United States. Pancreatitis (acute and chronic) was among the three most common benign gastrointestinal diagnoses and accounted for a 12% increase in emergency room visits since 2006 according to US registry-based analysis that was published in 2019 [5]. Considering the stable or decreasing tobacco and alcohol use in most western countries and the probable unchanging prevalence of genetic risk factors, greater sensitivity of diagnostic testing can be the cause of increased hospital admissions. Approximately 3–35% of patients with a first episode of acute pancreatitis will progress to chronic pancreatitis over 3–8 years [6, 7]. Oppositely, only about 50% of patients with chronic pancreatitis had previously documented episodes of acute pancreatitis [8].

Black patients suffer more severe pain and disability and have more advanced morphological changes on the imaging techniques compared with white patients [9]. These results can be explained by more frequent usage of alcohol and tobacco in those patients. CP, like in many countries, is a male predominance disease in Turkey. The median age of the disease is 46 for male patients and 50 for female patients. The main etiological factor for the disease is alcohol abuse [10].

3. Etiology

It is believed that alcohol is one of the major etiologic factors of chronic pancreatitis, but it is now recognized that alcohol is responsible for 50% of the cases [3]. Therefore, stigmatization of patients with chronic pancreatitis as having an alcohol use disorder is often inaccurate and unfitting. It has been estimated that patients must consume 4–5 alcoholic drinks per day consistently for over 5 years to be at risk [11]. Alcohol exposure has several unwanted effects to the pancreas tissue. Despite common knowledge, it makes pancreas more susceptible to injury rather than directly causing chronic pancreatitis.

Usage of tobacco products is another risk factor for chronic pancreatitis. In the past, it was assumed cigarette smoking caused chronic pancreatitis due to concurrent alcohol consumption, but studies demonstrated a link between an independent and dose-dependent response of tobacco usage and chronic pancreatitis [12]. Also, cigarette smoking is a strong risk factor for recurrent acute pancreatitis which can eventually progress to chronic pancreatitis. Smoking is related to the induction of interleukin-22 secondary to aryl hydrocarbons, which promote pancreatic fibrosis [13].

Recurrent episodes of acute pancreatitis can lead to pancreatic fibrosis, gland atrophy, loss of islet of Langerhans which eventually progress into chronic pancreatitis.

Hereditary pancreatitis is another etiologic factor for developing chronic pancreatitis. It is observed as an autosomal dominant mutation of the cationic trypsinogen gene (PRSS1). Hereditary pancreatitis is an autosomal dominant disease with high penetrance up to 80% but some patients can also develop the PRSS1 gene mutation de novo.

Another mutation can also be the cause of chronic pancreatitis. Including genes that encode serine peptidase inhibitor Kazal type 1 (SPINK1), chymotrypsin C (CTRC), calcium-sensing receptor (CASR), claudin (CLDN2) and cystic fibrosis transmembrane conductance regulator (CFTR). Due to CFTR gene mutation cystic fibrosis is another etiologic risk factor for chronic pancreatitis. Also, Carboxypeptidase A1 (CPA1) and carboxyl ester lipase (CEL) gene mutations are thought to be increasing risk factors for chronic pancreatitis.

There are two unique subtypes of chronic pancreatitis. The first subtype is referred to as tropical pancreatitis (previously fibro calculous pancreatitis) which is mostly seen in Southeast Asia, especially in India. Previously, the cause of tropical pancreatitis was believed to be cassava root ingestion. However, this hypothesis has not been supported. Half of the patients who suffer from tropical pancreatitis show SPINK1 gene mutation, but the pathogenesis of the tropical pancreatitis remains unexplained [14].

The other subtype of chronic pancreatitis is autoimmune pancreatitis (AIP) which is subclassified as type 1 AIP (lymphoplasmacytic sclerosing pancreatitis) and type 2 AIP (idiopathic duct-centric pancreatitis). AIP, especially lymphoplasmacytic sclerosing pancreatitis is associated with IgG4-secreting plasma cells in the pancreas. Type 1 AIP has also extra pancreatic manifestations like sclerosing cholangitis and retroperitoneal fibrosis. Patients eventually develop pancreatic calcifications and pancreatic insufficiencies that are indistinguishable from chronic pancreatitis.

Less commonly, hypercalcemia (generally due to parathyroid adenoma), hypertriglyceridemia, autoimmune disorders (eg, celiac disease, inflammatory bowel diseases) can cause chronic pancreatitis.

Approximately 40% of the chronic pancreatitis patients' etiology is unknown [15].

4. Pathogenesis

The exact pathogenesis underlying the chronic pancreatitis is not totally defined. The disease most commonly occurs due to environmental factors such as alcohol and smoking or in patients with genetic abnormalities. However, idiopathic CP affects almost 50% of people with this condition [15]. Some hypotheses for the pathophysiology are proposed to explain the etiologic factors. These can give us ideas about the mechanism about the development of the chronic pancreatitis.

4.1 Toxic – metabolic

Excessive alcohol consumption is responsible for 50% of the chronic pancreatic cases [16]. Alcohol is also the best-known etiologic factor in the world, so that patients can be stigmatized with alcoholism and this leads to lower quality of life. It is shown that alcohol is toxic to acinar cells, pancreatic ducts and its microcirculation [17, 18]. It was supposed that alcohol causes to spasm of the sphincter of Oddi, and it affects the character of pancreatic fluid to favor the formation of protein plugs and stones, which eventually lead to chronic pancreatitis [19]. However, these two theories failed to fully explain the pathogenesis of the alcoholic pancreatitis, scientists focused on the acinar the effect of the alcohol on the acinar cells, which are full of thousands digestive enzyme molecules. Normally, the enzymes are produced as inactive precursors, packed into zymogen granules, and segregated from mainly lysosomal enzymes in order to avoid premature activation [19]. Alcohol leads to destabilization of lysosomes and zymogen granules via by oxidant stress produced by cholesteryl esters (CEs), which accumulate in the pancreas during ethanol consumption; and fatty acid ethyl esters (FAEEs), which are nonoxidative metabolites of alcohol. The enzyme synthesis is increased, but the secretion is also impaired. Therefore, it predisposes the gland to autodigestive injury. The cytokines released during prolonged injury and the ethanol itself via its metabolite acetaldehyde causes activation of the PSC (specific, highly plastic type of myofibroblast) leading to excess deposition of extra cellular matrix and active tissue remodeling

and resulting in fibrosis and replacement of functional tissue [20–23]. Smoking is also common in patients with CP. It is convincingly demonstrated that smoking has an independent from alcohol, dose-dependent effect for developing CP. In addition, it is a facilitating factor for progressing of acute pancreatitis to CP. Furthermore, smoking promotes the fibrosis by inducing the IL-2 [13]. A potent toxic component of nicotine metabolite causes trypsinogen activation and cellular damage leading to pancreatitis [24].

4.2 Inappropriate protease activation

Pancreatic acinar cells secrete proteases as precursor enzymes, which are then activated by the serine protease in the duodenum [25]. Trypsin, the precursor of the major protease trypsinogen, starts the activation cascade of many other proteases, and itself in the duodenum (autoactivation). The natural inhibitors of the intrapancreatic activation are the SPINK1, trypsinogen degradation by CTRC and cathepsin L. Most genetic mutations associated with CP are trypsin dependent. Premature intrapancreatic activation or inappropriate inhibition of the trypsinogen can lead to pathologic event resulting in CP [26].

4.2.1 PRSS1 and PRSS2

Hereditary pancreatitis (HP) is a specific subtype of CP. The mutations in the human cationic trypsinogen (PRSS1) can cause the premature activation of the trypsinogen in various ways. 90% percent of the HP patients diagnosed with PRSS1 mutation carry one of the 3 mutations: p.N29I, p.R122C, or p.R122H in the heterozygous state. The p.N29I variant causes an increase in N-terminal processing, decreased CTRC -dependent degradation, and an increased propensity for autoactivation of the trypsin. The p.R122C and p.R122H mutations mainly prevent CTRC-mediated trypsinogen degradation [27–29].

There is no pathologic variants of human anionic trypsinogen (PRSS2) found in patients with CP. Even Genome wide association studies (GWASs) have identified a protective PRSS2 locus that slightly decreases CP risk, with a more pronounced effect in alcoholic [30].

4.2.2 SPINK1

The gene that encode serine peptidase inhibitor Kazal type 1 (SPINK1) is found to be associated with CP and commonly observed (40–50%) in tropical pancreatitis, which was referred as fibrocalculous pancreatitis [14]. The variant p.N34S in SPINK1 gene is ten times often in patient with CP compared to normal population [31]. However, the pathophysiologic mechanism is not yet known clearly although it is accepted as a major risk factor for CP.

4.2.3 CTRC

CTRC is a digestive protease synthesized and secreted by the pancreatic acinar cells as an inactive proenzyme (zymogen), which becomes activated in the duodenum. Physiologic functions include degradation of trypsin and trypsinogen, as an important defensive mechanism in chronic pancreatitis [32]. Besides, CTRC is not only a digestive enzyme but also plays a role in regulating the activity of other digestive enzymes such as stimulating autoactivation of human cationic trypsinogen [28]. Furthermore, CTRC is an essential co-activator of pro carboxypeptidase A1 (pro CPA1) and pro carboxypeptidase A2 (pro CPA2) [33].

Mutations in the *CTRC* gene have been shown to increase the risk of CP and they are 30% prevalent among patients with CP. The three main pathways explaining the increased risk of CP involve (i) impaired trypsinogen and/or trypsin degradation; (ii) impaired activation of A-type carboxypeptidases, and (iii) induction of ER stress due to defective secretion [32].

4.2.4 CTRB

CTRB1 and CTRB2 genes encode a member of the serine protease family of enzymes. The study by Rosendahl et al. reported the identification of *CTRB1-CTRB2* (chymotrypsin B1 and chymotrypsin B2) as a new chronic pancreatitis (CP) risk locus by means of GWAS. The inversion is found to decrease the CP risk by increasing trypsinogen degradation [34].

4.2.5 CELA3B

Recently, researchers found a new protease mutation linked to hereditary pancreatitis. The missense mutation in the gene encoding pancreas-specific protease elastase 3B (CELA3B), which upon secretion and activation by trypsin leads to uncontrolled proteolysis and recurrent pancreatitis [35].

4.3 Ductal dysfunction

After joining the common bile duct, the main pancreatic duct, after which both ducts perforate the medial side of the second portion of the duodenum. Therefore, any obstruction, compression or inflammation of the pancreatic tissue will increase the pressure within the pancreatic ducts leading to ductal dilation, stenosis and to atrophy of the acinar cells and replacement by fibrous tissue [36]. Long standing ductal obstructions by pseudocyst, calculi or pancreatic division can be a reason for recurrent pancreatitis attacks, which lead to eventually fibrosis and pancreatic insufficiency. Ductal obstruction can be also caused by concretions which increase the viscosity of the secretions and thereby promoting protein plugging [37].

A distinct form is the pancreatitis resulting due to a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CFTR is a chloride–bicarbonate channel expressed in the apical plasma membrane of secretory epithelia in many organs such as pancreas. The channel controls transepithelial fluid secretion and hence hydration of the epithelial luminal surfaces. It also controls the pH of the secretions, which is important for the optimal digestion [38]. Genetic variations in CFTR that affect membrane levels or channel activity led to various pancreatic phenotypes including chronic pancreatitis. Aberrant expression of CFTR causes to diminished fluid and HCO3– secretion leading to decreased intraluminal pH, decreased washout of the digestive enzymes, and more viscous protein rich ductal fluid. These changes promote the formation of intraluminal protein plugs [39, 40].

4.4 Oxidative distress

Moreover, a hypothesis is proposed which implies that mutation-induced misfolding, secretory blockage, and consequent endoplasmic reticulum (ER) stress can lead to acinar cell damage and pancreatitis [41]. Some of associated genes are CPA1 and CEL. Recent studies have also reported CLDN2, and MORC Family CW-Type Zinc Finger 4 (MORC4) gene are associated with CP, but the mechanism has not elicited, yet [4, 14].

Pathogenic CPA1 variants are detected both late but especially early onset CP due to proenzyme mis-folding, resulting in a secretion defect and intracellular retention [42, 43]. A deletion mutation in CEL is founded to cause an increasement in ER stress, through activation of the unfolded protein response and causing cell death by apoptosis [44].

The pancreas consists of three critical cell lineages: acinar, ductal and endocrine46. Adjacent to the acinar cells around small pancreatic ducts and blood vessels are pancreatic stellate cells, that compromise around 4–7% of all parenchymal cells [45, 46]. The hypotheses mentioned above lead to cellular injury, which turns into chronic inflammation and then eventually fibrosis.

As explained before, the secretory parenchyma but mainly the acinar cells are destroyed by processes such as toxification, inflammation, duct obstruction or oxidative stress. Increasing evidence indicates that pancreatic stellate cells (PSC) are the major mediators of fibrosis, resulting in the formation of extracellular matrix (ECM) in the organ. Fibrosis causes acinar cells and duct cells to injure and disappeared. This process ultimately leads to progressive loss of the lobular morphology and structure of the pancreas resulting in functional impairment of both exocrine and endocrine functions, eventually leading to clinical symptoms such as pain, malnutrition, or diabetes [47, 48]. Furthermore, the pancreatic stellate cells activate into myofibroblast-like phenotypes, proliferate, and secrete collagen I and III and fibronectin [49, 50]. Hence, the initial of the pancreas, leads to cell necrosis and/or apoptosis and consequently release of cytokines/growth factors (e.g., tumor growth factor b1, interleukin-8, platelet-derived growth factor and CC-chemokines), either from immigrating inflammatory cells, especially macrophages, and/or nearby preexistent epithelial or mesenchymal cells [51–54]. Thereafter damaged cells are phagocytosed by macrophages, causing release of cytokines, which in turn causes activation and proliferation of PCS [55]. So, a vicious circle of the irreversible event has started. These metalloproteinases are in return regulated by cytokine tumor growth factor (TGF)-β1s, which through autocrine inhibition enhances pancreatic fibrogenesis by reducing collagen degradation [50].

5. Diagnosis

The diagnosis of the chronic pancreatitis is still challenging especially in the early stages of the disease. Clinician must be suspected chronic pancreatitis in a patient with chronic abdominal pain (especially in upper quadrants), weight loss, steatorrhea, and endocrine pancreatic insufficiency. All patients with suspected chronic pancreatitis should have a dedicated pancreatic protocol to rule out pancreas carcinoma. Clinician should remember that any patient with chronic abdominal pain may also be had suffered from chronic abdominal pain syndrome, history of ERCP-related pancreatitis or any ductal changes. In most cases follow-up with serial imaging and physiological tests are recommended [56]. Once the diagnosis is confirmed, physician should characterize the etiology of chronic pancreatitis. TIGAR-O classification and modified MANNHEIM classification should be evaluated. TIGAR-O classification is a mnemonic for toxic metabolic, idiopathic, genetic mutations, autoimmune, recurrent, and severe acute pancreatitis associated chronic pancreatitis and obstructive etiologies [46]. Modified MANNHEIM classification is a mnemonic for multiple risk factors, alcohol consumption, nicotine consumption, nutritional factors (hyperlipidemia, hypertriglyceridemia), hereditary factors, efferent duct factors, immunologic factors, miscellaneous factors (hypercalcemia, hyperparathyroidism, chronic renal failure, toxins) [45].

Contrast-enhanced CT should be the initial diagnostic tool. CT scans have an overall sensitivity of 75% for chronic pancreatitis. Enlargement of the main duct (2–4 mm), glandular enlargement, heterogenous parenchyma, small (<10 mm) or lager (>10 mm) cavities, irregular ductal borders, irregular head/body contour and increased echogenicity of main duct wall are the probable pathologies that are seen in CT scan. After seeing these pathologies physician should suspect chronic pancreatitis and follow-up the patient. The other imaging technique for chronic pancreatitis is MRI and MRCP. Current MRI and MRCP technologies can provide high-quality images both parenchyma and ductal system [56]. T1 sequence in MRI is helpful for evaluating parenchymal changes in chronic pancreatitis. MRCP is used for evaluating ductal changes in chronic pancreatitis. Intravenous secretin administration during MRCP imaging stimulates pancreatic fluid secretion and can improve the visualization of ductal tree [57]. The other imaging technique for evaluating chronic pancreatitis is ultrasonography and endoscopic ultrasonography (EUS). EUS finding can be classified as two subgroups which are parenchymal features and ductal features [58]. EUS is one of the most promising imaging techniques for diagnosis and evaluating chronic pancreatitis. However, the EUS imaging needs experienced clinician. EUS is now considered to be the most sensitive CP diagnostic investigation, especially in the early stages of the disease [59, 60].

Blood amylase and lipase levels can help the physician to diagnose acute pancreatitis however, in chronic pancreatitis these levels often normal. The diagnosis of the chronic pancreatitis with blood tests are challenging. There can be some clues like hypertriglyceridemia, hypercalcemia, hyperparathyroidism and hyperlipidemia. On the other hand, fecal elastase levels are often decreased in chronic pancreatitis. Also, diagnosis of type 3c diabetes (defined as pancreatic islet dysfunction and islet loss due to diseases of endocrine pancreas) is helpful for diagnosing the disease. Increased levels of hemoglobin A1c (HbA1c), absence of insulin resistance, loss of incretin secretion and low levels of fat-soluble vitamin concentrations can support the diagnosis of the chronic pancreatitis. The secretin stimulation test can be used with MRCP and for research. Secretin stimulation test is a complex procedure. Firstly, the physician takes a sample from duodenal fluid as a baseline enzyme value then performs intravenous secretin administration after that the second sampling from duodenal fluid is done. Fecal elastase levels and secretin stimulation test results show the damage of exocrine pancreas.

6. Clinical presentation

The most common symptom of chronic pancreatitis is abdominal pain which is present more than 80% of patients. The pain is commonly described as a dull pain in the epigastrium radiating to the back that worsens after meals. The character, pattern and intensity of pain can vary among patients and does not correlate with the extent of pathological/morphologic changes [61]. Patients with alcohol related CP are more likely to experience pain, whereas late-onset CP is stated to be less painful [62]. Nausea, vomiting or both may accompany pain during exacerbations of pain attacks or during episodes of acute pancreatitis. Approximately 70% of adult patients with CP experience at least 1 episode of acute pancreatitis and 50% have recurrent pancreatitis during the clinical course of the disease [63].

Several anatomical complications can occur in CP due to local inflammation or glandular fibrosis symptoms. The formation of pancreatic pseudocysts, which can occur in 10–40% of patients during their lifetime, is one of the most frequent anatomic complications. Pseudocysts can cause gastroduodenal outlet obstruction and/or biliary obstruction, depending on their anatomic location and size [64].

Other anatomical complications are pancreatic stones, pancreatic strictures, biliary strictures and thrombosis of splanchnic vasculature.

One of the complications of CP is exocrine pancreatic insufficiency (EPI). EPI is a condition characterized by insufficient production and/or secretion of pancreatic enzymes for the digestion of nutrients. The predominant symptoms of EPI are related to fat malabsorption. Mild EPI can cause abdominal bloating and discomfort, while severe EPI can cause overt steatorrhea, weight loss and fat-soluble vitamin deficiencies. Generally, EPI does not develop for more than a decade after disease onset, due to the exceptional reserve of the exocrine pancreas and the redundant pathways for digestion of proteins and carbohydrates. Although prevalence of EPI at diagnosis of CP is 10–13%. EPI affects more than 70% of patients with CP throughout their lifespan and is especially frequent in those with proximal obstruction of the pancreatic duct or a history of pancreatic resection [64, 65].

Another complication of CP is metabolic bone disorder which has also been referred to as CP-associated osteopathy. A meta-analysis estimated that the pooled prevalence of osteoporosis was 23.4% and of osteopenia, 39.8% [66]. Additionally, patients with CP have a higher risk of low trauma fractures (vertebrae, hip, and wrist) and the risk of fractures in patients with CP was similar to other gastrointestinal diseases, such as cirrhosis, celiac disease and history of gastrectomy [67].

Diabetes mellitus (DM) is a frequent complication of CP. Prevalence of endocrine insufficiency at diagnosis of CP is 10–33% [4, 8]. A recent systematic review identified a 15% prevalence of new onset diabetes within 36 months and a 33% prevalence within 60 months of CP diagnosis [68]. DM usually occurs several years after the onset of the disease and can eventually affect up to 80% of patients over their lifespan [69]. Due to the high prevalence of CP-DM, annual screening for DM is recommended [70, 71]. In a recent study of participants with CP, DM was more likely to occur in participants who were older, obese, male, black race, or had a family history of DM and factors independently associated with DM included both obesity and the presence of exocrine pancreatic insufficiency [72]. A prolonged period of CP, the absence of pain, cigarette smoking, and an increase in visceral adipose tissue have all been linked to CP-DM [73, 74].

7. Medical treatment of the pain

Chronic Pancreatitis related pain is typically among the most severe pain of all chronic diseases and has a major impact on quality of life and disability [16, 17]. That is why pain control plays a key role in the treatment of CP. Combinations of medical, endoscopic, and surgical approaches may be used to relieve abdominal pain in patients with CP [75, 76].

All patients having pain should be offered medical management. Patients with inflammatory mass, pancreatic duct obstruction due to stricture and/or main duct stones or peripancreatic complications (e.g. pseudocyst) may require additional interventions. Even in patients who tend to be suitable for endoscopic or surgical therapy, initial medical management of pain is advised to provide relief, greater understanding of the mechanism of pain, response to treatment, and if there is any significant sensitization [77].

The World Health Organization analgesic ladder for cancer pain is widely used by physicians to treat CP pain as there are no recommendations for the choice, usage and dosage of analgesics [78]. This stepwise approach recommends acetaminophen and nonsteroidal anti-inflammatory drugs (e.g., diclofenac, ibuprofen, and naproxen) as initial choice. When patient has constant and/or severe pain that

cannot be controlled with non-narcotic analgesics, narcotic medications can be used. The first option of narcotics should be a weaker, mixed agonist–antagonist or partial agonist (e.g., tramadol) prior to the use of stronger narcotics (e.g., morphine, hydrocodone and hydromorphone). If opioids are needed, they should be administered orally in a long-acting form -lancet). Physicians must be aware of their side effects (e.g., constipation, nausea, sedation, increased risk of falls, and risk of dependence and substance misuse) and capable of managing them. That is why, patients that are likely to undergo long-term narcotic analgesia for pancreatic pain are most effectively assessed and treated at a pain clinic [77].

Because of these adverse effects of opioids, co-analgesics should also be tried, and interventional therapy (such as surgery) should be considered before starting opioids. Co-analgesics such as antidepressants and anticonvulsants (gabapentin, pregabalin) have been shown to be beneficial in the treatment of chronic visceral and neuropathic pain in chronic pancreatitis and can help to minimize the need for opioids [62, 79]. Pregabalin is shown to have better efficacy in decreasing daily pain scores than placebo, however central nervous symptoms were seen in significant number of participants on pregabalin, potentially limiting its clinical usefulness [80]. Alternative analgesics such as esketamine are currently being investigated for this indication [61].

Antioxidant supplementation in may be beneficial especially for those patients with nonalcoholic-derived CP but additional trials are needed [81–83]. A randomized control study showed that pain relief significantly higher in the antioxidant group than in the placebo group [84].

8. Endoscopic treatment of the CP

Unfortunately, 30 and 60% of all patients ultimately require intervention. Endoscopic interventions have an important place for both in the diagnosing/staging of the disease and in the management of the CP complications [85].

8.1 Treatment of the pain

Although all therapeutic approaches for pancreatic pain is not very effective, endoscopic therapy is still one of the choices in patients whose pain is refractory to non-interventional therapy and who has remarkable anatomic alterations in their pancreas and/or in the surrounding tissue. There is no evidence for the use of the endoscopy in the mild disease or in painless CP [86–88]. Endoscopic therapy could be beneficial in patients with a symptomatic pancreatic duct obstruction in the pancreatic head or neck, together with an upstream duct dilatation, Plastic stents and fully covered self-expandable metal or biodegradable stents are safe and effective options for the relief of pancreatic outflow obstruction, and eventually of the pain [89–91]. Although celiac plexus (endoscopic or percutaneous) is still commonly used in clinical practice, the evidence for its efficacy of celiac plexus block in CP remains weak [92].

8.2 Treatment of the pancreatic duct stones

Pancreatic stones are the result of the CP and they are usually getting calcified with progression of the disease [93]. Pancreatic ductal stones which cause symptoms such as pain by obstructing the flow of pancreatic juice, recurrent episodes of pancreatitis, or present with pseudocyst or fistula and other complications can be treated by endoscopic methods [94].

The location of the stone in the duct and its number is important for deciding endoscopic methods. Stones in the head and neck of the pancreas can be extracted with endoscopy, with or without stent replacement. However, endoscopic treatment is not suitable for stones, which already caused overt local complications or are located distally [85, 95, 96].

Pancreatic duct stones smaller than 5 mm are extracted by the ERCP, while extracorporeal shock wave lithotripsy (ESWL) is suggested for the clearance of radiopaque obstructive stones larger than 5 mm. Furthermore, recent studies suggest that performance of ESWL prior to the endoscopic attempt at stone extraction can provide more successful stone clearance [97–99].

8.3 Treatment of the pancreatic pseudocyst

Pancreatic pseudocysts develop as a frequent complication between 20 and 40% of CP patients [100]. It is most prevalent in alcoholic CP, followed by idiopathic CP [101, 102]. Almost 40% of the pseudocyst, especially smaller ones can resolve within the 6 weeks after the attack. However, if it does not, the probability for a complication such as infection or rupture is 2/3 of all cases. Endoscopic drainage, which has a lower morbidity rate than surgery, is a successful treatment strategy for a symptomatic or complicated pseudocyst [103]. There are two main technics for the drainage of the pseudocyst: transmural or transpapillary drainage. Whereas transmural drainage can be applied to every pseudocyst, transpapillary drainage is feasible, only if the pseudocyst has a connection to major pancreatic duct [104]. It is recommended that EUS- guided access has higher technical success than the conventional approach [105]. Another important consideration when planning a pseudocyst drainage is the existence of pseudoaneurysms and portal hypertension. EUS guided drainage is recommended in case of portal hypertension as bleeding is common complication in these patients [106]. And since the mortality is very high due to ruptured aneurysms, embolization of the artery prior to the endoscopic intervention is recommended [107].

8.4 Treatment of the biliary strictures

Biliary strictures are big obstacles during CP treatment. They are prevalent almost 46% of the CP patients. The symptoms include abdominal pain, jaundice, fever and the laboratory results show elevated serum alkaline phosphatase and/or bilirubin [108]. The endoscopic therapy is found to be long term effective only in 1/3 of the endoscopically treated patients. Therefore, endoscopic management is mostly used as transient therapy before the surgery [109, 110]. Studies suggest that placement of multiple plastic stents into the bile duct to treat bile duct obstruction in patients with chronic pancreatitis [111]. An important point about this clinical picture is absolute exclusion of the malignancy. It is essential to exchange the stents every 3 months to prevent the occlusion. However, this period is not such critical in multiple stents [111].

9. Surgical treatment

When medical treatments fail, endoscopy and surgical resection, drainage procedures, or both can be used to relieve pain. These procedures are used to treat pancreatic ductal obstruction caused by stones, strictures, or both in order to relieve intraductal hypertension and thereby pain [112]. Whether surgical or endoscopic therapy should be offered first is controversial [2].

Despite weaknesses in the study design, two randomized controlled trials found that surgery offered greater long-term pain relief than endoscopy [95, 96, 113]. This effect may be explained by the fact that surgical treatment not only relieves ductal hypertension by allowing drainage, but also removes inflamed tissue that causes neural changes and pain [114, 115]. In another clinical trial, comparing the cost-effectiveness of endoscopy and surgery, 38 CP patients were equally randomized and the mean number of ERCPs performed in the endoscopy group (6.3 vs. 0.4) was higher than in the surgery group [116].

Many patients prefer endoscopic therapy at first, in spite of the efficacy of surgery and frequent need for repeated procedures among people undergoing endoscopy because it is less invasive [112]. Patients with large inflammatory mass of the pancreatic head, distal pancreatic stenosis, and pancreatic head calcifications can be challenging to treat by endoscopy [85]. If endotherapy fails to provide immediate symptom relief without the need for repeated endoscopies, surgery should be considered by a multidisciplinary team [2]. Endoscopy is most frequently used as a therapeutic trial to determine patients most likely to benefit from surgery. While this approach is intuitive, the clinical evidence supporting this approach is not robust and more methods for predicting pain response are urgently required to prevent unhelpful interventions [117].

Surgery can be an effective first-line treatment for patients with CP who have large and multiple pancreatic stones or complicated strictures, an inflammatory mass of the head or a disease confined to the pancreatic tail [112]. Patients who are referred within 3–5 years of the onset of symptoms and have had less than four endoscopic procedures prior to surgery have better surgical outcomes [118].

The type of surgery is determined by the anatomy, the course of the disease, and local preferences [119]. The surgical approaches used to treat patients with CP are drainage options, resection options and neuroablative procedures [120]. Drainage options are cystojejunostomy, laterolateral pancreaticojejunostomy (Partington-Rochelle procedure) and caudal drainage (Puestow procedure). Resection options are pancreaticoduodenectomy (PD/Kausch-Whipple procedure) or pylorus preserving pancreaticoduodenectomy (PPPD/Traverso-Longmire-procedure), duodenum-preserving pancreatic head resection (DPPHR (Beger, Frey, Hamburg, Berne)), V-shaped excision, segmental resection and distal/total pancreatectomy. Neuroablative procedures are percutaneous radiofrequency ablation of the splanchnic nerves and thoracoscopic splanchnicectomy [120].

Total pancreatectomy accompanied by digestion of the pancreas, isolation of the islet cells and infusion into the patient's portal circulation is a radical surgical alternative that enables glucose homeostasis to be maintained without the need for immunosuppression of allogeneic islet transplantation [121]. Outside of the United States, total pancreatectomy with autoislet transplantation is still not widely available [2]. The primary indication for total pancreatectomy and islet auto transplantation is intractable pain that has a significant effect on quality of life (TPIAT) according to current clinical guidelines [122]. The procedure is successful in reducing or eliminating pain with a positive impact on quality of life [121–123]. However, severe pain persists in a large number of patients even after total pancreatectomy [124].

10. Treatment of endocrine insufficiency/CP-related DM

CP-related DM (CP-DM) is the most frequent cause of pancreatogenic DM (which has also been referred to as type 3c DM). Biannual fasting glucose and glycated hemoglobin should be obtained to assess for diabetes in CP patients [70]. The management of type 3c diabetes follows general recommendations for diabetics.

A healthy lifestyle with regular exercise and a balanced diet should accompany medical treatment. Optimized pancreatic enzyme replacement therapy improves duodenal sensing and uptake of complex nutrients, thus stabilizes blood sugar levels. Due to a lack of counter regulation, patients with type 3c diabetes have an increased risk for hypoglycemia and should be counseled accordingly. The treatment of choice is often insulin, but in mild hyperglycemia (HbA1c <8%) metformin has also been recommended [2]. In addition to its glucose lowering effect, a meta-analysis of 12 observational studies showed that metformin reduced the risk of pancreatic cancer development in people with diabetes [125]. Sulfonylureas should be avoided. Although glinides, thiazolidinediones, α-glycosidase inhibitors, incretin-based therapies, and SGLT2 inhibitors have not been tested in randomized trials, they may be effective in certain cases [61]. In order to understand the pathogenesis better and to inform the prevention and treatment of CP-DM, a detailed characterization of changes in glucose homeostasis in CP DM compared to type 2 DM is required [61].

11. Treatment of exocrine pancreatic insufficiency

The assessment of functional deficiencies should be part of the initial evaluation and monitoring of patients with CP. Exocrine pancreatic insufficiency (EPI) is indicated by symptoms of steatorrhea (foul-smelling, oily stool), diarrhea, and weight loss. The gold standard for the diagnosis of EPI is a decreased coefficient of fat absorption (CFA) [1]. CFA of less than 93% (or >7 g of fat per 24 hours from a 72-hour fecal fat collection in a patient who is consuming 100 g of dietary fat each day during stool collection) defines steatorrhea or fat malabsorption [112]. Although this is a highly accurate test for fat malabsorption, it is rarely used in clinical practice because it is difficult for patients to perform properly. Several other indirect measures (e.g. fecal elastase (FE-1), serum trypsin) and clear tests (endoscopic secretin) are used to diagnose exocrine insufficiency [126]. The accuracy of these tests is highest in the presence of severe exocrine insufficiency (defined as steatorrhea). FE −1 is an indirect measure of exocrine function that is performed on a random stool sample. Since false positive test results are common due to diarrhea, the fecal elastase-1 test should not be used to evaluate patients with unexplained diarrhea [127]. Furthermore, the sensitivity and specificity of this test is open to discuss [126]. Shortly, there are no established criterion standard for mild to moderate exocrine insufficiency. The lack of a reliable and easy test to diagnose and monitor the treatment of EPI remains one of the biggest challenges for the management of EPI. All patients with chronic pancreatitis and pancreatic exocrine insufficiency, or signs of malnutrition should be treated with 40,000–50,000 lipase units of pancreatic enzymes per meal, and dose should be increased until symptoms are relieved [2]. In patients with EPI with persistent symptoms despite pancreatic enzyme replacement therapy (PERT) initiation, additional treatment strategies to consider are increase in the dosage of PERT, addition of a proton pump inhibitor (if not currently used), consideration of alternative etiologies of symptoms in CP, such as small intestinal bacterial overgrowth or lactose intolerance, and consideration of other causes of fat malabsorption [128]. According to a large randomized controlled trial in unselected noncritically ill inpatients, nutritional evaluation and treatment can reduce morbidity and mortality [129].

12. Treatment of metabolic bone disorder

The high prevalence of CP-related osteopathy can be partly explained by common risk factors such as cigarette smoking and heavy alcohol consumption.

Furthermore, chronic inflammation caused by CP is likely to contribute to a pro-inflammatory environment that leads to net bone loss [130]. Ultimately, patients with CP are at high risk of vitamin D deficiency, especially when EPI is present [131].

CP-associated osteopathy management follows general treatment guidelines, including calcium and vitamin D supplementation, weight-bearing exercises, and smoking cessation. Oral bisphosphonate therapy, when indicated, should be closely monitored to ensure that patients tolerate it. If patient cannot tolerate it, switching to an alternative anti-resorptive therapies should be considered. Lastly, uncontrolled data indicates that PERT could potentially reduce the risk of fractures in subjects with CP, but further studies are required before this can be universally recommended [132].

In other gastrointestinal conditions, such as celiac disease, cholestatic liver disease, and inflammatory bowel disease, baseline screening with a DEXA scan has been widely adopted. That is why, baseline screening with DEXA in CP is reasonable considering that CP has higher odds of fractures compared with other gastrointestinal conditions [67, 71].

13. CP and pancreatic cancer surveillance

Pancreatic cancer is expected to be the second to third most common cause of cancer-related deaths by 2030 due to late diagnosis and inadequate treatment choices [133]. The relationship between chronic pancreatitis and pancreatic cancer is complicated since common risk factors and the course of the disease affect the rate of malignant transformation [2]. Epidemiological studies have consistently demonstrated an increased risk of pancreatic cancer (i.e., pancreatic ductal adenocarcinoma) in patients with CP, which is thought to be a result of chronic inflammation leading to hyperproliferation of pancreatic stellate cells [134]. In a meta-analysis, the risk of developing pancreatic cancer is increased in patients with chronic pancreatitis, but this is potentially confounded by smoking, which is an independent risk factor [135, 136].

Patients with hereditary pancreatitis have a 70-fold increased risk of developing pancreatic cancer compared to the control population [137, 138]. Patients with tropical pancreatitis can have a relative risk of more than 100; however, recent updates are required to see if there has been a similar decline over time [139].

Patients with hereditary chronic pancreatitis should be screened starting at age 40 or 20 years after the diagnosis of chronic pancreatitis, regardless of gene carrier status.

While PDAC screening is not routinely recommended, it is advised to retain high clinical suspicion in those with unexplained symptoms, such as unexplained weight loss or changes in abdominal pain characteristics [1, 71]. In all patients with chronic pancreatitis, newly diagnosed diabetes may be an early sign of pancreatic cancer and may prompt further research. Unfortunately, the baseline morphological changes in the pancreas (especially the main pancreatic duct dilatation) in CP make it difficult to recognize a small neoplasm in cross-sectional imaging. In patients with multiple calcifications which may mask changes in the parenchyma, there is a chance of sampling error with EUS-guided fine needle aspiration [1].

14. Conclusion

CP is a multifactorial disease resulting in fibroinflammatory changes, endocrine and exocrine dysfunction of the pancreas. Although some etiologic factors such

as alcohol, hereditary changes are well established, idiopathic cases constitute a considerable percentage. Both the endoscopic and radiologic techniques are helping the clinicians for diagnosing the disease. Medical, endoscopic and surgical treatment options are also effective and long-lasting. The main challenge in the field is early diagnosis of the CP before the symptoms exaggerate and staging the disease to monitor and treat the patients in a more appropriate way. Therefore, future prospective clinical trials and translational studies in search of novel diagnostic markers and staging methods are absolutely needed.

Author details

Didem Saka[1], Can Boynukara[1], Elif Reyyan Çadırcıbaşı[1] and Gürhan Şişman[2*]

1 School of Medicine, Acıbadem Mehmet Ali Aydınlar University, İstanbul, Turkey

2 Department of Gastroenterology, Acıbadem Mehmet Ali Aydınlar University, İstanbul, Turkey

*Address all correspondence to: gurhan.sisman@acibadem.edu.tr

References

[1] Hart PA, Conwell DL. Chronic Pancreatitis: Managing a Difficult Disease. Am J Gastroenterol. 2020;115(1):49-55.

[2] Beyer G, Habtezion A, Werner J, Lerch MM, Mayerle J. Chronic pancreatitis. Lancet. 2020;396(10249): 499-512.

[3] Conwell DL, Banks PA, Sandhu BS, Sherman S, Al-Kaade S, Gardner TB, et al. Validation of Demographics, Etiology, and Risk Factors for Chronic Pancreatitis in the USA: A Report of the North American Pancreas Study (NAPS) Group. Dig Dis Sci. 2017;62(8):2133-40.

[4] Whitcomb DC, LaRusch J, Krasinskas AM, Klei L, Smith JP, Brand RE, et al. Common genetic variants in the CLDN2 and PRSS1-PRSS2 loci alter risk for alcohol-related and sporadic pancreatitis. Nat Genet. 2012;44(12):1349-54.

[5] Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL, et al. Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2018. Gastroenterology. 2019;156(1): 254-72.e11.

[6] Sankaran SJ, Xiao AY, Wu LM, Windsor JA, Forsmark CE, Petrov MS. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. Gastroenterology. 2015;149(6):1490-500.e1.

[7] Ahmed Ali U, Issa Y, Hagenaars JC, Bakker OJ, van Goor H, Nieuwenhuijs VB, et al. Risk of Recurrent Pancreatitis and Progression to Chronic Pancreatitis After a First Episode of Acute Pancreatitis. Clin Gastroenterol Hepatol. 2016;14(5): 738-46.

[8] Hori Y, Vege SS, Chari ST, Gleeson FC, Levy MJ, Pearson RK, et al. Classic chronic pancreatitis is associated with prior acute pancreatitis in only 50% of patients in a large single-institution study. Pancreatology. 2019;19(2):224-9.

[9] Wilcox CM, Sandhu BS, Singh V, Gelrud A, Abberbock JN, Sherman S, et al. Racial Differences in the Clinical Profile, Causes, and Outcome of Chronic Pancreatitis. Am J Gastroenterol. 2016;111(10):1488-96.

[10] Şişman G, Köroğlu E, Erzin Y, Hatemi İ, Tuncer M, Şentürk H. Demographic characteristics of chronic pancreatitis patients in the era of endosonography: Experience of a single tertiary referral center in Turkey. Turk J Gastroenterol. 2016;27(3):284-9.

[11] Irving HM, Samokhvalov AV, Rehm J. Alcohol as a risk factor for pancreatitis. A systematic review and meta-analysis. Jop. 2009;10(4):387-92.

[12] Yadav D, Hawes RH, Brand RE, Anderson MA, Money ME, Banks PA, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Arch Intern Med. 2009;169(11):1035-45.

[13] Xue J, Zhao Q, Sharma V, Nguyen LP, Lee YN, Pham KL, et al. Aryl Hydrocarbon Receptor Ligands in Cigarette Smoke Induce Production of Interleukin-22 to Promote Pancreatic Fibrosis in Models of Chronic Pancreatitis. Gastroenterology. 2016;151(6):1206-17.

[14] Giri AK, Midha S, Banerjee P, Agrawal A, Mehdi SJ, Dhingra R, et al. Common Variants in CLDN2 and MORC4 Genes Confer Disease Susceptibility in Patients with Chronic Pancreatitis. PLoS One. 2016;11(1): e0147345.

[15] V K. Robins basic pathology e-book. AK A, editor. Elsevier Health Sciences2017.

[16] Gardner TB, Kennedy AT, Gelrud A, Banks PA, Vege SS, Gordon SR, et al. Chronic pancreatitis and its effect on employment and health care experience: results of a prospective American multicenter study. Pancreas. 2010;39(4):498-501.

[17] Gukovskaya AS, Mouria M, Gukovsky I, Reyes CN, Kasho VN, Faller LD, et al. Ethanol metabolism and transcription factor activation in pancreatic acinar cells in rats. Gastroenterology. 2002;122(1): 106-18.

[18] Grauvogel J, Grauvogel TD, Gebhard MM, Werner J. Combined effects of chronic and acute ethanol on pancreatic injury and microcirculation. Pancreas. 2012;41(5):717-23.

[19] Vonlaufen A, Wilson JS, Pirola RC, Apte MV. Role of alcohol metabolism in chronic pancreatitis. Alcohol Res Health. 2007;30(1):48-54.

[20] Gu H, Werner J, Bergmann F, Whitcomb DC, Büchler MW, Fortunato F. Necro-inflammatory response of pancreatic acinar cells in the pathogenesis of acute alcoholic pancreatitis. Cell Death Dis. 2013;4(10):e816.

[21] Apte MV, Wilson JS. Stellate cell activation in alcoholic pancreatitis. Pancreas. 2003;27(4):316-20.

[22] Sendler M, van den Brandt C, Glaubitz J, Wilden A, Golchert J, Weiss FU, et al. NLRP3 Inflammasome Regulates Development of Systemic Inflammatory Response and Compensatory Anti-Inflammatory Response Syndromes in Mice With Acute Pancreatitis. Gastroenterology. 2020;158(1):253-69.e14.

[23] Xue J, Sharma V, Hsieh MH, Chawla A, Murali R, Pandol SJ, et al. Alternatively activated macrophages promote pancreatic fibrosis in chronic pancreatitis. Nat Commun. 2015;6:7158.

[24] Alahmari AA, Sreekumar B, Patel V, Ashat M, Alexandre M, Uduman AK, et al. Cigarette toxin 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) induces experimental pancreatitis through α7 nicotinic acetylcholine receptors (nAChRs) in mice. PLoS One. 2018;13(6):e0197362.

[25] Rinderknecht H. Activation of pancreatic zymogens. Normal activation, premature intrapancreatic activation, protective mechanisms against inappropriate activation. Dig Dis Sci. 1986;31(3):314-21.

[26] Mayerle J, Sendler M, Hegyi E, Beyer G, Lerch MM, Sahin-Tóth M. Genetics, Cell Biology, and Pathophysiology of Pancreatitis. Gastroenterology. 2019;156(7): 1951-68.e1.

[27] Hegyi E, Sahin-Tóth M. Genetic Risk in Chronic Pancreatitis: The Trypsin-Dependent Pathway. Dig Dis Sci. 2017;62(7):1692-701.

[28] Nemoda Z, Sahin-Tóth M. Chymotrypsin C (caldecrin) stimulates autoactivation of human cationic trypsinogen. J Biol Chem. 2006;281(17):11879-86.

[29] Szabó A, Sahin-Tóth M. Increased activation of hereditary pancreatitis-associated human cationic trypsinogen mutants in presence of chymotrypsin C. J Biol Chem. 2012;287(24):20701-10.

[30] Witt H, Sahin-Tóth M, Landt O, Chen JM, Kähne T, Drenth JP, et al. A degradation-sensitive anionic trypsinogen (PRSS2) variant protects against chronic pancreatitis. Nat Genet. 2006;38(6):668-73.

[31] Aoun E, Chang CC, Greer JB, Papachristou GI, Barmada MM, Whitcomb DC. Pathways to injury in chronic pancreatitis: decoding the role of the high-risk SPINK1 N34S haplotype using meta-analysis. PLoS One. 2008;3(4):e2003.

[32] Zhou J, Sahin-Tóth M. Chymotrypsin C mutations in chronic pancreatitis. J Gastroenterol Hepatol. 2011;26(8):1238-46.

[33] Szmola R, Bence M, Carpentieri A, Szabó A, Costello CE, Samuelson J, et al. Chymotrypsin C is a co-activator of human pancreatic procarboxypeptidases A1 and A2. J Biol Chem. 2011;286(3):1819-27.

[34] Rosendahl J, Kirsten H, Hegyi E, Kovacs P, Weiss FU, Laumen H, et al. Genome-wide association study identifies inversion in the CTRB1-CTRB2 locus to modify risk for alcoholic and non-alcoholic chronic pancreatitis. Gut. 2018;67(10):1855-63.

[35] Moore PC, Cortez JT, Chamberlain CE, Alba D, Berger AC, Quandt Z, et al. Elastase 3B mutation links to familial pancreatitis with diabetes and pancreatic adenocarcinoma. J Clin Invest. 2019;129(11):4676-81.

[36] Klöppel G, Detlefsen S, Feyerabend B. Fibrosis of the pancreas: the initial tissue damage and the resulting pattern. Virchows Arch. 2004;445(1):1-8.

[37] AA A. Pathogenesis of Chronic Pancreatitis. Pancreapedia: Exocrine Pancreas Knowledge Base2016.

[38] Hegyi P, Wilschanski M, Muallem S, Lukacs GL, Sahin-Tóth M, Uc A, et al. CFTR: A New Horizon in the Pathomechanism and Treatment of Pancreatitis. Rev Physiol Biochem Pharmacol. 2016;170:37-66.

[39] Ko SB, Azuma S, Yoshikawa T, Yamamoto A, Kyokane K, Ko MS, et al. Molecular mechanisms of pancreatic stone formation in chronic pancreatitis. Front Physiol. 2012;3:415.

[40] Sarles H, Sarles JC, Camatte R, Muratore R, Gaini M, Guien C, et al. Observations on 205 confirmed cases of acute pancreatitis, recurring pancreatitis, and chronic pancreatitis. Gut. 1965;6(6):545-59.

[41] Sahin-Tóth M. Genetic risk in chronic pancreatitis: the misfolding-dependent pathway. Curr Opin Gastroenterol. 2017;33(5):390-5.

[42] Witt H, Beer S, Rosendahl J, Chen JM, Chandak GR, Masamune A, et al. Variants in CPA1 are strongly associated with early onset chronic pancreatitis. Nat Genet. 2013;45(10): 1216-20.

[43] Kujko AA, Berki DM, Oracz G, Wejnarska K, Antoniuk J, Wertheim-Tysarowska K, et al. A novel p.Ser282Pro CPA1 variant is associated with autosomal dominant hereditary pancreatitis. Gut. 662017. p. 1728-30.

[44] Xiao X, Jones G, Sevilla WA, Stolz DB, Magee KE, Haughney M, et al. A Carboxyl Ester Lipase (CEL) Mutant Causes Chronic Pancreatitis by Forming Intracellular Aggregates That Activate Apoptosis. J Biol Chem. 2016;291(44):23224-36.

[45] Schneider A, Löhr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. J Gastroenterol. 2007;42(2):101-19.

[46] Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology. 2001;120(3): 682-707.

[47] Lévy P, Barthet M, Mollard BR, Amouretti M, Marion-Audibert AM, Dyard F. Estimation of the prevalence and incidence of chronic pancreatitis and its complications. Gastroenterol Clin Biol. 2006;30(6-7):838-44.

[48] Andrén-Sandberg A, Hoem D, Gislason H. Pain management in chronic pancreatitis. Eur J Gastroenterol Hepatol. 2002;14(9):957-70.

[49] Apte MV, Haber PS, Darby SJ, Rodgers SC, McCaughan GW, Korsten MA, et al. Pancreatic stellate cells are activated by proinflammatory cytokines: implications for pancreatic fibrogenesis. Gut. 1999;44(4):534-41.

[50] Shek FW, Benyon RC, Walker FM, McCrudden PR, Pender SL, Williams EJ, et al. Expression of transforming growth factor-beta 1 by pancreatic stellate cells and its implications for matrix secretion and turnover in chronic pancreatitis. Am J Pathol. 2002;160(5):1787-98.

[51] Andoh A, Takaya H, Saotome T, Shimada M, Hata K, Araki Y, et al. Cytokine regulation of chemokine (IL-8, MCP-1, and RANTES) gene expression in human pancreatic periacinar myofibroblasts. Gastroenterology. 2000;119(1):211-9.

[52] Ebert M, Kasper HU, Hernberg S, Friess H, Büchler MW, Roessner A, et al. Overexpression of platelet-derived growth factor (PDGF) B chain and type beta PDGF receptor in human chronic pancreatitis. Dig Dis Sci. 1998;43(3):567-74.

[53] Luttenberger T, Schmid-Kotsas A, Menke A, Siech M, Beger H, Adler G, et al. Platelet-derived growth factors stimulate proliferation and extracellular matrix synthesis of pancreatic stellate cells: implications in pathogenesis of pancreas fibrosis. Lab Invest. 2000;80(1):47-55.

[54] Saurer L, Reber P, Schaffner T, Büchler MW, Buri C, Kappeler A, et al. Differential expression of chemokines in normal pancreas and in chronic pancreatitis. Gastroenterology. 2000;118(2):356-67.

[55] Haber PS, Keogh GW, Apte MV, Moran CS, Stewart NL, Crawford DH, et al. Activation of pancreatic stellate cells in human and experimental pancreatic fibrosis. Am J Pathol. 1999;155(4):1087-95.

[56] Conwell DL, Lee LS, Yadav D, Longnecker DS, Miller FH, Mortele KJ, et al. American Pancreatic Association Practice Guidelines in Chronic Pancreatitis: evidence-based report on diagnostic guidelines. Pancreas. 2014;43(8):1143-62.

[57] Zhang L, Chari S, Smyrk TC, Deshpande V, Klöppel G, Kojima M, et al. Autoimmune pancreatitis (AIP) type 1 and type 2: an international consensus study on histopathologic diagnostic criteria. Pancreas. 2011;40(8):1172-9.

[58] Gardner TB, Taylor DJ, Gordon SR. Reported findings on endoscopic ultrasound examinations for chronic pancreatitis: toward establishing an endoscopic ultrasound quality benchmark. Pancreas. 2014;43(1):37-40.

[59] Löhr JM, Dominguez-Munoz E, Rosendahl J, Besselink M, Mayerle J, Lerch MM, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United European Gastroenterol J. 2017;5(2):153-99.

[60] Iglesias-García J, Lindkvist B, Lariño-Noia J, Domínguez-Muñoz JE. The role of EUS in relation to other imaging modalities in the differential diagnosis between mass forming chronic pancreatitis, autoimmune pancreatitis and ductal pancreatic

adenocarcinoma. Rev Esp Enferm Dig. 2012;104(6):315-21.

[61] Wilcox CM, Yadav D, Ye T, Gardner TB, Gelrud A, Sandhu BS, et al. Chronic pancreatitis pain pattern and severity are independent of abdominal imaging findings. Clin Gastroenterol Hepatol. 2015;13(3):552-60; quiz e28-9.

[62] Drewes AM, Bouwense SAW, Campbell CM, Ceyhan GO, Delhaye M, Demir IE, et al. Guidelines for the understanding and management of pain in chronic pancreatitis. Pancreatology. 2017;17(5):720-31.

[63] Schwarzenberg SJ, Uc A, Zimmerman B, Wilschanski M, Wilcox CM, Whitcomb DC, et al. Chronic Pancreatitis: Pediatric and Adult Cohorts Show Similarities in Disease Progress Despite Different Risk Factors. J Pediatr Gastroenterol Nutr. 2019;68(4):566-73.

[64] Machicado JD, Chari ST, Timmons L, Tang G, Yadav D. A population-based evaluation of the natural history of chronic pancreatitis. Pancreatology. 2018;18(1):39-45.

[65] Layer P, Yamamoto H, Kalthoff L, Clain JE, Bakken LJ, DiMagno EP. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. Gastroenterology. 1994;107(5):1481-7.

[66] Duggan SN, Smyth ND, Murphy A, Macnaughton D, O'Keefe SJ, Conlon KC. High prevalence of osteoporosis in patients with chronic pancreatitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2014;12(2):219-28.

[67] Tignor AS, Wu BU, Whitlock TL, Lopez R, Repas K, Banks PA, et al. High prevalence of low-trauma fracture in chronic pancreatitis. Am J Gastroenterol. 2010;105(12):2680-6.

[68] Zhu X, Liu D, Wei Q, Lin H, Zhi M, Chen Y, et al. New-Onset Diabetes Mellitus After Chronic Pancreatitis Diagnosis: A Systematic Review and Meta-analysis. Pancreas. 2019;48(7):868-75.

[69] Hart PA, Bellin MD, Andersen DK, Bradley D, Cruz-Monserrate Z, Forsmark CE, et al. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. Lancet Gastroenterol Hepatol. 2016;1(3):226-37.

[70] Rickels MR, Bellin M, Toledo FG, Robertson RP, Andersen DK, Chari ST, et al. Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: recommendations from PancreasFest 2012. Pancreatology. 2013;13(4):336-42.

[71] Sheth SG, Conwell DL, Whitcomb DC, Alsante M, Anderson MA, Barkin J, et al. Academic Pancreas Centers of Excellence: Guidance from a multidisciplinary chronic pancreatitis working group at PancreasFest. Pancreatology. 2017;17(3):419-30.

[72] Bellin MD, Whitcomb DC, Abberbock J, Sherman S, Sandhu BS, Gardner TB, et al. Patient and Disease Characteristics Associated With the Presence of Diabetes Mellitus in Adults With Chronic Pancreatitis in the United States. Am J Gastroenterol. 2017;112(9):1457-65.

[73] Kumar K, Sharma R, Manrai M, Sood AK. Visceral Adipose Tissue as a Risk Factor for Diabetes Mellitus in Patients with Chronic Pancreatitis: A Cross-sectional, Observational Study. Diabetes Ther. 2017;8(5):1057-64.

[74] Wang W, Guo Y, Liao Z, Zou DW, Jin ZD, Zou DJ, et al. Occurrence of and risk factors for diabetes mellitus in Chinese patients with chronic

pancreatitis. Pancreas. 2011;40(2): 206-12.

[75] Mullady DK, Yadav D, Amann ST, O'Connell MR, Barmada MM, Elta GH, et al. Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: a prospective cohort study. Gut. 2011;60(1):77-84.

[76] Drewes AM, Olesen AE, Farmer AD, Szigethy E, Rebours V, Olesen SS. Gastrointestinal pain. Nat Rev Dis Primers. 2020;6(1):1.

[77] Anderson MA, Akshintala V, Albers KM, Amann ST, Belfer I, Brand R, et al. Mechanism, assessment and management of pain in chronic pancreatitis: Recommendations of a multidisciplinary study group. Pancreatology. 2016;16(1):83-94.

[78] Jadad AR, Browman GP. The WHO analgesic ladder for cancer pain management. Stepping up the quality of its evaluation. Jama. 1995;274(23): 1870-3.

[79] Juel J, Olesen SS, Olesen AE, Poulsen JL, Dahan A, Wilder-Smith O, et al. Study protocol for a randomised, double-blinded, placebo-controlled, clinical trial of S-ketamine for pain treatment in patients with chronic pancreatitis (RESET trial). BMJ Open. 2015;5(3):e007087.

[80] Olesen SS, Bouwense SA, Wilder-Smith OH, van Goor H, Drewes AM. Pregabalin reduces pain in patients with chronic pancreatitis in a randomized, controlled trial. Gastroenterology. 2011;141(2):536-43.

[81] Bhardwaj P, Garg PK, Maulik SK, Saraya A, Tandon RK, Acharya SK. A randomized controlled trial of antioxidant supplementation for pain relief in patients with chronic pancreatitis. Gastroenterology. 2009;136(1):149-59.e2.

[82] Rustagi T, Njei B. Antioxidant therapy for pain reduction in patients with chronic pancreatitis: a systematic review and meta-analysis. Pancreas. 2015;44(5):812-8.

[83] Siriwardena AK, Mason JM, Sheen AJ, Makin AJ, Shah NS. Antioxidant therapy does not reduce pain in patients with chronic pancreatitis: the ANTICIPATE study. Gastroenterology. 2012;143(3): 655-63.e1.

[84] Yaghoobi M, McNabb-Baltar J, Bijarchi R, Cotton PB. Pancreatic Enzyme Supplements Are Not Effective for Relieving Abdominal Pain in Patients with Chronic Pancreatitis: Meta-Analysis and Systematic Review of Randomized Controlled Trials. Can J Gastroenterol Hepatol. 2016;2016:8541839.

[85] Hoffmeister A, Mayerle J, Beglinger C, Büchler MW, Bufler P, Dathe K, et al. English language version of the S3-consensus guidelines on chronic pancreatitis: Definition, aetiology, diagnostic examinations, medical, endoscopic and surgical management of chronic pancreatitis. Z Gastroenterol. 2015;53(12):1447-95.

[86] Hookey LC, RioTinto R, Delhaye M, Baize M, Le Moine O, Devière J. Risk factors for pancreatitis after pancreatic sphincterotomy: a review of 572 cases. Endoscopy. 2006;38(7):670-6.

[87] Okolo PI, 3rd, Pasricha PJ, Kalloo AN. What are the long-term results of endoscopic pancreatic sphincterotomy? Gastrointest Endosc. 2000;52(1):15-9.

[88] Seza K, Yamaguchi T, Ishihara T, Tadenema H, Tawada K, Saisho H, et al. A long-term controlled trial of endoscopic pancreatic stenting for treatment of main pancreatic duct stricture in chronic pancreatitis.

Hepatogastroenterology. 2011;58(112):2128-31.

[89] Tringali A, Vadalà di Prampero SF, Landi R, Bove V, Familiari P, Hamanaka J, et al. Fully covered self-expandable metal stents to dilate persistent pancreatic strictures in chronic pancreatitis: long-term follow-up from a prospective study. Gastrointest Endosc. 2018;88(6):939-46.

[90] Cahen DL, van der Merwe SW, Laleman W, Poley JW, Bruno MJ. A biodegradable non-covered self-expandable stent to treat pancreatic duct strictures in chronic pancreatitis: a proof of principle. Gastrointest Endosc. 2018;87(2):486-91.

[91] Ahmed Ali U, Issa Y, Bruno MJ, van Goor H, van Santvoort H, Busch OR, et al. Early surgery versus optimal current step-up practice for chronic pancreatitis (ESCAPE): design and rationale of a randomized trial. BMC Gastroenterol. 2013;13:49.

[92] Drewes AM, Kempeneers MA, Andersen DK, Arendt-Nielsen L, Besselink MG, Boermeester MA, et al. Controversies on the endoscopic and surgical management of pain in patients with chronic pancreatitis: pros and cons! Gut. 2019;68(8):1343-51.

[93] Sarles H, Camarena J, Gomez-Santana C. Radiolucent and calcified pancreatic lithiasis: two different diseases. Role of alcohol and heredity. Scand J Gastroenterol. 1992;27(1):71-6.

[94] Widdison AL, Alvarez C, Karanjia ND, Reber HA. Experimental evidence of beneficial effects of ductal decompression in chronic pancreatitis. Endoscopy. 1991;23(3):151-4.

[95] Cahen DL, Gouma DJ, Laramée P, Nio Y, Rauws EA, Boermeester MA, et al. Long-term outcomes of endoscopic vs surgical drainage of the pancreatic duct in patients with chronic pancreatitis. Gastroenterology. 2011;141(5):1690-5.

[96] Ceyhan GO, Bergmann F, Kadihasanoglu M, Altintas B, Demir IE, Hinz U, et al. Pancreatic neuropathy and neuropathic pain--a comprehensive pathomorphological study of 546 cases. Gastroenterology. 2009;136(1):177-86.e1.

[97] Farnbacher MJ, Schoen C, Rabenstein T, Benninger J, Hahn EG, Schneider HT. Pancreatic duct stones in chronic pancreatitis: criteria for treatment intensity and success. Gastrointest Endosc. 2002;56(4):501-6.

[98] Dumonceau JM, Devière J, Le Moine O, Delhaye M, Vandermeeren A, Baize M, et al. Endoscopic pancreatic drainage in chronic pancreatitis associated with ductal stones: long-term results. Gastrointest Endosc. 1996;43(6):547-55.

[99] Ang TL. Chronic pancreatitis with pancreatic duct stricture and calculi treated by fully covered self-expandable metal stent placement and intraductal pancreatoscopy-guided laser lithotripsy. Endoscopy. 2017;49(6):E145-e6.

[100] Barthet M, Bugallo M, Moreira LS, Bastid C, Sastre B, Sahel J. Management of cysts and pseudocysts complicating chronic pancreatitis. A retrospective study of 143 patients. Gastroenterol Clin Biol. 1993;17(4):270-6.

[101] Andrén-Sandberg A, Dervenis C. Surgical treatment of pancreatic pseudocysts in the 2000's--laparoscopic approach. Acta Chir Iugosl. 2003;50(4):21-6.

[102] Ammann RW, Akovbiantz A, Largiader F, Schueler G. Course and outcome of chronic pancreatitis. Longitudinal study of a mixed medical-surgical series of 245 patients.

Gastroenterology. 1984;86(5 Pt 1): 820-8.

[103] Lerch MM, Stier A, Wahnschaffe U, Mayerle J. Pancreatic pseudocysts: observation, endoscopic drainage, or resection? Dtsch Arztebl Int. 2009;106(38):614-21.

[104] Barthet M, Lamblin G, Gasmi M, Vitton V, Desjeux A, Grimaud JC. Clinical usefulness of a treatment algorithm for pancreatic pseudocysts. Gastrointest Endosc. 2008;67(2):245-52.

[105] Panamonta N, Ngamruengphong S, Kijsirichareanchai K, Nugent K, Rakvit A. Endoscopic ultrasound-guided versus conventional transmural techniques have comparable treatment outcomes in draining pancreatic pseudocysts. Eur J Gastroenterol Hepatol. 2012;24(12):1355-62.

[106] Sriram PV, Kaffes AJ, Rao GV, Reddy DN. Endoscopic ultrasound-guided drainage of pancreatic pseudocysts complicated by portal hypertension or by intervening vessels. Endoscopy. 2005;37(3):231-5.

[107] Delhaye M, Matos C, Devière J. Endoscopic technique for the management of pancreatitis and its complications. Best Pract Res Clin Gastroenterol. 2004;18(1):155-81.

[108] Abdallah AA, Krige JE, Bornman PC. Biliary tract obstruction in chronic pancreatitis. HPB (Oxford). 2007;9(6):421-8.

[109] Barrioz T, Ingrand P, Besson I, de Ledinghen V, Silvain C, Beauchant M. Randomised trial of prevention of biliary stent occlusion by ursodeoxycholic acid plus norfloxacin. Lancet. 1994;344(8922):581-2.

[110] Ghosh S, Palmer KR. Prevention of biliary stent occlusion using cyclical antibiotics and ursodeoxycholic acid. Gut. 1994;35(12):1757-9.

[111] Catalano MF, Linder JD, George S, Alcocer E, Geenen JE. Treatment of symptomatic distal common bile duct stenosis secondary to chronic pancreatitis: comparison of single vs. multiple simultaneous stents. Gastrointest Endosc. 2004;60(6): 945-52.

[112] Singh VK, Yadav D, Garg PK. Diagnosis and Management of Chronic Pancreatitis: A Review. Jama. 2019;322(24):2422-34.

[113] Cahen DL, Gouma DJ, Nio Y, Rauws EA, Boermeester MA, Busch OR, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. N Engl J Med. 2007;356(7):676-84.

[114] Olesen SS, Krauss T, Demir IE, Wilder-Smith OH, Ceyhan GO, Pasricha PJ, et al. Towards a neurobiological understanding of pain in chronic pancreatitis: mechanisms and implications for treatment. Pain Rep. 2017;2(6):e625.

[115] Tringali A, Bove V, Vadalà di Prampero SF, Boškoski I, Familiari P, Perri V, et al. Long-term follow-up after multiple plastic stenting for refractory pancreatic duct strictures in chronic pancreatitis. Endoscopy. 2019;51(10): 930-5.

[116] Laramée P, Wonderling D, Cahen DL, Dijkgraaf MG, Gouma DJ, Bruno MJ, et al. Trial-based cost-effectiveness analysis comparing surgical and endoscopic drainage in patients with obstructive chronic pancreatitis. BMJ Open. 2013;3(9):e003676.

[117] Kwon RS, Young BE, Marsteller WF, Lawrence C, Wu BU, Lee LS, et al. Narcotic Independence After Pancreatic Duct Stenting Predicts Narcotic Independence After Lateral Pancreaticojejunostomy for Chronic Pancreatitis. Pancreas. 2016;45(8): 1126-30.

[118] Olesen SS, Krarup H, Poulsen JL, Christensen JH, Sheel ARG, Sutton R, et al. Pancreas-specific plasma amylase for assessment and diagnosis of chronic pancreatitis: New insights on an old topic. United European Gastroenterol J. 2019;7(7):955-64.

[119] Beger HG, Schlosser W, Friess HM, Büchler MW. Duodenum-preserving head resection in chronic pancreatitis changes the natural course of the disease: a single-center 26-year experience. Ann Surg. 1999;230(4): 512-9; discussion 9-23.

[120] Plagemann S, Welte M, Izbicki JR, Bachmann K. Surgical Treatment for Chronic Pancreatitis: Past, Present, and Future. Gastroenterol Res Pract. 2017;2017:8418372.

[121] JC C. Chronic Pancreatitis — Update on Pathophysiology and Therapeutic Approaches. 2020.

[122] Bellin MD, Freeman ML, Gelrud A, Slivka A, Clavel A, Humar A, et al. Total pancreatectomy and islet autotransplantation in chronic pancreatitis: recommendations from PancreasFest. Pancreatology. 2014;14(1):27-35.

[123] Bellin MD, Forlenza GP, Majumder K, Berger M, Freeman ML, Beilman GJ, et al. Total Pancreatectomy With Islet Autotransplantation Resolves Pain in Young Children With Severe Chronic Pancreatitis. J Pediatr Gastroenterol Nutr. 2017;64(3):440-5.

[124] Chinnakotla S, Beilman GJ, Dunn TB, Bellin MD, Freeman ML, Radosevich DM, et al. Factors Predicting Outcomes After a Total Pancreatectomy and Islet Autotransplantation Lessons Learned From Over 500 Cases. Ann Surg. 2015;262(4):610-22.

[125] Kirkegård J, Mortensen FV, Cronin-Fenton D. Chronic Pancreatitis and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis. Am J Gastroenterol. 2017;112(9): 1366-72.

[126] Domínguez-Muñoz JE, P DH, Lerch MM, Löhr MJ. Potential for Screening for Pancreatic Exocrine Insufficiency Using the Fecal Elastase-1 Test. Dig Dis Sci. 2017; 62(5):1119-30.

[127] Bekkali NL, Murray S, Johnson GJ, Bandula S, Amin Z, Chapman MH, et al. Pancreatoscopy-Directed Electrohydraulic Lithotripsy for Pancreatic Ductal Stones in Painful Chronic Pancreatitis Using SpyGlass. Pancreas. 2017;46(4):528-30.

[128] Domínguez-Muñoz JE. Pancreatic exocrine insufficiency: diagnosis and treatment. J Gastroenterol Hepatol. 2011;26 Suppl 2:12-6.

[129] Andersen DK, Korc M, Petersen GM, Eibl G, Li D, Rickels MR, et al. Diabetes, Pancreatogenic Diabetes, and Pancreatic Cancer. Diabetes. 2017;66(5):1103-10.

[130] Duggan SN, Purcell C, Kilbane M, O'Keane M, McKenna M, Gaffney P, et al. An association between abnormal bone turnover, systemic inflammation, and osteoporosis in patients with chronic pancreatitis: a case-matched study. Am J Gastroenterol. 2015;110(2): 336-45.

[131] Sikkens EC, Cahen DL, Koch AD, Braat H, Poley JW, Kuipers EJ, et al. The prevalence of fat-soluble vitamin deficiencies and a decreased bone mass in patients with chronic pancreatitis. Pancreatology. 2013;13(3):238-42.

[132] Bang UC, Benfield T, Bendtsen F, Hyldstrup L, Beck Jensen JE. The risk of fractures among patients with cirrhosis or chronic pancreatitis. Clin Gastroenterol Hepatol. 2014;12(2): 320-6.

[133] Hao L, Zeng XP, Xin L, Wang D, Pan J, Bi YW, et al. Incidence of and risk factors for pancreatic cancer in chronic pancreatitis: A cohort of 1656 patients. Dig Liver Dis. 2017;49(11):1249-56.

[134] Algül H, Treiber M, Lesina M, Schmid RM. Mechanisms of disease: chronic inflammation and cancer in the pancreas--a potential role for pancreatic stellate cells? Nat Clin Pract Gastroenterol Hepatol. 2007;4(8): 454-62.

[135] Tamura K, Yu J, Hata T, Suenaga M, Shindo K, Abe T, et al. Mutations in the pancreatic secretory enzymes CPA1 and CPB1 are associated with pancreatic cancer. Proc Natl Acad Sci U S A. 2018;115(18):4767-72.

[136] Goggins M, Overbeek KA, Brand R, Syngal S, Del Chiaro M, Bartsch DK, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. Gut. 2020;69(1):7-17.

[137] Whitcomb DC, Shelton CA, Brand RE. Genetics and Genetic Testing in Pancreatic Cancer. Gastroenterology. 2015;149(5):1252-64.e4.

[138] Hao W, Komar HM, Hart PA, Conwell DL, Lesinski GB, Friedman A. Mathematical model of chronic pancreatitis. Proc Natl Acad Sci U S A. 2017;114(19):5011-6.

[139] Chari ST, Mohan V, Pitchumoni CS, Viswanathan M, Madanagopalan N, Lowenfels AB. Risk of pancreatic carcinoma in tropical calcifying pancreatitis: an epidemiologic study. Pancreas. 1994;9(1):62-6.