Known Factors of Acute Pancreatitis

Subjects: Surgery

Contributor: Julia Walkowska, Nicol Zielinska, Piotr Karauda, R. Shane Tubbs, Konrad Kurtys, Łukasz Olewnik

Pancreatitis is regarded by clinicians as one of the most complicated and clinically challenging of all disorders affecting the abdomen. It is classified on the basis of clinical, morphological, and histological criteria. Causes of acute pancreatitis can easily be identified in 75–85% of patients. The main causes of acute, recurrent acute, and chronic pancreatitis are gallstone migration and alcohol abuse. Other causes are uncommon, controversial, or unexplained. For instance, cofactors of all forms of pancreatitis are pancreas divisum and hypertriglyceridemia. Another factor that should be considered is a complication of endoscopic retrograde cholangiopancreatography: post-endoscopic retrograde cholangiopancreatography acute pancreatitis.

Keywords: pancreas ; surgery ; risk factors

1. Introduction

The pancreas is a secondary retroperitoneal organ located in the upper part of the abdomen. Macroscopically, it has conventionally been divided into three main parts: the head, the body, and the tail [1]. Anatomically, some structures such as the uncinate process are commonly regarded as parts of the head, which is located below the superior mesenteric artery and vein, and the neck, situated above those vessels [2][3]. The head is surrounded by a loop of the duodenum. The body, extending almost perpendicular to the median plane, is located below the stomach. It crosses the superior mesenteric artery and vein, the abdominal aorta, the inferior vena cava, and the hepatic portal vein. Finally, the tail approaches the hilum of spleen.

The pancreas is a key organ in overall body homeostasis; it is responsible for regulating macronutrient digestion and releasing hormones that control digestive processes and the blood glucose level. It has two distinct components: the exocrine pancreas and the endocrine islets [4][5]. Anatomical variations of the pancreas and pancreatic ducts are uncommon. The structure of the pancreatic ducts is normal in 94.3% of cases; the remaining 5.7% show many different variations, many of which remain asymptomatic and undetected until adulthood. They are frequently detected as incidental findings on clinical imaging [1]. Distinct diseases affect the exocrine and endocrine pancreas. They can affect physiological functions or arise from pancreatic dysfunction. Those concerning the exocrine pancreas are acute and chronic pancreatitis [6]; pancreatic cancers [7], most of which are ductal carcinomas; cystic fibrosis [8]; and pancreatic insufficiency leading to malabsorption syndrome [9]. Diabetes [10][11] and rare pancreatic neuroendocrine tumors arise from the endocrine islets [5][12].

2. Gallstones

The biliary etiology of pancreatitis has a female predominance, which can be explained by cross-sectional studies showing that 50% of women and only 15% of men have cholelithiasis [13][14]. According to reports by the European Association for the Study of the Liver published in 2016, gallstones in both the gallbladder and the bile duct increase the risk of pancreatitis. Three quarters of patients with cholecystolithiasis are asymptomatic, while 8% of those with gallstones eventually develop AP [15].

Often the first symptom of biliary stones is AP, though most patients recover completely after a mild edematous pancreatitis episode. Unfortunately, 15–30% develop severe necrotizing pancreatitis, necessitating intensive care and multidisciplinary treatment strategies [6]. Acute biliary pancreatitis is triggered by gallstone migration, leading to obstruction of the bile duct or pancreatic duct, or both. The most common location of obstruction is the terminal common bile–pancreatic duct. Most researchers agree that bile–pancreatic duct obstruction and pancreatic hyperstimulation are the main causal factors in acute biliary pancreatitis [16].

Two predominant causal hypotheses, gallstone migration and common pathway [16], agree that bile–pancreatic duct obstruction is the most crucial factor for acute biliary pancreatitis. Duct obstruction increases pancreatic duct pressure,

activates bile and trypsin reflux, and causes trypsin activation, pancreatic auto-digestion, and local inflammation. However, such an obstruction does not induce the kind of morphological changes typical for AP, suggesting that other factors must be involved [17]. It is hypothesized, without supportive evidence, that pancreatic acinar hyperstimulation causes and aggravates AP in the presence of duct obstruction [18].

3. Alcohol Abuse

The second most common cause of AP is alcohol abuse [6][16]. It has been established that excessive alcohol consumption can initiate an episode of AP and increase susceptibility to CP. However, although epidemiological data support the connection between alcohol and pancreatitis, only a minority of alcoholics ever experience AP or CP. This suggests that alcohol consumption is rarely the only factor precipitating pancreatitis. Alcohol sensitizes the pancreas to cofactors such as infectious agents, tobacco smoke, and a high fat diet. Interestingly, tobacco smoke is an independent and probably a stronger risk factor than alcohol consumption in the etiology of CP [6] (Weiss et al., 2019).

According to Gao et al. [19], the development of pancreatitis is influenced by environmental and genetic factors, and alcoholic pancreatitis could be favored by unsuccessful inhibition of trypsin activation or unsuccessful removal of active trypsin from the pancreatic ducts. Thanks to the expression of relevant genes, including aldehyde dehydrogenase (ALDH), alcohol dehydrogenase (ADH), cytochrome P450 (CYP2E1) and catalase, the pancreas, like the liver, can metabolize alcohol by oxidative and non-oxidative pathways. The oxidative pathway generates reactive oxygen species and acetaldehyde; fatty ester ethyl esters, which can injure the pancreas, are formed through the non-oxidative pathway. Ethanol and its metabolites disturb intracellular homeostasis in the pancreatic acini, for instance leading to endoplasmic reticulum stress, impaired autophagy, or activation of lysosomal and pancreatic digestive enzymes [6].

4. Hypertriglyceridemia

Ten percent of AP cases are associated with an elevated triglyceride level [6]. Most patients with hypertriglyceridemia remain asymptomatic. It is assumed that elevated serum levels of triglycerides and chylomicrons increase blood viscosity, causing local ischemia of the pancreatic tissue. Tissue ischemia changes metabolism from aerobic to anaerobic; cells produce ATP through anaerobic glycolysis, the final product of which is l-lactate. Local ischemia promotes an increase in l-lactate concentration and causes acidosis, which enhances the toxicity of free fatty acids and causes the auto-activation of trypsinogen. When combined with other risk factors such as alcohol, drugs, or tobacco, ischemia associated with hypertriglyceridemia can cause AP.

An idiosyncratic risk of recurrent episodes of AP is observed in patients with familial lipoprotein lipase deficiency [20]. Owing to the increased levels of cholesterol and triglycerides caused by hormones, pregnant women also have an inherent risk of hypertriglyceridemia-induced AP [21].

There are two types of hypertriglyceridemia, primary and secondary, which show specific differences. According to Fredrickson's classification [22], there are five types of primary hypertriglyceridemia, of which types I, IV, and V are associated with a higher risk of AP. Primary hypertriglyceridemia is caused by inherited autosomal recessive (type I) or autosomal dominant (types IV and V) mutations. Type I is characterized by increased chylomicrons, type IV is associated with high very-low-density lipoproteins (VLDLs), while in type V there are increased concentrations of both chylomicrons and VLDL. Secondary hypertriglyceridemia is associated with modifiable and environmental factors: pregnancy, obesity, inappropriately controlled diabetes, acute and chronic alcohol abuse, or medications.

According to the Atlanta classification system [6], a serum triglyceride level exceeding 1000 mg/dL is the basis for diagnosing hypertriglyceridemia-induced AP. A fifth of all patients meeting this criterion are at increased risk of developing at least one attack of AP.

5. Endoscopic Retrograde Cholangiopancreatography (ERCP)

An iatrogenic cause of acute pancreatitis is a complication of ERCP, termed post-ERCP acute pancreatitis. Post-ERCP acute pancreatitis is the most common serious adverse event attributed to the procedure. It is defined as pancreatitis with the presence of new or worsened abdominal pain, amylase at least three times normal at more than 24 h after the procedure, requiring admission or prolongation of planned admission to 2–3 days [23][24]. The relevant factors can be patient-related, operator-related, or procedure-related [6][16]. After the procedure, 35–70% of patients exhibit asymptomatic hyperamylasemia. ERCP is associated with a higher risk of inducing AP when the procedure is used to treat a dysfunctional sphincter of Oddi than to remove gallstones from the bile ducts [16]. Patient-related factors are gender, age,

Oddi sphincter anomalies or pancreatic anomalies (e.g., pancreas divisium), preexisting pancreatitis, and biliary pancreatitis, an indication for ERCP [6]. Other risk factors for post-ERCP AP include the number of attempts to cannulate a papilla and poor emptying of the pancreatic duct after opacification [6]. Improper canulation of the greater papilla of the duodenum can cause swelling, sphincter contraction, and obstruction of the pancreatic ducts [25]. The physicochemical properties of the contrast medium such as osmolarity, pH, and composition can contribute to hydrostatic and chemical injury to the pancreas. Additionally, the administration of contrast, which entails an increase in pressure, can induce the activation of pancreatic digestive enzymes, which then cause pancreatic autodigestion and local inflammation [26]. In order to prevent post-ERCP AP in high-risk patients, a temporary pancreatic stent is being introduced [6].

6. Pancreas Divisium

A common congenital anatomical variant of the pancreatic ducts is a lack of connection between the ventral and dorsal ductal systems, called pancreas divisium. This variation can cause inadequate patency or stenosis in the minor papilla, which leads to the prevention of drainage of pancreatic secretions and, consequently, increases the intraductal pressure. However, whether pancreas divisum is associated with AP is controversial [16].

7. Intraduct Papillary Mucinous Tumor

An intraduct papillary mucinous tumor can also cause AP. The tumor, or mucus produced by the cancer cells, blocks the pancreatic duct or its side branches, or both. A consequence of pancreatic duct obstruction resulting from mucus deposits and pancreatic hyperstimulation is an increase in pressure in the pancreatic ducts. Thus, pancreatic tumors that produce mucus can cause AP by the same mechanism that underpins acute biliary pancreatitis [4].

8. Autoimmune Pancreatitis

A unique form of chronic pancreatitis is called autoimmune pancreatitis (AIP), in which autoimmunity against unidentified auto antigens is responsible for the chronic fibro-inflammatory responses in the pancreas [27][28]. AIP is classified into type 1 AIP and type 2 AIP on the basis of clinical features, pathological findings, and IgG4 antibody (Ab) responses [29]. In general, it is accepted that type 1 AIP is a pancreatic manifestation of the systemic IgG4-related disease (IgG4-RD). IgG4-RD is a newly defined disease characterized by elevated serum levels of IgG4 Ab and involvement of multiple organs. Predominant pathological feature of IgG4-RD, as well as type 1 AIP, is a massive infiltration of IgG4-expressing plasmacytes into the affected organs, accompanied by storiform fibrosis [30][31][32]. The presence of neutrophils, but not IgG4-expressing plasmacytes, is a pathological characteristic of type 2 AIP [33][34].

It is worth mentioning that Shiokawa et al. [35] were the first to show that the incidence of cancer after the diagnosis of AIP is significantly higher in patients with AIP than in a sex-, age-, and observation period-matched standard population in a multicenter, retrospective cohort study. Yamamoto et al. [36] also showed that the incidence of cancer after the diagnosis of IgG4-RD is markedly higher in patients with IgG4-RD than in a sex-, age-, and observation period-matched standard population. Several case reports showed that the presence of AIP may be more closely associated with the risk of cancers of extra-pancreatic organs, such as the stomach, lung, and prostate, rather than pancreatic cancer. Therefore, it is unlikely that the presence the presence of AIP and/or IgG4-RD promote the development of pancreatic cancer through inflammation-associated carcinogenesis [35][37][38][39], in contrast to chronic pancreatitis, which is one of the strongest risk factors for the development of pancreatic cancer [40]. The large number of AIP patients in whom cancers are detected at or within one year of the AIP diagnosis strongly suggests, according to a concept proposed by Shiokawa et al.—that AIP and/or IgG4-RD sometimes arise as a paraneoplastic syndrome [35].

9. Genetic Risk

Genetic risk for RAP and CP is similar, whereas, due to the absence of adequate follow-up that can exclude RAP and CP cases, genetic studies in AP are difficult to interpret. As mentioned before, AP, RAP, and CP form a disease continuum [6][41]. Genetic risk factors, as well as chronic alcohol consumption, often lead to the progression of a sentry attack of AP to RAP and eventually to CP. Proteins highly expressed in the pancreas, such as digestive proteases and a trypsin inhibitor, are products of the majority of the pancreatitis risk genes. The various mutations and other genetic alterations, concerning aforementioned pancreatitis risk genes, are classified into pathological pathways responsible for pancreatitis onset and progression, namely the trypsin-dependent, misfolding-dependent, and ductal pathways [42].

Digestive proteases, secreted in inactive precursor forms by pancreatic acinar cells, are flushed from the ductal system in a sodium bicarbonate-rich fluid. The precursor of trypsin-trypsinogen becomes activated by the serine protease

enteropeptidase in the duodenum. Additionally, trypsinogen can be activated in the process called autoactivation, in which it is activated by trypsin [43]. Autoactivation or catalyzation by the lysosomal cysteine protease cathepsin B may lead to premature, intra-pancreatic activation of trypsinogen. Protective mechanisms that avert trypsinogen activation in the pancreas comprise trypsin inhibition by the serine protease inhibitor Kazal type 1 (SPINK1) and trypsinogen degradation by chymotrypsin C (CTRC) and cathepsin L [44][45][46]. As mentioned before, the main function of CTRC is to promote trypsinogen degradation, however it also enhances trypsinogen activation by processing the trypsinogen activation peptide to a shorter form, which is more sensitive to trypsin-mediated activation [47][48]. Trypsinogen activation may be stimulated to a pathological extent due to specific trypsinogen mutations that hijack the aforementioned mechanism.

According to the human genetic studies, trypsinogen autoactivation and CTRC dependent trypsinogen degradation are the key mechanisms determining intrapancreatic trypsin activity [42]. Mutations in specific genes have been established, such as PPSS1, SPINK1 and CTRC mutations. Mutations in human cationic trypsinogen cause autosomal dominant hereditary pancreatitis (HP) with incomplete penetrance or act as risk factors in sporadic CP [46]. Additionally, PRSS1 mutations stimulate activation of cationic trypsinogen by reducing CTRC-dependent trypsinogen degradation, increasing CTRC-mediated processing of the activation peptide, or directly stimulating autoactivation. Furthermore, the association between the most common p.N34S SPINK1 variant and CP was proved, making the p.N34S the clinically most SIGNIFICANT risk factor for CP [46]. Moreover, the specific heterozygous mutations in CTRC gene, discovered in patients with nonalcoholic CP by the use of direct DNA sequencing, increased CP risk by 5-fold on average [49]. The mutations cause loss of CTRC function by various mechanisms, which include defective secretion due to misfolding, catalytic deficiency, resistance to trypsin-mediated activation, or increased degradation by trypsin [50]. However, the protective mutations have also been revealed, for instance protective anionic trypsinogen (PRSS2) variant or CTRB1-CTRB2 locus inversion, which reduce CP risk [51][52].

Testing the patients' DNA may help the clinicians to better understand the pathomechanism of pancreatitis, as well as other diseases, to introduce appropriate therapy. For instance, in the case of RAP, diagnosing a specific genetic CP risk factor allows the introduction of preventive actions. Thorough description of all pathways and connected mutations is too extensive for the research. Researchers would like to present and thus prove, on the basis of one pathologic pathway, that knowledge in the genetic field is the future of medicine.

10. Rare Causes

10.1. Hypercalcemia

A rare cause of AP is hypercalcemia. The low incidence of AP among patients with chronic hypercalcemia indicates that additional factors are needed for AP to develop [6][53].

10.2. Drugs

Cases of drug-induced pancreatitis (DIP) have been reported, although they are rare (0.1–2%) [6]. The most cases of drug-induced pancreatitis (DIP) are mild to moderate in severity. Nevertheless, severe and fatal cases can occur [54]. A retrospective cohort study performed by Sánchez-Aldehuelo et al. [55] included patients with DIP between 2008 and 2018. They concluded that drugs are a rare cause of pancreatitis, and furthermore, DIP mostly occurs within the first month of treatment, is usually mild, and is associated with a low risk of recurrence. Management of DIP includes withdrawal of the suspected active substance and supportive care [54].

Firstly, the diagnosis of DIP requires a diagnosis of AP, which is done on the basis of two of three criteria-typical belt-like abdominal pain, elevated serum lipase level three times above the normal threshold and radiological imaging signs of pancreatitis [56][57][58]. The first two are present in the majority of cases, whereas the latter occurs slightly less frequently. Due to that, in most of the patients, diagnosis of AP can be already established on the basis of abdominal pain and an elevation of pancreatic enzymes [58]. In the second step in diagnosing DIP, more common etiologies, such as gallstone pancreatitis and ethanol-induced acute pancreatitis, have to be ruled out. Therefore, a detailed medical history and the patient's medications must be established. The history should include previous symptoms and any record of gallstones, ethanol abuse, hypercalcemia, hypertriglyceridemia, and trauma. Additionally, laboratory assays, such as serum amylase, lipase, triglyceride level, calcium level, and liver function tests, should be performed. Moreover, abdominal and endoscopic ultrasounds should be performed to evaluate the condition of bile and pancreatic ducts for gallstones and other obstructive possibilities such as tumors of the pancreas head. ERCP should not be performed after an episode of AP in the absence of imaging or chemical evidence of choledocholithiasis [57][59]. The next step is to discontinue any drugs with the potential to cause pancreatitis or to exchange for a drug of a different class, if possible. Suspicion of DIP increases if the pancreatitis resolves after discontinuation of the drug. Finally, a reliable diagnosis can be established with

a rechallenge of the suspected drug that results in the recurrence of pancreatitis symptoms [54][60][61]. Mostly due to delays in diagnosis, cases of DIP are associated with higher morbidity, extended hospital stays, and increased healthcare costs. Therefore, patients presenting with pancreatitis of unknown etiology should be thoroughly questioned regarding drugs that could be connected with DIP [62].

The pathomechanism of DIP is associated with cytotoxic and metabolic effects, sphincter contraction, hypersensitivity reactions, arteriolar thrombosis, and local angioedema. Commonly prescribed drugs associated with AP include angiotensin-converting enzyme (localized angioedema), statins (direct and accumulation toxicity), oral contraceptives or hormone replacement therapy, especially estrogen (hypertriglyceridemia, local arteriolar thrombosis), antiviral therapy (HIV), diuretics, valproic acid, and antidiabetic agents such as GLP-1 mimetic [54][63][64][65]. The best-known medicaments causing DIP are 6-mercaptopurine or azathioprine, isoniazid, loop diuretics, and didanosine [60][62][66].

Other causes of DIP include antibiotics (metronidazole, tetracycline class, erythromycin, ampicillin, ceftriaxone, clarithromycin, trimethoprim-sulfamethoxazole, and nitrofurantoin), immunotherapy (interleukin-2 immunotherapy, programmed cell death protein 1 blockers, anti-cytotoxic T-lymphocyte-associated protein 4 agents), antiacids (2-blockers and proton-pump inhibitors), antidepressants, antiseizure medications, steroids, and non-steroidal anti-inflammatory drugs (NSAIDs) [62]. However, both diclofenac and indomethacin, representatives of NSAIDs, may significantly reduce the risk of post-ERCP acute pancreatitis [67][68]. Furthermore, cases of vitamin-induced acute pancreatitis have been reported involving vitamin D. Cases involved oral vitamin D, where pancreatitis seemed to be associated with the hypercalcemic effect of vitamin D, and a vitamin D-analog (tacolcitol) ointment. Another group that should be mentioned is antineoplastics, both antimetabolite and alkylating [62]. Interestingly, a selective estrogen receptor modulator commonly used for the treatment of estrogen/progesterone receptor positive breast cancer, namely tamoxifen, can also lead to pancreatitis as a side effect. Tamoxifen, like oestrogens, increases the plasma level of triglycerides and liver secretion of Very Low Density Lipoprotein. Furthermore, it inhibits the key enzymes of triglyceride metabolism. However, only few cases of severe tamoxifen induced hypertriglyceridemia and pancreatitis have been reported. Clinicians must be aware of this rare side effect of tamoxifen, as well as in the case of other high-risk drugs. Consequently, while using tamoxifen, baseline and periodic testing of triglyceride level must be done, and care has to be taken, especially in previously diabetic and hypertriglyceridemic females [69].

Many cases go unreported due to the absence of mandatory adverse drug reporting systems, decreasing the ability of clinicians to causally link acute pancreatitis with medications. It is worth introducing similar reporting systems, as well as classification systems or probability assessment scales, in order to facilitate the management of patients. The earliest classification system of drug-induced pancreatitis was developed in 1980 by Trivedi et al. and included three classes [70]. The most recent classification system, developed by Badalov et al. [60], categorized implicated drugs into four classes. Moreover, the adverse drug reaction probability scale by Naranjo et al. [71] can be used to establish the degree of association between a drug and an adverse reaction. The scale determines the probability of an adverse drug reaction on the basis of the cumulative score on 10 questions. Weissman et al. [62] recently proposed a specific drug-induced pancreatitis probability assessment scale, which is modified from the Naranjo scale to be more pancreatitis-specific. It can be helpful in determining the likelihood of DIP based on the aggregate score from a series of 10 questions. It was suggested that the aforementioned scale increases the ability to accurately identify and implicate potential acute pancreatitis-causing drugs.

10.3. Viruses

Viral pancreatitis is also described, most often the result of mumps, measles, coxsackie, Epstein–Barr virus, and hepatitis-A virus infections [72]. Recently, Aloysius et al. [73] reported the case of a patient with COVID-19 who presented with AP without other risk factors.

11. Clinical Aspects

It is substantial to identify the etiology of AP on admission in order to introduce the best and, in the case of some patients, the most specific therapy. The best intervention in biliary AP with cholangitis is early ERCP, in hypertriglyceridemia-induced AP the introduction of lipid-lowering therapy, in the case of obstruction-evoked AP pancreatic stent placement pancreatic duct is performed, while in autoimmune pancreatitis the steroid therapy is implemented [74].

Unfortunately, the IAP/APA guidelines, concerning the management with the patients with AP, inter alia, determining the etiology of the disease, are insufficiently introduced into daily clinical practice. The etiology of AP remains unclear in almost a quarter of all cases, which can be caused by an insufficient diagnostic work-up or other unknown etiological

factors. The study by Zádori et al. [74] showed that 5% of the patients left the hospital after the first and second attacks of AP without any imaging at all, whereas 25% of patients had no diagnostic work-up for biliary AP, such as laboratory tests. The greatest insufficiency in etiology screening, amounting to 71–76%, concerned lipid-induced (triglyceride or cholesterol) pancreatitis. In the case of additional diagnostic work-up for all idiopathic AP after index admission, in 91% of the cases there was no search for biliary, anatomic, or cancer etiology by EUS or MRCP, for autoimmune AP in 98% cases, for genetic AP in 99%, or for virus-induced AP after the first attack in 94%.

It is worth mentioning that the cause of about 40% of fatal AP cases is idiopathic, which emphasizes the significance of determining the etiology. Moreover, defining the etiology is crucial for index AP, as well as for preventing recurrent or chronic pancreatitis [74]. It is important to know the latest guidelines and use them in everyday clinical practice.

References

1. Dimitriou, I.; Katsourakis, A.; Nikolaidou, E.; Noussios, G. The Main Anatomical Variations of the Pancreatic Duct System: Review of the Literature and Its Importance in Surgical Practice. J. Clin. Med. Res. 2018, 10, 370–375.
2. Suda, K.; Nobukawa, B.; Takase, M.; Hayashi, T. Pancreatic segmentation on an embryological and anatomical basis. J. Hepato-Biliary-Pancreat. Surg. 2006, 13, 146–148.
3. Dolenšek, J.; Rupnik, M.S.; Stožer, A. Structural similarities and differences between the human and the mouse pancreas. Islets 2015, 7, e1024405.
4. Röder, P.V.; Wu, B.; Liu, Y.; Han, W. Pancreatic regulation of glucose homeostasis. Exp. Mol. Med. 2016, 48, e219.
5. Arsenijevic, T.; Perret, J.; van Laethem, J.L.; Delporte, C. Aquaporins involvement in pancreas physiology and in pancreatic diseases. Int. J. Mol. Sci. 2019, 20, 5052.
6. Weiss, F.U.; Laemmerhirt, F.; Lerch, M.M. Etiology and risk factors of acute and chronic pancreatitis. Visc. Med. 2019, 35, 73–81.
7. Conroy, T.; Bachet, J.-B.; Ayav, A.; Huguet, F.; Lambert, A.; Caramella, C.; Maréchal, R.; Van Laethem, J.-L.; Ducreux, M. Current standards and new innovative approaches for treatment of pancreatic cancer. Eur. J. Cancer 2016, 57, 10–22.
8. Madácsy, T.; Pallagi, P.; Maleth, J. Cystic Fibrosis of the Pancreas: The Role of CFTR Channel in the Regulation of Intracellular Ca2+ Signaling and Mitochondrial Function in the Exocrine Pancreas. Front. Physiol. 2018, 9, 1585.
9. Dominguez-Muñoz, J.E. Management of pancreatic exocrine insufficiency. Curr. Opin. Gastroenterol. 2019, 35, 455–459.
10. Alexandre-Heymann, L.; Mallone, R.; Boitard, C.; Scharfmann, R.; Larger, E. Structure and function of the exocrine pancreas in patients with type 1 diabetes. Rev. Endocr. Metab. Disord. 2019, 20, 129–149.
11. Hu, F.; Qiu, X.; Bu, S. Pancreatic islet dysfunction in type 2 diabetes mellitus. Arch. Physiol. Biochem. 2020, 126, 235–241.
12. Zhou, Q.; Melton, D.A. Pancreas regeneration. Nature 2018, 557, 351–358.
13. Völzke, H.; Baumeister, S.E.; Alte, D.; Hoffmann, W.; Schwahn, C.; Simon, P.; John, U.; Lerch, M.M. Independent risk factors for gallstone formation in a region with high cholelithiasis prevalence. Digestion 2005, 71, 97–105.
14. Buch, S.; Schafmayer, C.; Völzke, H.; Seeger, M.; Miquel, J.F.; Sookoian, S.C.; Egberts, J.H.; Arlt, A.; Pirola, C.J.; Lerch, M.M.; et al. Loci from a genome-wide analysis of bilirubin levels are associated with gallstone risk and composition. Gastroenterology 2010, 139, 1942–1951.e2.
15. Lammert, F.; Acalovschi, M.; Ercolani, G.; van Erpecum, K.J.; Gurusamy, K.; van Laarhoven, C.J.; Portincasa, P. EASL Clinical Practice Guidelines on the prevention, diagnosis and treatment of gallstones. J. Hepatol. 2016, 65, 146–181.
16. Wang, G.J.; Gao, C.F.; Wei, D.; Wang, C.; Ding, S.Q. Acute pancreatitis: Etiology and common pathogenesis. World J. Gastroenterol. 2009, 15, 1427–1430.
17. Meyerholz, D.K.; Samuel, I. Morphologic characterization of early ligation-induced acute pancreatitis in rats. Am. J. Surg. 2007, 194, 652–658.
18. Samuel, I.; Toriumi, Y.; Zaheer, A.; Joehl, R.J. Mechanism of acute pancreatitis exacerbation by enteral bile-pancreatic juice exclusion. Pancreatology 2004, 4, 527–532.
19. Gao, Y.J.; Li, Y.Q.; Wang, Q.; Li, S.L.; Li, G.Q.; Ma, J.; Zeng, X.Z.; Huang, L.Y.; Yuan, S.A.; Liu, C.A.; et al. Analysis of the clinical features of recurrent acute pancreatitis in China. J. Gastroenterol. 2006, 41, 681–685.

20. de Pretis, N.; Amodio, A.; Frulloni, L. Hypertriglyceridemic pancreatitis: Epidemiology, pathophysiology and clinical management. United Eur. Gastroenterol. J. 2018, 6, 649–655.
21. Jin, J.; Yu, Y.H.; Zhong, M.; Zhang, G.W. Analyzing and identifying risk factors for acute pancreatitis with different etiologies in pregnancy. J. Matern.-Fetal Neonatal Med. 2015, 28, 267–271.
22. Linares, C.L.; Pelletier, A.L.; Czernichow, S.; Vergnaud, A.C.; Bonnefont-Rousselot, D.; Levy, P.; Ruszniewski, P.; Bruckert, E. Acute pancreatitis in a cohort of 129 patients referred for severe hypertriglyceridemia. Pancreas 2008, 37, 13-2.
23. Kochar, B.; Akshintala, V.S.; Afghani, E.; Elmunzer, B.J.; Kim, K.J.; Lennon, A.M.; Khashab, M.A.; Kalloo, A.N.; Singh, V.K. Incidence, severity, and mortality of post-ERCP pancreatitis: A systematic review by using randomized, controlled trials. Gastrointest. Endosc. 2015, 81, 143–149.e9.
24. Chandrasekhara, V.; Khashab, M.A.; Muthusamy, V.R.; Acosta, R.D.; Agrawal, D.; Bruining, D.H.; Eloubeidi, M.A.; Fanelli, R.D.; Faulx, A.L.; Gurudu, S.R.; et al. Adverse events associated with ERCP. Gastrointest. Endosc. 2017, 85, 32–47.
25. Fluhr, G.; Mayerle, J.; Weber, E.; Aghdassi, A.; Simon, P.; Gress, T.; Seufferlein, T.; Mössner, J.; Stallmach, A.; Rösch, T.; et al. Pre-Study protocol MagPEP: A multicentre randomized controlled trial of magnesium sulphate in the prevention of post-ERCP pancreatitis. BMC Gastroenterol. 2013, 13, 11.
26. Noble, M.D.; Romac, J.; Vigna, S.R.; Liddle, R.A. A pH-sensitive, neurogenic pathway mediates disease severity in a model of post-ERCP pancreatitis. Gut 2008, 57, 1566–1571.
27. Blaho, M.; Dítě, P.; Kunovský, L.; Kianička, B. Autoimmune pancreatitis—An ongoing challenge. Adv. Med. Sci. 2020, 65, 403–408.
28. Khandelwal, A.; Inoue, D.; Takahashi, N. Autoimmune pancreatitis: An update. Abdom. Radiol. 2020, 45, 1359–1370.
29. Kamisawa, T.; Chari, S.T.; Lerch, M.M.; Kim, M.H.; Gress, T.M.; Shimosegawa, T. Recent advances in autoimmune pancreatitis: Type 1 and type 2. Postgrad. Med. J. 2014, 90, 18–25.
30. Pieringer, H.; Parzer, I.; Wöhrer, A.; Reis, P.; Oppl, B.; Zwerina, J. IgG4- related disease: An orphan disease with many faces. Orphanet J. Rare Dis. 2014, 9, 110.
31. Hirabayashi, K.; Zamboni, G. IgG4-related disease. Pathologica 2012, 104, 43–55.
32. Pitz, S. IgG4-related disease. Ophthalmologe 2021, 118, 787–793.
33. Hart, P.A.; Zen, Y.; Chari, S.T. Recent Advances in Autoimmune Pancreatitis. Gastroenterology 2015, 149, 39–51.
34. Mitsuyama, T.; Uchida, K.; Sumimoto, K.; Fukui, Y.; Ikeura, T.; Fukui, T.; Nishio, A.; Shikata, N.; Uemura, Y.; Satoi, S.; et al. Comparison of neutrophil infiltration between type 1 and type 2 autoimmune pancreatitis. Pancreatology 2015, 15, 271–280.
35. Shiokawa, M.; Kodama, Y.; Yoshimura, K.; Kawanami, C.; Mimura, J.; Yamashita, Y.; Asada, M.; Kikuyama, M.; Okabe, Y.; Inokuma, T.; et al. Risk of cancer in patients with autoimmune pancreatitis. Am. J. Gastroenterol. 2013, 108, 610–617.
36. Yamamoto, M.; Takahashi, H.; Tabeya, T.; Suzuki, C.; Naishiro, Y.; Ishigami, K.; Yajima, H.; Shimizu, Y.; Obara, M.; Yamamoto, H.; et al. Risk of malignancies in IgG4-related disease. Mod. Rheumatol. 2012, 22, 414–418.
37. Fukui, T.; Mitsuyama, T.; Takaoka, M.; Uchida, K.; Matsushita, M.; Okazaki, K. Pancreatic cancer associated with autoimmune pancreatitis in remission. Intern. Med. 2008, 47, 151–155.
38. Schneider, A.; Hirth, M.; Münch, M.; Weiss, C.; Löhr, J.M.; Ebert, M.P.; Pfützer, R.H. Risk of Cancer in Patients with Autoimmune Pancreatitis: A Single-Center Experience from Germany. Digestion 2017, 95, 172–180.
39. Hirano, K.; Tada, M.; Sasahira, N.; Isayama, H.; Mizuno, S.; Takagi, K.; Watanabe, T.; Saito, T.; Kawahata, S.; Uchino, R.; et al. Incidence of malignancies in patients with IgG4-related disease. Intern. Med. 2014, 53, 171–176.
40. Watanabe, T.; Kudo, M.; Strober, W. Immunopathogenesis of pancreatitis. Mucosal Immunol. 2017, 10, 283–298.
41. Yadav, D.; Lowenfels, A.B. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology 2013, 144, 1252–1261.
42. Mayerle, J.; Sendler, M.; Hegyi, E.; Beyer, G.; Lerch, M.M.; Sahin-Tóth, M. Genetics, Cell Biology, and Pathophysiology of Pancreatitis. Gastroenterology 2019, 56, 1951–1968.e1.
43. Rinderknecht, H. Activation of pancreatic zymogens—Normal activation, premature intrapancreatic activation, protective mechanisms against inappropriate activation. Dig. Dis. Sci. 1986, 31, 314–321.
44. Szmola, R.; Sahin-Tóth, M. Chymotrypsin C (caldecrin) promotes degradation of human cationic trypsin: Identity with Rinderknecht's enzyme Y. Proc. Natl. Acad. Sci. USA. 2007, 104, 11227–11232.

45. Wartmann, T.; Mayerle, J.; Kähne, T.; Sahin-Tóth, M.; Ruthenbürger, M.; Matthias, R.; Kruse, A.; Reinheckel, T.; Peters, C.; Weiss, F.U.; et al. Cathepsin L Inactivates Human Trypsinogen, Whereas Cathepsin L-Deletion Reduces the Severity of Pancreatitis in Mice. Gastroenterology 2010, 138, 726–737.

46. Hegyi, E.; Sahin-Tóth, M. Genetic Risk in Chronic Pancreatitis: The Trypsin-Dependent Pathway. Dig. Dis. Sci. 2017, 62, 1692–1701.

47. 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, 20701–20710.

48. Aoun, E.; Chang, C.C.H.; Greer, J.B.; Papachristou, G.I.; Barmada, M.M.; Whitcomb, D.C. Pathways to injury in chronic pancreatitis: Decoding the role of the high-risk SPINK1 N34S haplotype using meta-analysis. PLoS ONE 2008, 3, e2003.

49. Rosendahl, J.; Witt, H.; Szmola, R.; Bhatia, E.; Ózsvári, B.; Landt, O.; Schulz, H.-U.; Gress, T.M.; Pfützer, R.; Löhr, M.; et al. Chymotrypsin C (CTRC) variants that diminish activity or secretion are associated with chronic pancreatitis. Nat. Genet. 2008, 40, 78–82.

50. Beer, S.; Zhou, J.; Szabó, A.; Keiles, S.; Chandak, G.R.; Witt, H.; Sahin-Tóth, M. Comprehensive functional analysis of chymotrypsin C (CTRC) variants reveals distinct loss-of-function mechanisms associated with pancreatitis risk. Gut 2013, 62, 1616–1624.

51. Rosendahl, J.; Kirsten, H.; Hegyi, E.; Kovacs, P.; Weiss, F.U.; Laumen, H.; Lichtner, P.; Ruffert, C.; Chen, J.-M.; Masson, E.; 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, 1855–1863.

52. Witt, H.; Sahin-Tóth, M.; Landt, O.; Chen, J.M.; Kähne, T.; Drenth, J.P.H.; Kukor, Z.; Szepessy, E.; Halangk, W.; Dahm, S.; et al. A degradation-sensitive anionic trypsinogen (PRSS2) variant protects against chronic pancreatitis. Nat. Genet. 2006, 38, 668–673.

53. Bess, M.A.; Edis, A.J.; van Heerden, J.A. Hyperparathyroidism and Pancreatitis: Chance or a Causal Association? J. Am. Med. Assoc. 1980, 243, 246–247.

54. Jones, M.R.; Hall, O.M.; Kaye, A.M.; Kaye, A.D. Drug-induced acute pancreatitis: A review. Ochsner J. 2015, 15, 45–51.

55. Aldehuelo, R.S.; de Paredes, A.G.G.; Lázaro, D.R.; Ortega, A.M.; de la Filia Molina, I.G.; López-Durán, S.; Rodríguez-Gandía, M.Á.; López-Sanromán, A.; Albillos, A. Outcomes of drug-induced acute pancreatitis: A ten-year experience of an academic center. Rev. Esp. Enferm. Dig. 2021, 113, 276–279.

56. Machicado, J.D.; Yadav, D. Epidemiology of Recurrent Acute and Chronic Pancreatitis: Similarities and Differences. Dig. Dis. Sci. 2017, 62, 1683–1691.

57. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013, 13 (Suppl. S2), e1–e15.

58. Párniczky, A.; Kui, B.; Szentesi, A.; Balázs, A.; Szûcs, Á.; Mosztbacher, D.; Czimmer, J.; Sarlós, P.; Bajor, J.; Gódi, S.; et al. Prospective, Multicentre, Nationwide Clinical Data from 600 Cases of Acute Pancreatitis. PLoS ONE 2016, 11, e0165309.

59. Leppäniemi, A.; Tolonen, M.; Tarasconi, A.; Lohse, H.A.S.; Gamberini, E.; Kirkpatrick, A.W.; Ball, C.G.; Parry, N.; Sartelli, M.; Wolbrink, D.R.J.; et al. 2019 WSES guidelines for the management of severe acute pancreatitis. World J. Emerg. Surg. 2019, 14, 27.

60. Badalov, N.; Baradarian, R.; Iswara, K.; Li, J.; Steinberg, W.; Tenner, S. Drug-Induced Acute Pancreatitis: An Evidence-Based Review. Clin. Gastroenterol. Hepatol. 2007, 5, 648–661.e3.

61. Spanier, M.B.; Tuynman, H.A.; van der Hulst, R.W.; Dijkgraaf, M.G.; Bruno, M.J. Acute pancreatitis and concomitant use of pancreatitis-associated drugs. Am. J. Gastroenterol. 2011, 106, 2183–2188.

62. Weissman, S.; Aziz, M.; Perumpail, R.B.; Mehta, T.I.; Patel, R.; Tabibian, J.H. Ever-increasing diversity of drug-induced pancreatitis. World J. Gastroenterol. 2020, 26, 2902–2915.

63. Thisted, H.; Jacobsen, J.; Munk, E.M.; Norgaard, B.; Friis, S.; McLaughlin, J.K.; Sørensen, H.T.; Johnsen, S.P. Statins and the risk of acute pancreatitis: A population-based case-control study. Aliment. Pharmacol. Ther. 2006, 23, 185–190.

64. Alves, C.; Batel-Marques, F.; Macedo, A.F. A meta-analysis of serious adverse events reported with exenatide and liraglutide: Acute pancreatitis and cancer. Diabetes Res. Clin. Pract. 2012, 98, 271–284.

65. Nitsche, C.; Maertin, S.; Scheiber, J.; Ritter, C.A.; Lerch, M.M.; Mayerle, J. Drug-induced pancreatitis. Curr. Gastroenterol. Rep. 2012, 14, 131–138.

66. Wolfe, D.; Kanji, S.; Yazdi, F.; Barbeau, P.; Rice, D.; Beck, A.; Butler, C.; Esmaeilisaraji, L.; Skidmore, B.; Moher, D.; et al. Drug induced pancreatitis: A systematic review of case reports to determine potential drug associations. PLoS ONE 2020, 15, e0231883.
67. Sotoudehmanesh, R.; Khatibian, M.; Kolahdoozan, S.; Ainechi, S.; Malboosbaf, R.; Nouraie, M. Indomethacin may reduce the incidence and severity of acute pancreatitis after ERCP. Am. J. Gastroenterol. 2007, 102, 978–983.
68. Murray, B.; Carter, R.; Imrie, C.; Evans, S.; O'Suilleabhain, C. Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. Gastroenterology 2003, 124, 1786–1791.
69. Kataria, P.S.C.; Kendre, P.P.; Patel, A.A.; Bohra, M.Z.; Tahiliani, N. Tamoxifen induced pancreatitis: An unusual complication of commonly used drug. J. Clin. Diagn. Res. 2017, 11, XD05–XD06.
70. Zheng, J.; Yang, Q.J.; Dang, F.T.; Yang, J. Drug-induced pancreatitis: An update. Arab. J. Gastroenterol. 2019, 20, 183–188.
71. Naranjo, C.A.; Busto, U.; Sellers, E.M.; Sandor, P.; Ruiz, I.; Roberts, E.A.; Janecek, E.; Domecq, C.; Greenblatt, D.J. A method for estimating the probability of adverse drug reactions. Clin. Pharmacol. Ther. 1981, 30, 239–245.
72. Kottanattu, L.; Lava, S.A.G.; Helbling, R.; Simonetti, G.D.; Bianchetti, M.G.; Milani, G.P. Pancreatitis and cholecystitis in primary acute symptomatic Epstein-Barr virus infection—Systematic review of the literature. J. Clin. Virol. 2016, 82, 51–55.
73. Aloysius, M.M.; Thatti, A.; Gupta, A.; Sharma, N.; Bansal, P.; Goyal, H. COVID-19 presenting as acute pancreatitis. Pancreatology 2020, 20, 1026–1027.
74. Zádori, N.; Párniczky, A.; Szentesi, A.; Hegyi, P. Insufficient implementation of the IAP/APA guidelines on aetiology in acute pancreatitis: Is there a need for implementation managers in pancreatology? United Eur. Gastroenterol. J. 2020, 8, 246–248.