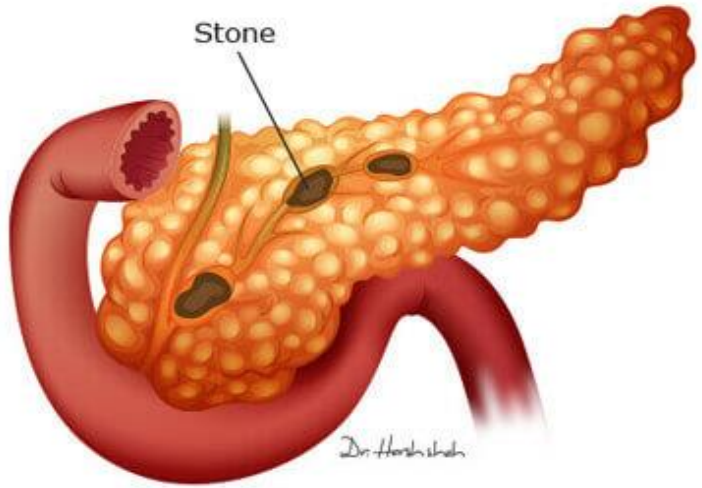
CHRONIC PANCREATITIS



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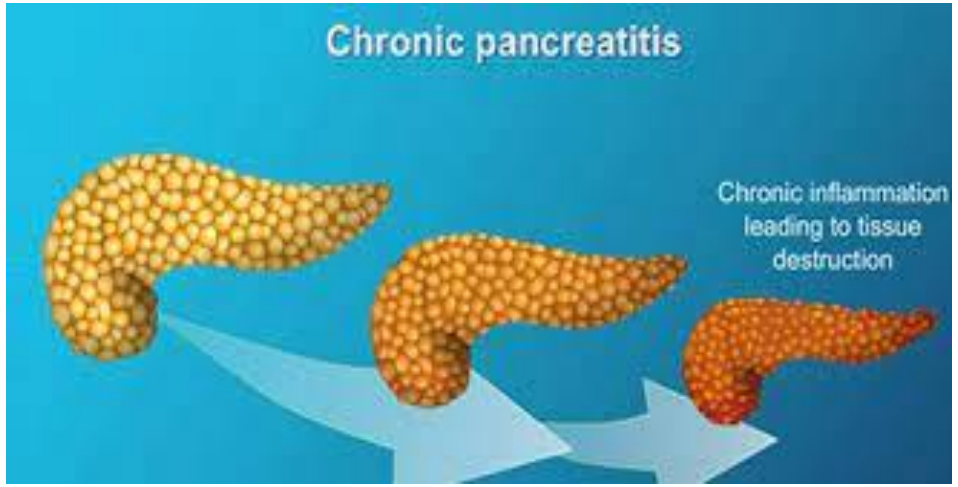
2.7.2022

What is chronic pancreatitis?

- *Chronic pancreatitis defined as a fibro-inflammtory syndrome of the pancreas in individuals with genetic, environmental and / or other risk factors who develop persistent pathological responses to parenchymal injury or stress.*

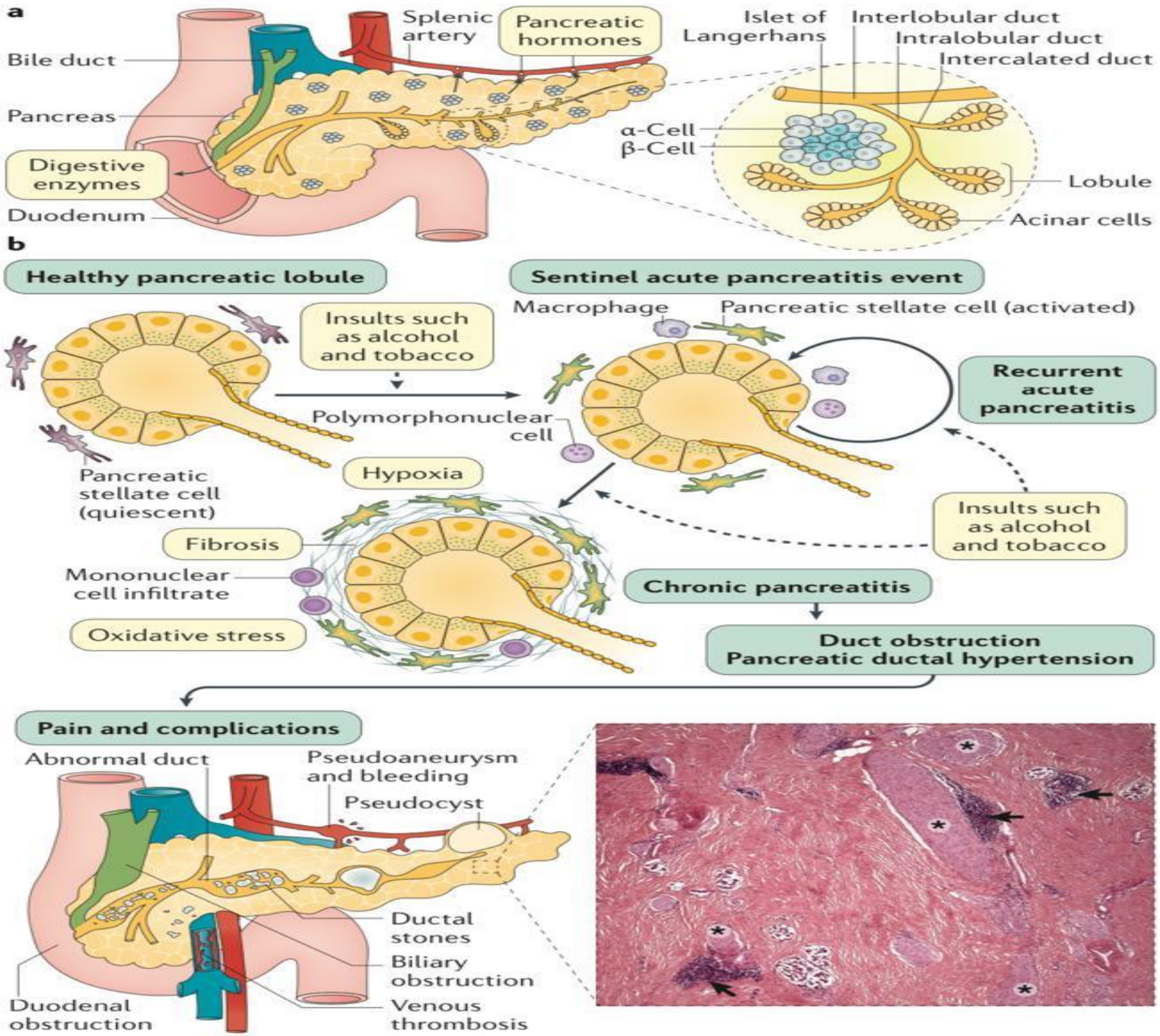


The annual incidence rates reported worldwide are roughly similar in all countries and range from 5 to 14 per 100,000 individuals, with a prevalence of approximately 30–50 per 100,000 individuals

➢The pathophysiology of chronic pancreatitis is fairly complex and includes acinar cell injury, acinar stress responses, duct dysfunction, persistent or altered inflammation, and/or neuro-immune crosstalk, but these mechanisms are not completely understood.

➢Chronic pancreatitis is characterized by ongoing inflammation of the pancreas that results in **progressive loss of the endocrine and exocrine compartment** owing to atrophy and/or replacement with fibrotic tissue.

➢Functional consequences include recurrent or constant abdominal pain, diabetes mellitus (endocrine insufficiency) and maldigestion (exocrine insufficiency).


a
Splenic artery
Pancreatic hormones
Bile duct
Pancreas
Digestive enzymes
Duodenum
Islet of Langerhans
Interlobular duct
Intralobular duct
Intercalated duct
α-Cell
β-Cell
Lobule
Acinar cells
b
Healthy pancreatic lobule
Insults such as alcohol and tobacco
Pancreatic stellate cell (quiescent)
Sentinel acute pancreatitis event
Macrophage
Pancreatic stellate cell (activated)
Polymorphonuclear cell
Recurrent acute pancreatitis
Hypoxia
Fibrosis
Mononuclear cell infiltrate
Oxidative stress
Insults such as alcohol and tobacco
Chronic pancreatitis
Duct obstruction
Pancreatic ductal hypertension
Pain and complications
Abnormal duct
Pseudoaneurysm and bleeding
Pseudocyst
Ductal stones
Biliary obstruction
Duodenal obstruction
Venous thrombosis

- Pancreatic stellate cells are key cells involved in pancreatic injury.

- During pancreatitis, in response to **oxidative stress, cytokines, growth factors and toxins**, pancreatic stellate cells are transformed from a quiescent state to an **activated myofibroblastlike phenotype** in which the cells synthesize and **secrete excessive amounts of extracellular matrix proteins.**

- Numerous studies have demonstrated the key role of pancreatic stellate cells in the development of fibrosis in acute and chronic pancreatitis due to the imbalance between fibrogenesis and matrix degradation.

- *In vitro* studies have confirmed the role of hypoxia in pancreatic stellate cell activation with the increased release of factors, such as **type I collagen, fibronectin and VEGF**

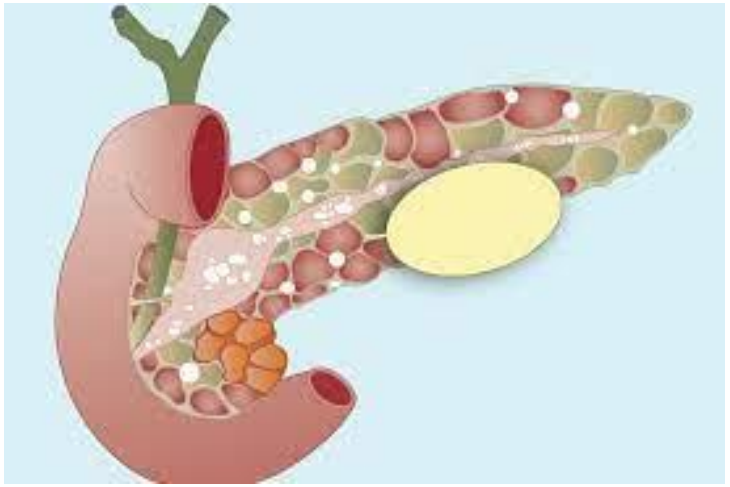
- Pancreatic stellate cells contribute to the fibrotic and hypoxic milieu by amplifying abnormal extracellular matrixdeposition

Box 1 | **Aetiologies of chronic pancreatitis according to the TIGAR-O system***

- Toxic-metabolic: chronic pancreatitis caused by alcohol abuse, tobacco smoking, hypercalcaemia, hyperlipidaemia, chronic kidney failure, medications or toxins.
- Idiopathic: chronic pancreatitis that is not associated with any known gene mutations, such as early-onset chronic pancreatitis, late-onset chronic pancreatitis and tropical chronic pancreatitis (an early-onset form of non-classic chronic pancreatitis that is almost exclusively observed in tropical countries in the developing world and that is characterized by an aggressive course).
- Gene mutations: chronic pancreatitis caused by Mendelian diseases involving the pancreas, complex genetics or modifying genes (for example, *PRSS1*, *CFTR* and *SPINK1*).
- Autoimmune: steroid-responsive chronic pancreatitis, which can be isolated or syndromic.
- Recurrent and severe acute pancreatitis: chronic pancreatitis that is associated with necrosis (severe necrotizing acute pancreatitis), vascular disease (including ischaemia) and post-irradiation damage.
- Obstructive: chronic pancreatitis that is associated with pancreas divisum (a congenital abnormality of the pancreas), sphincter of Oddi disorders, duct obstruction (for example, from a tumour) and post-traumatic pancreatic duct scars.

*See REF. 216.

DIAGNOSIS AND INVESTIGATIONS



- Classic chronic pancreatitis can be further subdivided into **typical chronic pancreatitis**, which is dominated by fibrosis, and **atypical chronic pancreatitis**, which is dominated by atrophy.

- Abdominal pain is the Cardinal symptom

- Earlier, diagnosis was based on the **triad of steatorrhoea, diabetes mellitus and pancreatic calcifications** visible on abdominal radiography.

- However, diagnosis based on these criteria could only be made in endstage disease, after the pancreas was essentially destroyed.

Box 3 | **Diagnostic criteria for chronic pancreatitis**

The diagnosis of chronic pancreatitis involves several criteria[3,125,128].

- Recurrent bouts of pain with or without ≥3-fold the normal upper limit of amylase or lipase levels and one or more of the following criteria:
- Radiological evidence comprising strictures and dilatation in side branches and/or the main pancreatic duct and/or intraductal and/or parenchymal pancreatic calcifications by contrast-enhanced CT and magnetic resonance cholangiopancreatography.
- Histological proof of chronic pancreatitis from biopsy samples undertaken by endoscopic ultrasonography or from a surgically resected specimen.

Suspicion of Chronic Pancreatitis

	Clinical Features	← PLUS →	Risk (TIGAR-O)	← PLUS →	Biomarkers	
a	Pancreatitis-like pain Maldigestion Weight loss Glucose intolerance Older age		Alcohol / Smoking Hypertriglyceridemia Other metabolic / drugs AP / RAP Obstruction benign anatomic change Tumor		**Imaging** CT scan EUS (+/- FNA)	**Serum markers** High amylase/lipase High triglycerides High IgG4 High glucose Low vitamins (ADK B12) Tumor markers
b	Family history Early age of onset CF organ involvement Syndromic features		Genetic Testing (Genetic counseling: risk-based) Other toxic / metabolic risks		sMRCP	Sweat Chloride Exocrine function test
c	IBD or evidence of IgG4 disease Clinical response to Rx? Pain management with antioxidants Improved digestion with PERT Steroid trial for AIP Type 2		Known causes ruled out / unlikely Expand differential diagnosis Initiate low-risk therapy (lifestyle, antioxidants) Consider referral			Histology

Box 2 | **Causes of pain in chronic pancreatitis**

Primary (genuine) pancreatic pain

- Duct obstruction and tissue hypertension
- Active inflammation
- Tissue ischaemia
- Altered nociception, owing to cholecystokinin-related changes in pain threshold, local nerve damage (neuropathic pain), peripheral and central sensitization of the nervous system and increased sympathetic drive

Secondary pain

- Local complications, including pseudocysts, an inflammatory mass in the pancreas, small bowel strictures and adenocarcinoma
- Remote complications, including obstruction of the bile duct and duodenum, peptic ulcer due to changes in blood flow, bacterial overgrowth due to changes in motility, mesenteric ischaemia after acute pancreatitis, small bowel strictures after acute pancreatitis and diabetes mellitus type 3c-related visceral neuropathy

Treatment-related pain

- Surgical and/or endoscopical complications
- Adverse effect to medication (opioid-induced bowel dysfunction and opioid-induced hyperalgesia)

SCORING

- Several scoring systems exist to evaluate the severity of chronic pancreatitis.

- The **Cambridge classification** for severity grading using ERCP, and its adaptation for other types of imaging is still used for diagnosing and scoring chronic pancreatitis in adults.

- The **ABC system** uses a classification that consists of three stages combining clinical criteria (pain, recurrent attacks of pancreatitis, local complications, steatorrhoea and diabetes mellitus) with imaging (ductal or parenchymal changes).

- The **Rosemont classification** can diagnose chronic pancreatitis using only endoscopic ultrasonography criteria. The number of parameters correlates with the severity of the disease as confirmed by histopathology.

- The **MANNHEIM classification** attempts to characterize patients according to aetiology, clinical stage and severity. The severity of the inflammatory reaction is evaluated using clinical symptoms and therapeutic interventions (for example, whether it is responsive to steroids).

- Rather complex classification criteria involve a points system describing the severity of chronic pancreatitis. The **Chronic Pancreatitis Prognosis Score (COPPS)** predicts individual shortterm (12month) prognosis using **C-reactive protein levels, thrombocyte count, glycosylated haemoglobin levels, BMI and pain levels.**

Cambridge classification

Class	Definition
0 – Normal	Visualization of entire duct system with uniform filling of side branches without acinar opacification, with a normal main duct and normal side branches
1 – Equivocal	Normal main duct
	1–3 abnormal side branches
2 – Mild	Normal main duct
	>3 abnormal side branches
3 – Moderate	Dilated main duct with irregularity
	>3 abnormal side branches
	Small cysts (<10 mm)
4 – Marked or severe	Large cysts (>10 mm)
	Gross irregularity of main pancreatic duct
	Intraductal calculus or calculi
	Stricture(s)
	Obstruction with severe dilation

Data from reference 12

LABORATORY INVESTIGATIONS : ROUTINE

Complete haemogram

Liver function tests

Amylase and Lipase

Electrolytes

FBS, PPBS, HbA1c

SPECIFIC –

AUTOIMMUNE - IgG4, rheumatoid factor, ANA and anti-smooth muscle antibody may be detected

Lipid Profile

GENETIC PROFILE - autosomal dominant disease,
chronic pancreatitis disease is identified in cationic trypsinogen gene PRSS1, and mutation, R122H. R122H is the most common mutation for hereditary chronic pancreatitis with replacement of arginine with histidine at amino acid position 122 of the trypsinogen protein.

NON INVASIVE PANCREATIC FUNCTION TESTS

Table 1 | **Sensitivity and specificity of the available non-invasive pancreatic function tests***

Test	Marker	Mild exocrine deficiency	Moderate exocrine deficiency	Severe exocrine deficiency	
		Sensitivity (%)	Sensitivity (%)	Sensitivity (%)	Specificity (%)
Pancreatic elastase tests (faeces)	Marker for pancreatic enzyme secretion	54	75	95	85
Qualitative faecal fat test	Marker for steatorrhoea	0	0	78	70
Chymotrypsin activity in faeces	Marker for pancreatic enzyme secretion	<50	60	80–90	80–90
^{13}C (mixed triglyceride) breath test	Marker for impaired fat digestion	ND	ND	90–100	80–90

ND, not determined. *Sensitivity and specificity compared with invasive pancreatic function tests (secretin and secretin–pancreozymin-stimulated tube tests were used as reference methods)[108].

IMAGING

➢CT provides excellent information about morphological changes of the pancreas, such as PD dilatation or strictures, atrophy, calcification and pseudo cystic changes .

➢The main drawbacks of CT are the limited visualization of the pancreatic ductal system and lack of sensitivity and specificity for mild forms of chronic pancreatitis, although the **sensitivity for the detection of calcifications is better than that of MRI.**

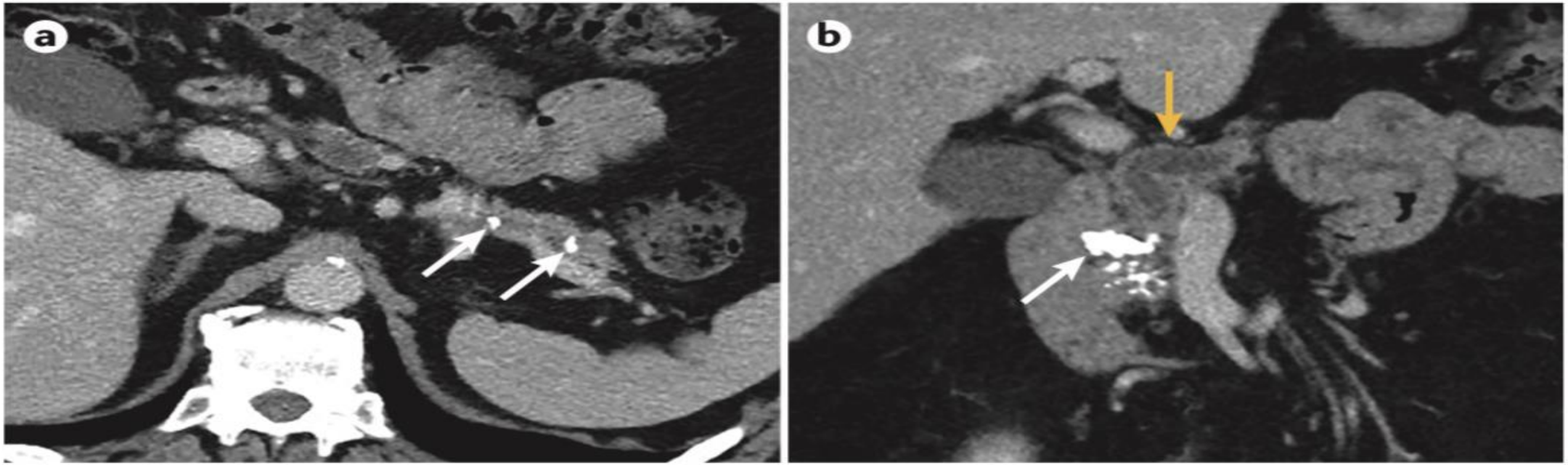


Figure 5 | **CT imaging in chronic pancreatitis.** Post-contrast CT image of severe chronic pancreatitis shows ductal stones (white arrows in part **a** and part **b**) within the dilated pancreatic duct (orange arrow; part **b**).

➢MRCP has a **high sensitivity for detecting strictures and dilatation in (the side branches of) the PD**. Images obtained by MRCP are essentially identical to those obtained by ERCP , which was once used for diagnosis .

➢Dynamic MRCP , in which images are acquired every 30 or 60 seconds over a 10minute period following iv secretin hormone injection, provides excellent spatial resolution and functional information on **exocrine pancreatic insufficiency**.

➢MRCP or dynamic MRCP can be considered as the 1ST choice for classification and staging in chronic pancreatitis.

➢**The major limitation of MRCP is in the identification of parenchymal calcifications and small ductal calculi, where CT is especially sensitive.**

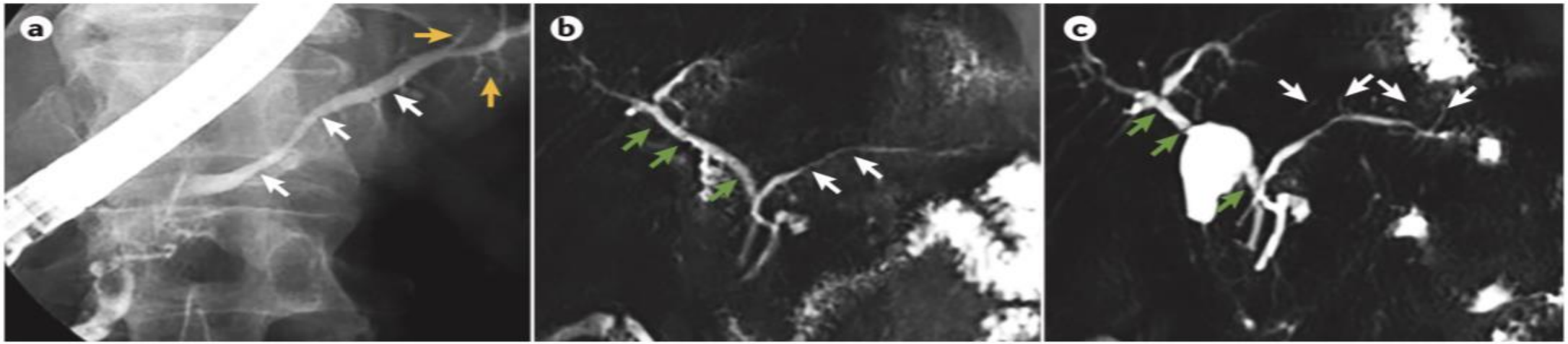


Figure 6 | **ERCP and MRCP imaging in chronic pancreatitis. a** | Endoscopic retrograde cholangiopancreatography (ERCP) showing moderate chronic pancreatitis as evidenced by a slightly dilated duct (white arrows) and visible side branches (orange arrows). **b**,**c** | Magnetic resonance cholangiopancreatography (MRCP) imaging shows abnormal pancreatic duct (white arrows; part **b**) and enables the visualization of multiple abnormal side branches after secretin injection (white arrows; part **c**). Note the bile duct in part **b** and part **c** (green arrows).

Although EUS has an important role in obtaining diagnostic biopsies and therapeutic interventions, the relatively poor inter-observer agreement for EUS limits its diagnostic accuracy for chronic pancreatitis

MANAGEMENT OF CHRONIC PANCREATITIS

- The aim of management is to alleviate symptoms (most commonly pain, followed by exocrine and endocrine insufficiency) and to prevent further disease progression and disease related complications, such as bile duct obstruction, gastric outlet obstruction and portal vein thrombosis.

- Pain is most often genuine, but there are **several secondary** causes that should always be considered, as they are easier to treat than genuine pancreatic.

- Pathology such as pancreatic duct stones and strictures are typically treated invasively, including by endoscopic stone removal and stenting, ESWL and surgical resections, and drainage procedures.

- Endoscopic treatment can be combined with ESWL in the presence of large (>4 mm in size) obstructive stones

Box 4 | **Different treatment modalities for pain in chronic pancreatitis**

Before treatment is initiated, all secondary causes of pain should be considered and treated appropriately. Not all treatments have been evaluated in chronic pancreatitis, and evidence often comes from randomized trials in other chronic pain conditions.

Risk factor modification

- Alcohol abstinence
- Tobacco smoking cessation
- Dietary therapy (to improve the condition in general, including pain)

Initiatives to minimize pressure in the duct system and parenchyma

- Pancreatic rest by tube feeding into the jejunum or nutritional products that do not activate cholecystokinin
- Uncoated pancreatic enzymes that may degrade cholecystokinin-releasing factor
- Cholecystokinin inhibitors
- Proton pump inhibitors (to increase the efficacy of enzyme treatment)

Analgesics

- Simple analgesics such as paracetamol and NSAIDs (combined with proton pump inhibitors)
- Adjuvant analgesics; for example, gabapentinoids
- Weak or strong opioids plus laxatives

Invasive procedures

- Endoscopy
- Extracorporeal shock wave lithotripsy
- Surgery
- Celiac ganglion neurolysis (temporal neuronal block performed under CT) and splanchnicectomy (surgical excision of part of the greater splanchnic nerve) aimed at pain suppression
- Spinal cord stimulation aimed at pain suppression
- Intrathecal opioids aimed at pain suppression

Treatment of anxiety and depression

- Tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin–noradrenaline reuptake inhibitors; these drugs also have a direct effect on the pain system
- Cognitive–behavioural therapy, including sleep therapy
- Anxiolytics

Neuromodulation aimed at improving pain

- Acupuncture
- Transcutaneous electrical nerve stimulation
- Transcranial magnetic stimulation
- Direct current stimulation
- Physiotherapy

Experimental therapies aimed at improving pain and health status in general

- Ketamine, antipsychotics and clonidine
- Radiotherapy of the pancreas
- Nerve growth factor inhibitors
- Cannabinoids

For details and further information, the reader is referred to www.pancreapedia.org.

Exocrine Substitution

Maldigestionrelated symptoms (diarrhoea, steatorrhea, weight loss, flatulence and abdominal distention) and nutritional deficiencies are the **main consequences of exocrine pancreatic insufficiency**, which can be avoided by appropriate pancreatic enzyme replacement therapy.

Pancreatic enzymes (usually a combination of lipase, amylase and protease) should be administered orally together with each meal or snack.

Entericcoated enzyme preparations in form of **microspheres or minimicrospheres** improve digestion and absorption of nutrients, relieve symptoms and improve the nutritional status of patients.

Enzyme dose should be adjusted based on the volume, fat and calorific content of meals. As a guide, a starting dose of **40,000–50,000 U** with main meals, and half of the dose with snacks is generally recommended. Enzyme dose should be further individualized based on symptom response and objective evaluation of nutritional status.

MANAGEMENT OF DIABETES MELLITUS

- Diabetes therapy in chronic pancreatitis should be individually tailored, not only to control for hyperglycemia but also to reduce the risk of hypoglycemia.

- An adequate and balanced food intake together with oral pancreatic enzymes and alcohol abstinence are required for appropriate glycemic control.

- Pain treatment should also be optimized, as postprandial pain compromises food intake and hence glycemic control.

- Insulin substitution is usually required for diabetes mellitus type 3c, and longacting basal insulin analogues together with ondemand short term insulin is recommended.

- Controlling mild hyperglycemia with oral hypoglycemic agents, such as metformin, may be a valid approach

ENDOSCOPY

- 30%-60% of patients with chronic pancreatitis will ultimately require some type of endoscopic or surgical intervention for treatment. The indication for endoscopic therapy is most often intractable pain,and treatment should be considered before patients become opiate dependent.

- The most common indications for endoscopic treatment are strictures of the pancreatic duct, obstruction of the common bile duct and pancreatic pseudocysts. Several endoscopic procedures are available, which differ in their potential benefits and prognosis.

- When increased pressure in the pancreatic duct owing to a dilated duct with strictures is assumed to be the cause of either pain or recurrent disease episodes, endoscopic sphincterotomy is performed first - in which the muscular valve that controls the flow of bile and pancreatic juice is cut, and is usually followed by insertion of one or more plastic stents into the pancreatic duct. Whether the removal of intraductal stones or their disintegration by prior ESWL is of additional benefit is still being discussed and is not necessarily supported by highquality clinical evidence.

- Observational studies suggest that approximately 2/3rd of patients experience some pain reduction after endoscopic therapy involving sphincterotomy and/or stent placement

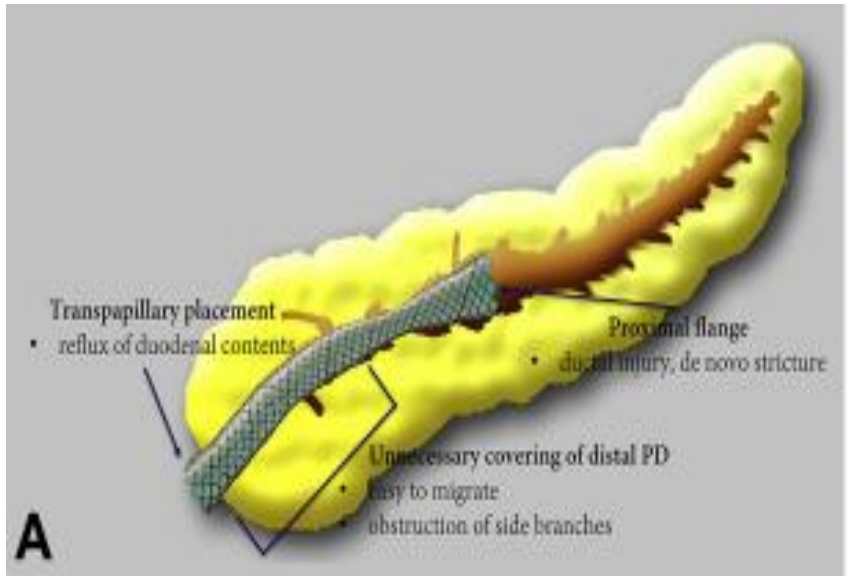
- In obstruction of the CBD, one or more plastic stents can be inserted into the bile duct after biliary sphincterotomy to restore patency.

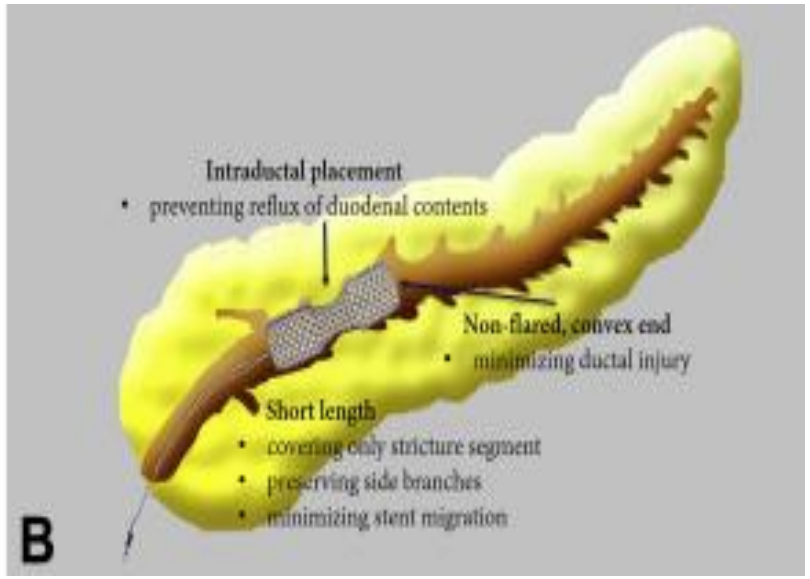
- Recently, fully covered (membranecovered metal or polymer) selfexpanding stents (FCSEMS) have become popular.

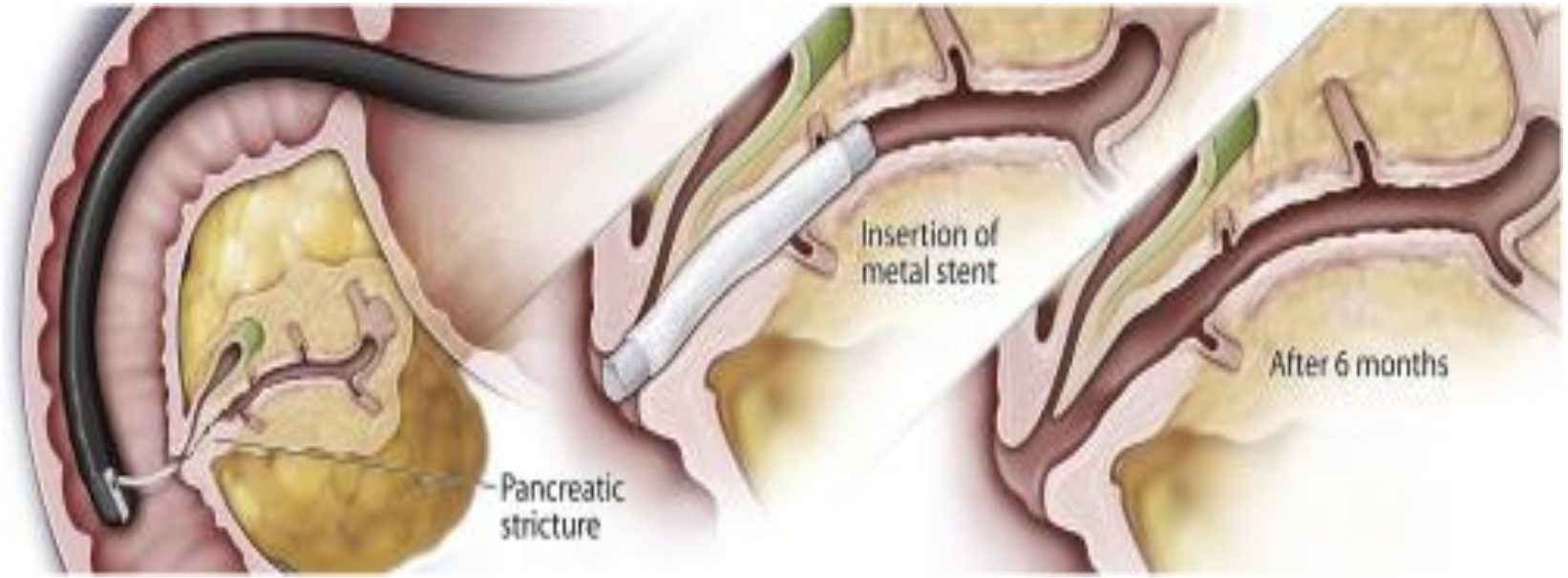
- Like stents in PD, stents in the bile duct need to be regularly exchanged to prevent occlusion and cholangitis

- A suggested exchange interval for plastic stents is 3 months, whereas FCSEMS remain open for 6 months or longer.

- FCSEMS seem to improve outcome in case series, nonrandomized and randomized trials, with a stricture resolution rate of 76–93% and a recurrence rate of strictures of only

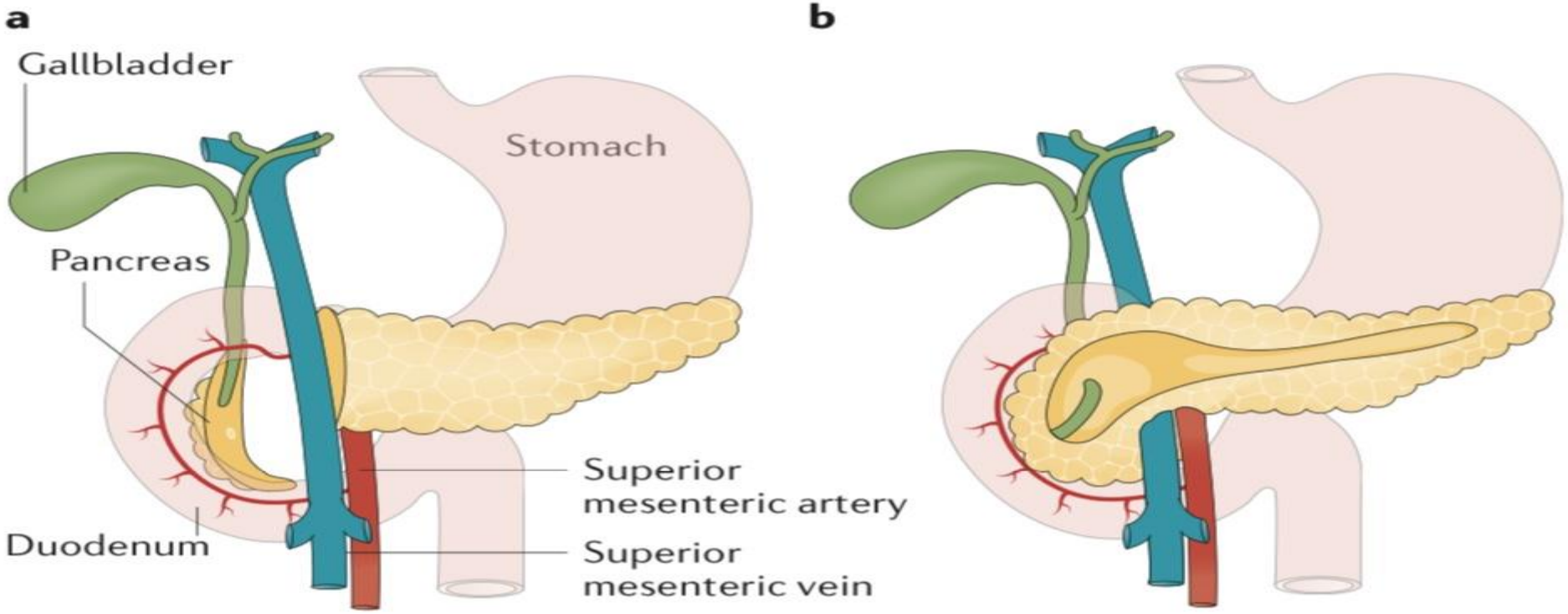

Transpapillary placement
• reflux of duodenal contents
Proximal flange
• ductal injury, de novo stricture
Unnecessary covering of distal PD
• easy to migrate
• obstruction of side branches
A


Intraductal placement
• preventing reflux of duodenal contents
Non-flared, convex end
• minimizing ductal injury
Short length
• covering only stricture segment
• preserving side branches
• minimizing stent migration
B


Insertion of metal stent
Pancreatic stricture
After 6 months

Surgery

The aim of surgical intervention is to alleviate severe, constant or recurrent abdominal pain and to cure or prevent additional organ complications, including biliary compression that results in jaundice, duodenal compression that causes gastric outlet obstruction, or vascular obstruction that potentially leads to portal hypertension or portal vein thrombosis with subsequent varicose collaterals.



CONCLUSION

- Chronic pancreatitis is commonly defined as a continuing, chronic, inflammatory process of the pancreas, characterized by irreversible morphologic changes.
- Abdominal pain is the presenting symptom
- Causes exocrine and endocrine insufficiency
- Laboratory investigations – Routine and special and Imaging CT and MRCP / Dynamic MRCP
- Pain management followed by management of exocrine and endocrine complications - mainstay of medical management. Endoscopic management and Surgical management to be undertaken depending on the persistance of symptoms and complications.

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ANY
QUESTIONS?