IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
October 2017 Vol.:10, Issue: 3

Pancreatitis: An Overview

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

LAKSHMI. K*, KARISHMA. SK, NARENDRA BABU. A

Chalapathi Institute of Pharmaceutical Sciences, Lam, Guntur-522 034, Andhra Pradesh, India.

Submission: 22 September 2017
Accepted: 3 October 2017
Published: 30 October 2017

Keywords: pancreatitis, Pathophysiology, diagnosis, treatment

ABSTRACT

Pancreatitis is the inflammation of the pancreas with variable involvement of regional tissue. It is of two types, they are acute pancreatitis (AP) and chronic pancreatitis (CP). This article provides a comprehensive review of this subject with a focus on the clinical manifestations of acute & chronic pancreatitis, including new insights into the pathophysiology, diagnosis, and treatment.

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INTRODUCTION

Pancreatitis is the inflammation of the pancreas associated with injury to the exocrine parenchyma. The clinical manifestations range in severity from a mild, self-limited disease to a life-threating acute inflammatory process, and the duration of the disease can be range from a transient attack to a permanent loss of function. They are two types of pancreatitis. In acute pancreatitis, the gland can be returned to normal if the underlying cause of pancreatitis is removed. By contrast, chronic pancreatitis is delivered by the irreversible loss of exocrine pancreatic parenchyma. Both entities share similar pathogenic mechanism and indeed recurrent AP can result in CP. Ductal obstruction and alcohol are the most common causes of both forms. Inappropriate activation of pancreatic digestive enzymes (due to mutations in genes encoding trypsinogen (or) trypsin inhibitor) and primary acinar injury (due to toxins, infections, ischemia (or) trauma) also cause pancreatitis (1-2).

TYPES:

There are two types of pancreatitis (3):

Acute pancreatitis: AP is characterized by severe pain in the upper abdomen and elevations of pancreatic enzymes in the blood.

Chronic pancreatitis: CP is characterized by permanent damage to pancreatic structure and function because of progressive inflammation and long standing pancreatic injury.

EPIDEMIOLOGY:

- Worldwide incidence ranges between 5 and 80 per 100000 populations.
- The annual incidence of AP ranges from 13 to 45 per 100000 persons.
- The annual incidence of CP ranges from 5 to 12 per 100000 persons.
- **Age:**-Although equal proportions of men and women develop AP, CP Is more common among men the conditions occurs in adult between 40 to 70 years and is common in females than males.
- **Race**- the risk of pancreatitis is 2 to 3 fold higher among blacks than whites (4).

1) ACUTE PANCREATITIS:

Reversible process characterized by (5):

- Interstitial edema
- Infiltration by acute inflammatory cells
- Necrosis, apoptosis, and haemorrhage

Etiology:

- **Well-established causes:**

➢ **Gallstones:** Gallstones cause about 40% of cases of pancreatitis. Proposed mechanisms include reflux of noxious bile into the pancreatic duct from transient obstruction of the ampulla during gallstone passage and pancreatic ductal hypertension from either a stone impacted at the ampulla (or) ampullary trauma caused by stone passage.

➢ **Alcoholism:** Alcoholism is responsible for about 35% of cases of acute pancreatitis. The Pathophysiology may be multifactorial. Proposed mechanisms include sphincter of Oddi spasm, precipitation of insoluble protein plugs that obstruct the pancreatic ductules, activation of pancreatic proteases and over stimulation of pancreatic secretion by cholecystokinin.

➢ **Hypertriglyceridemia:** Hypertriglyceridemia causes about 2% of cases of acute pancreatitis. A serum triglyceride level greater than 1000 mg/dL suggests this possible cause, and a triglyceride level greater than 2000 mg/dL is diagnostic.

➢ **Pancreatitis after endoscopic retrograde Cholangiopancreatography (ERCP):** About 2% of cases of pancreatitis are caused by ERCP. Pancreatitis is the most common complication of ERCP. Pancreatitis occurs in approximately 5% of ERCPs, with a range from 2% to 7% depending on the criteria for defining pancreatitis. Pancreatitis is diagnosed reliably after ERCP by abdominal pain that is consistent with pancreatitis, that is associated with an at least a threefold increase in the serum lipase or amylase level.

➢ **Drug-induced pancreatitis:** Drugs are responsible for about 2% of cases of pancreatitis.

➢ **Drugs commonly implicated as causes of pancreatitis:**

- Drug-induced hypersensitivity reaction: 5-Aminosalicylic acid/ sulfasalazine, Azathioprine, 6-Mercaptopurine, Metronidazole, Tetracycline
- Toxic metabolite: Pentamidine, Valproic acid, Didanosine
- Drug-induced hypertriglyceridemia: Thiazides, Isotretinoin, Tamoxifen
- Overdose reaction: Acetaminophen, Erythromycin

➢ **Autoimmune pancreatitis:** Patients often present with subacute pancreatitis with jaundice, a lymphoplasmacytic infiltrate on pathologic examination of a pancreatic biopsy, a focal mass in the pancreatic head on CT, and irregular narrowing of the proximal pancreatic duct on ERCP. Patients characteristically have elevated IgG4 levels in the serum and an infiltrate of IgG4-containing plasma cells in the pancreas.

➢ **Genetic causes of pancreatitis:** Mutations of several genes can cause pancreatitis. Hereditary pancreatitis sis associated with mutations in the trypsinogen gene PRSS1 that promotes premature conversion of trypsinogen to active trypsin that causes pancreatic autodigestion. Mutations in SPINK1, a gene that encodes for a pancreatic trypsin inhibitor, are associated with acute and chronic pancreatitis resulting from an impaired ability to counteract the effects of activated trypsin within pancreatic acinar cells.

➢ **Abdominal trauma:** Pancreatic injury occurs in about 0.2% of cases of blunt trauma and in about 1% of penetrating injuries. These low rates result from the retroperitoneal location of the pancreas. This pancreatic injury can cause acute pancreatitis.

➢ **Postoperative pancreatitis:** The mechanisms of postoperative pancreatitis include transient intraoperative hypotension or pancreatic trauma caused by intraoperative pancreatic manipulation. Intraoperative or postoperative medications may also cause pancreatitis. Percutaneous pancreatic biopsy and renal lithotripsy may cause traumatic pancreatitis.

➢ **Ischemia:** Pancreatic ischemia is a rare cause of pancreatitis due to the rich perfusion of the pancreas from the superior and inferior pancreaticoduodenal arterial arcades derived from the celiac axis and the superior mesenteric artery.

➢ **Hypercalcemia:** Hypercalcemia and primary hyperparathyroidism are associated with acute pancreatitis

➢ **Posterior penetrating duodenal ulcer:** Rarely a posterior duodenal ulcer can penetrate into the pancreas and thereby cause acute pancreatitis. This complication can produce significant haemorrhage.

➢ **Scorpion venom:** The venom of two species of scorpions found in Trinidad and Brazil can induce pancreatitis after introduction into the bloodstream via a scorpion bite. The mechanism is massive cholinergic stimulation of the pancreas.

➢ **Controversial causes of pancreatitis:** The following three etiologies occasionally definitely cause pancreatitis and are postulated to cause many cases of otherwise idiopathic pancreatitis.

➢ **Pancreas divisum:** Pancreas divisum occurs in about 7% of the healthy population. Pancreas divisum sometimes is associated with pancreatitis because of ductal hypertension from increased resistance to flow through a narrowed dorsal duct at its papillary origin.

➢ **Sphincter of Oddi dysfunction:** The sphincter of Oddi is a segment of circular and longitudinal muscle 6 to 10 mm long that encircles the distal common bile duct and pancreatic duct. Sphincter of Oddi dysfunction is a controversial cause of acute pancreatitis. In an animal model, transient sphincter contraction induced by local application of carbachol with simultaneous stimulation of pancreatic secretion induced by cholecystokinin/secretin caused pancreatic injury and hyperamylasemia characteristic of acute pancreatitis.

➢ **Biliary sludge/microlithiasis:** Biliary sludge is a viscous suspension of fluid that contains small stones, cholesterol monohydrate crystals, or calcium bilirubinate granules (6).

Pathophysiology of AP:

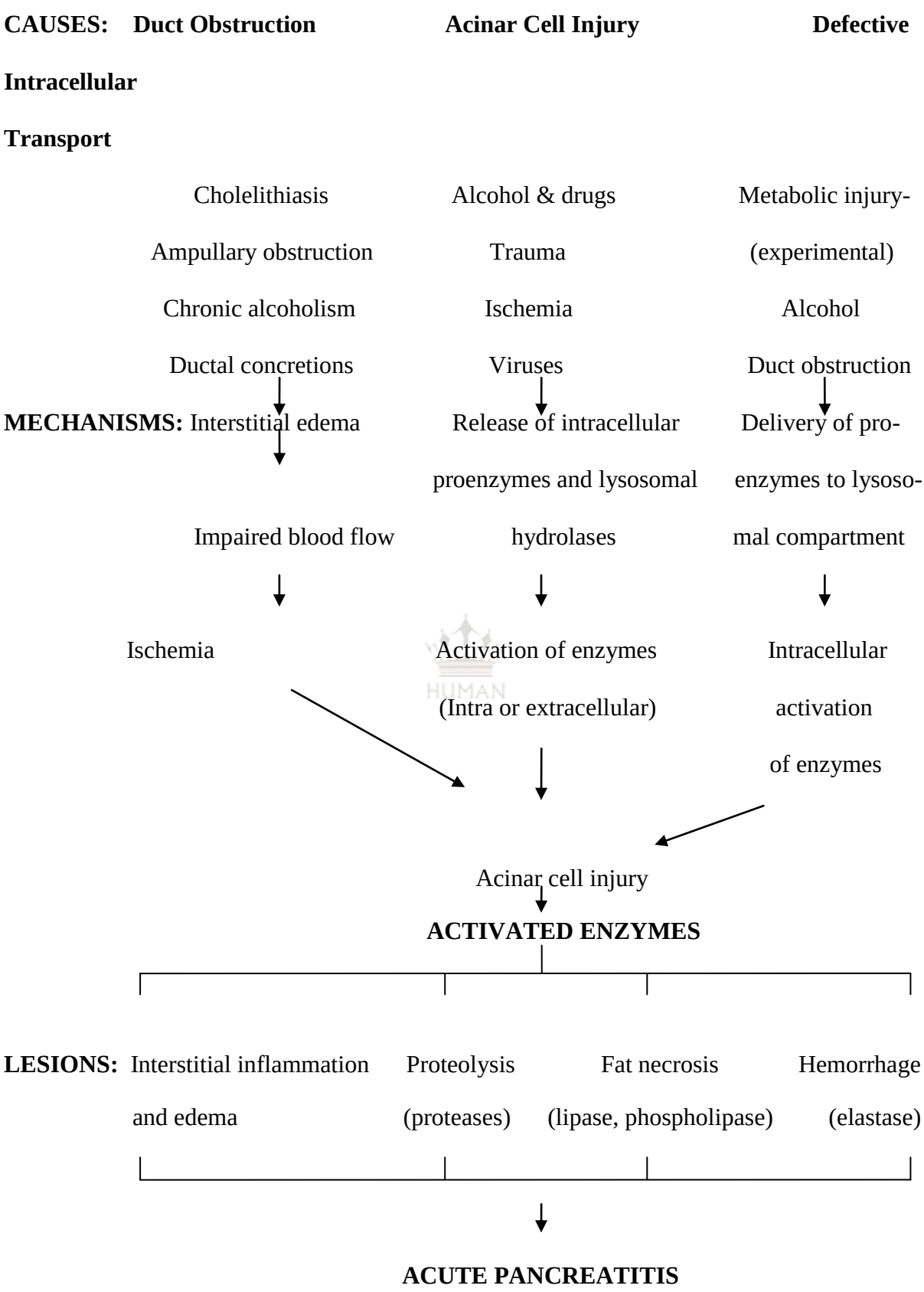


Fig-1: Pathophysiology of acute pancreatitis (1)

Clinical manifestations:

SIGNS	SYMPTOMS
• General condition:- Distressed, Anxious • Vitals:- Fever, Tachycardia, Hypotension, Tachypnea • Cardinals:-Jaundice, Cyanosis, Dehydration • Respiratory:- Signs of pleural effusion – usually left sided (sometimes) • Abdominal: - Marked epigastric tenderness with voluntary and involuntary guarding +/- rigidity, abdominal distension, reduced bowel sound. • Uncommon signs associated with severe necrotizing pancreatitis:- 1. Cullen's sign (Periumbilical discolouration due to peritoneal hemorrhage) 2. Grey-Turner's sign (Flank discoloration due to retroperitoneal hemorrhage) 3. Fox's sign (Discoloration below inguinal ligament or at the base of penis) 4. Erythematous skin nodules (Subcutaneous fat necrosis)	1. **L**ocation: Upper abdomen/Epigastric 2. **L**ength (Duration): Hours to a day 3. **I**ntensity: Gradually becomes severe (not relieved by ordinary analgesics) 4. **Q**uality: Constant and Dull 5. **O**nset: Sudden 6. **R**adiation: Back 7. **A**ssociated symptoms: Nausea, Vomiting, Anorexia, Abdominal distension 8. **A**ggravating factors: Eating or drinking (specially alcohol) 9. **A**lleviating factors: Leaning forward, Curl up (Fetal position) (5)

Complications:

1) Local complications - acute fluid collection, pancreatic necrosis, infection, abscess (collection of pus in or adjacent to the pancreas), and Pseudocysts (collection of pancreatic juice and tissue debris enclosed by a wall of fibrous or granulation tissue)

2) Systemic complications - cardiovascular, renal, pulmonary, metabolic, hemorrhagic, and central nervous system abnormalities.

a. Cardiovascular complications: Hypotension, hypovolemia, sudden death, non- specific ST-changes in electrocardiogram stimulating myocardial infarction

b. Renal complications: Caused by oliguria, azothemia, renal artery (or) renal vein thrombosis, acute tubular necrosis.

c. Pulmonary complications: Develop when fluid accumulates within the pleural space and compresses the lung and the acute respiratory distress syndrome (ARDS) restricts gas exchange.

d. Metabolic complications: Hyperglycemia, hypertriglyceridemia, hypocalcaemia, encephalopathy, sudden blindness (purtscher's retinopathy).

e. Haemorrhagic complications: Disseminated intravascular coagulation

f. C.N.S complications: Psychosis, fat emboli (3).

Diagnosis:

- **Laboratoratory tests*:***

a. *Serum amylase and lipase*: ↑ by 3X of upper-limit is diagnostic

Lipase is more specific than amylase (hence preferred). Lipase rises within 4-8 hours of pain onset. Amylase rises within 6 hours of pain onset. Amylase may be normal during acute inflammation due to significant pancreatic destruction. Amylase normalizes in blood by 3-5 days due to increased excretion in urine. Lipase remains elevated for 7-10 days.

Other causes of ↑ amylase: Macroamylasemia, Renal failure, Mumps parotitis, ERCP induced, esophageal perforation, Pregnancy.

b. *LFTs*:(liver function tests):

- ↑ ALT (*Alanine aminotransferase*) and AST (*aspartate aminotransferase*) (ALT ↑ by around 3X i.e. >150 IU/L is diagnostic of gallstone pancreatitis)

- ↑ALP (*Alkaline phosphatase*), ↑bilirubin, ↓albumin

c. *RFTs(Renal function tests)*: BUN **(**Blood urea nitrogen) and Creatinine (to rule out renal failure)

d. *CBC (COMPLETE BLOOD COUNT) and HCt(hematocrit)* :

- Leukocytosis with shift to left (Inflammation or SIRS)

- ↑HCt (Hemoconcentration due to fluid sequestration)

- ↓HCt (Dehydration or Hemorrhage)

e. *Blood biochemistry*:

- Blood sugar: may ↑ due to insulin producing Beta-cell dysfunction

- Serum calcium: ↓ (due to hypoalbuminemia or fat necrosis) or ↑ (due to hypercalcemia)

- Lipid profile: to rule out hypertriglyceridemia as the cause

f. *ABG* (*Arterial blood gas*): every 12 hrs for 1st 3 days (to monitor oxygenation and acid-base status)

g. *Other*: CRP (C-reactive protein), Trypsin, Trypsinogen-2, LDH **(**Lactate dehydrogenase), PhospholipaseA

- **Imaging Studies:**

i. *Plain Chest X-Ray*: Pleural effusion, ARDS (Atelectasis and Basal infiltrates), Elevation of left diaphragm

ii. *Plain Abdominal X-Ray* (erect):

- To rule out perforated peptic ulcer
- Sentinel loop sign, Colon 'cut-off' sign, Renal halo sign
- May show gallstone, pancreatic calcification

iii. *Abdominal USG* (Ultrasonography): Can detect gallstones, biliary obstruction, and pseudocysts formation.

iv. *CT abdomen*: CT abdomen may be required if diagnosis uncertain, to rule out and find degree of Peripancreatic collection; Necrosis and Abscess (5).

Treatment:

- **Non-pharmacological therapy:** It includes ERCP for removal of an underlying biliary tract, gallstones, surgery and nutritional support. Surgery is indicated in patients with pseudocysts, pancreatic abscess or to drain the pancreatic bed if haemorrhagic or necrotic material is present.

- **Pharmacological therapy:** Patients with mild AP respond to supportive care, intravenous fluid resuscitation, nutrition and relief of pain and nausea. Pain and nausea can be treated with moderate doses of intravenous analgesics and anti-emetics, antibiotics are not indicated in mild disease. Patients with severe AP requires intensive care, vigorous fluid resuscitation, nutritional support and analgesia, antisecretory drugs may be used to prevent stress related mucosal bleeding (3).

- Antiproteases: Gabexate
- Antisecretory agents: Octreotide and Somatostatin
- Anti-inflammatory agents: Lexipafant (5)

2. CHRONIC PANCREATITIS:

It is defined as progressive destruction of the pancreases due to repeated mild and subclinical attacks AP.Weight loss, jaundice, diabetes mellitus, steatorrhoea are also often associated (7).

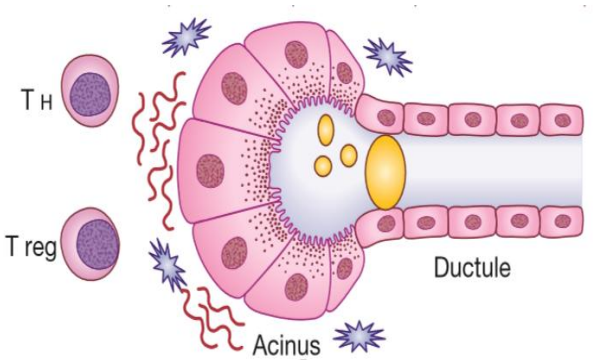
Etiology:

- CP can be classified etiologically according to the TIGAR-O-system
- **T**- toxic, eg: alcohol, drugs, renal failure, hypercalcaemia, post-actinic
- **I** - idiopathic, eg: idiopathic "juvenile" CP, "Senile" CP, tropical CP
- **G** - genetic; autosomal dominant trypsinogen gene mutation or mutations of modifier genes, eg: CFTR (cystic fibrosis genes), SPINK-1-genes (trypsin secretory inhibitor gene)
- **A** - autoimmune pancreatitis
- **R** - recurrent severe acute pancreatitis
- **O** - obstructive pancreatitis (9)

Pathophysiology:

Causes: Alcohol, Smoking | Idiopathic | Genetic | Autoimmune | Obstructive

Mechanisms: Oxidative stress | Toxic-metabolic | Necrosis fibrosis | Recurrent AP | Duct obstruction



Clinical course:

Normal → AP → Recurrent AP → CP

Fig-2: Pathophysiology of chronic pancreatitis (7)

Clinical manifestations:

Signs	Symptoms	Complications
➢ Epigastria tender mass of fullness(pseudocysts) ➢ Advanced malnutrition, decreased fat. ➢ Steatorrhoea, Azotorrhea ➢ Malabsorption ➢ Jaundice ➢ Pancreatic diabetes (pancreatic calcification) ➢ Neuro and nephropathy	➢ Mid upper abdominal pain –intermittently severe may radiates to back ➢ Diarrhoea ➢ Steatorrhoea ➢ Nausea and vomiting	➢ Diabetes mellitus ➢ Pancreatic insufficiency with steatorrhoea & Azotorrhea ➢ Malabsorption and formation of pancreatic Pseudocysts ➢ G.I bleeding, jaundice, biliary cirrhosis, bone pain ➢ Pancreatic cancer, ➢ Subcutaneous fat necrosis, impaired glucose tolerance, gastroparesis, narcotic addiction, cobalamin Malabsorption ➢ Non-diabetic retinopathy and effusions with high amylase content (3).

Diagnosis:

- **Imaging Studies**:

1) *Computed Tomography* (CT): Helpful for the diagnosis of moderate to severe chronic pancreatitis and its complications. CT features of chronic pancreatitis include pancreatic ductal dilatation, parenchymal atrophy, calcification and calculi.

2) *Endoscopic Retrograde Cholangiopancreatography* (ERCP): "Gold standard" imaging procedure for diagnosing chronic pancreatitis and planning treatment. Main indications for ERCP in chronic pancreatitis are:

- To assist the diagnosis

- To evaluate the status of the pancreatic and biliary ducts
- To detect anatomical variations such as pancreatic divisum
- To define the relation between a fluid collection and the pancreatic duct Prior to Percutaneous or surgical drainage

3) *Endoscopic Ultrasound* (EUS): Detects changes of mild chronic pancreatitis that may not be detectable from other imaging modalities, but can be confirmed by histology.

4) *Magnetic Resonance Cholangiopancreatography* (MRCP): Non invasive alternative to diagnostic ERCP, with comparable accuracy. Useful in identify pancreatic duct anomalies; e.g. pancreas divisum.

5) *Ultrasound*:

An ultrasound feature of chronic pancreatitis includes:

- Pancreatic calcification
- Pancreatic enlargement or atrophy
- Asymmetric and irregular contours of the pancreas
- Dilatation of pancreatic ducts
- Pancreatic calculi
- Heterogeneous parenchyma texture pattern with increased echogenicity
- Pancreatic cysts, pseudocysts, and abscesses (9)

Treatment:

- **Non-pharmacological therapy:** Abstinence from alcohol is the most important factor in preventing abdominal pain in the early stages of alcoholism. Small and frequent meals and a diet restricted in fat are recommended to minimize postprandial pancreatic secretion and resulting pain.

- **Pharmacological therapy:** Pain management should begin with non-narcotic analgesics such as acetaminophen or NSAIDs. If pain persists the response to exogenous non-enteric-coated pancreatic enzymes should be evaluated in patients with mild to moderate CP. If these measures fail, an oral narcotic should be added to the drug regimen. Parental narcotics should be reserved for patients with severe pain that is unresponsive to oral analgesics (3).

- **Surgical therapy:** Pancreatio-jejunostomy, partial pancreatic resection, preserving the Duodenum, removal of calculi (mechanical or shock wave lithotripsy) (7).

- Surgical procedures described for pain (10):

a. Drainage procedures

➢ Duval procedure

➢ Puestow and Gillispie

➢ Partington and Rochellea

b. Resection procedures

➢ Distal pancreatectomy with or without splenectomy

➢ Subtotal pancreatectomy

➢ Duodenum preserving pancreatectomy

➢ Kausch–Whipple pancreatoduodenectomy

➢ Pylorus preserving pancreatoduodenectomy

c. Drainage and resection procedures

➢ Beger's head excision and drainage

➢ Frey's head coring and drainage

➢ Others: Berne procedure and Izbicki operation

d. Denervation procedures

- Splanchnicectomy
- Coeliac ganglionectomy
- Denervated pancreatic flap surgery

Indications of surgery in CP:-

- Pain
- Mechanical obstruction
- CBD, duodenum, splenic and portal vein, and colon
- Pancreatic complications
- Pseudocysts, pancreatic fistula, pancreatic ascites, pancreatic pleural effusion, and bleeding
- Malignancy

3. FUTURE PERSPECTIVES:

Breakthroughs in genetics:

Over the past few years, breakthroughs in the field of genetic variations have broadened our understanding of the pathogenesis of recurrent acute pancreatitis (AP) and chronic pancreatitis (CP).Several genetic factors of rare gain-of-function and loss-of-function mutations associated with CP indicate an important role for trypsinogen expression, and its activation and degradation within the pancreas (for example mutations in PRSS1, PRSS2, SPINK1, CFTR, CTRC, and CASR). The central role of trypsinogen in the pathogenesis of CP was confirmed in a genome wide association study; a gene locus encoding both PRSS1 and PRSS2 can alter expression of the trypsinogen gene and thereby affect the susceptibility to develop recurrent acute pancreatitis and CP.

- The most frequent cause of Acute Pancreatitis is gallstone complications, which can change the direction of bile flow from the gallbladder so that it enters the pancreas. In this way, bile acids can act directly on the pancreatic cells.

- The recent development of medical imaging technology, chronic pancreatitis can only be diagnosed when the disease is fully established. This is due to the lack of specific and sensitive markers (C-reactive protein (CRP), polymorphonuclear granulocytes-elastase and LDH (lactate dehydrogenase)

- Clinical and experimental studies aim to target the maintenance of the integrity of the intestinal barrier and function, to preserve pancreatic microcirculation, and to balanced and modulate the inflammatory response.

- An individualized concept is mandatory to evaluate the best surgical approach for the individual patient according to the preoperative diagnostics and intraoperative findings.

- In the future, success in diagnosis and treatment of patients with the signs or the potential of chronic pancreatitis will require use of panels of genetic tests, biomarkers, systems analysis and mathematical modelling.

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