Chronic Pancreatitis

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ABSTRACT

Chronic pancreatitis is a progressive inflammation in pancreas results in fibrosis and irreversible damage lead to loss of exocrine and endocrine function. Mortality and complication rate is high. Appropriate management of chronic pancreatitis begin from accurate diagnosis to adequate treatment. Diagnosis is still a challenge for clinician, mostly in early-stage disease. Several diagnostic modalities such computed tomography scan, magnetic resonance cholangiopancreaticography, endoscopic ultrasound, endoscopic retrograde cholangiopancreaticography, and direct-indirect pancreatic function test help diagnosis establishment. Endoscopic approach has an important role, both during diagnosis and treatment.

Keywords: *chronic pancreatitis, endoscopic ultrasound, endoscopic retrograde cholangiopancreatography, direct pancreatic function testing, indirect pancreatic function testing*

ABSTRAK

Pankreatitis kronis merupakan peradangan kronis pada pankreas, bersifat progresif, disertai adanya jaringan parut, yang merusak pankreas secara ireversibel, dan mengakibatkan hilangnya fungsi eksokrin dan endokrin dari pankreas. Kasus ini memberikan konsekuensi mortalitas dan komplikasi yang cukup besar. Pengelolaan pankreatitis kronik yang tepat bermula dengan penegakkan diagnosis secara akurat. Ini menjadi tantangan tersendiri terutama pada pasien yang masih dalam stadium awal, dimana tidak selalu memberikan bukti definitif pankreatitis kronik. Berbagai modalitas diagnostik seperti computed tomography scan (CT Scan), Magnetic resonance cholangipancreoticography (MRCP), hingga penunjang perendoskopik baik itu endoscopic ultasound (EUS) dan endoscopic retrograde cholangiopancreatography (ERCP), dan uji fungsi pankreas langsung dan tak langsung, dapat membantu penegakkan diagnosis pankreatitis kronik. Penunjang perendoskopik (EUS maupun ERCP) tidak hanya memberikan pencitraan tapi juga sebagai modalitas terapi.

Kata kunci**:** *pankreatitis kronis, endoscopic ultrasound, endoscopic retrograde cholangiopancreatography, direct pancreatic function testing, indirect pancreatic function testing*

INTRODUCTION

Chronic pancreatitis is defined as progressive chronic inflammation of pancreas tissue that lead to fibrosis. It irreversibly damaged pancreatic tissue, so both exocrine and endocrine function could loss over the time.[1]

A population-based study across countries reported global incidence of 4.4 – 11.9 per 100,000 population annually. Male was having higher incidence 1.5-3 times than female.[2-9] It prevalence was relatively low, account to 36.9-41.8 cases in 100,000 population.[4,5] Study by Siecean et al reported mortality among chronic pancreatitis patients is 17% during first 59 month after diagnosis. Cause of mortality were malignancy (3.6%), surgical complication (3.6%), and upper gastrointestinal tract bleeding (2.4%).[10]

Management of chronic pancreatitis is still challenging. Yet, none treatment was said to be effective to slow its progression nor improve clinical condition. Several new evidence have been revealed in chronic pancreatitis management. A good management was started by accurate diagnosis, followed by adequate treatment since patients have various signs and symptoms.[11]

DEFINITION

Chronic pancreatitis described as fibroinflammatory disease that damage pancreatic tissue and lead to exocrine and endocrine function loss.[12]

ETIOLOGY AND CLASSIFICATION

Chronic pancreatitis is a disease entity, classified into three main form: (1) chronic calcific pancreatitis; (2) chronic obstructive pancreatitis; (3) chronic autoimmune pancreatitis (steroid-responsive pancreatitis). Clinical presentations were vary based on its etiology, but the main symptom is abdominal pain.[12]

Table 1. Chronic pancreatitis classification [12]

Chronic calcific pancreatitis	Chronic obstructive pancreatitis	Chronic autoimmune pancreatitis
Alcohol Smoking Genetic Idiopathic: Juvenille onset, Tropical Senile onset	Stricture: Blunt trauma Post endoscopic stenting Acute pancreatitis Anastomosis stricture Tumor: Adenocarsinoma, intraductal papillary mucinous neoplasm (IPMN), serous cystadenoma, Islet cell tumor	Autoimunne Type 1 Type 2

Chronic Calcific Pancreatitis

Chronic calcific pancreatitis development begins with acute pancreatitis. As disease progress, intraductal stone (in main or branch pancreatic duct), duct distortion, stricture, and pancreatic tissue atrophy appeared. Extensive parenchym destruction would lead to steatorrhea and diabetes. Others chronic pancreatitis type were rarely forming a clacification.[12]

Chronic Obstructive Pancreatitis

Chronic obstructive pancreatitis was defined as chronic pancreatitis results from primary disease in pancreatic duct or obstruction (both complete or partial) of pancreatic duct. Obstruction mostly caused by stricture, as a complication from endoscopic procedure, surgery, acute necrotizing pancreatitis, abdominal blunt trauma, narrowing of pancreatico-enteric anastomosis, and obstructing tumor (ductal adenocarcinoma or intraductal papillar mucinous tumor). Later, this could lead to chronic calcific pancreatitis. In obstructive pancreatitis, only proximal area that affected while distal pancreatis function is reserve. Partial obstruction of pancreatic duct increase the risk of recurrent acute pancreatitis. Most of chronic obstructive pancreatitis is asymptomatic.[12]

Chronic Autoimmune Pancreatitis

Chronic autoimmune pancreatitis is a unique type of pancreatitis which the inflammation is responsive to steroid therapy. Chronic autoimmune pancreatitis was classified into type 1 and 2, which contrastly different. The word 'autoimmune' was more relevant for type 1 disease, so that several expert labelled type 2 chronic autoimmune pancreatitis as ductal idiopathic chronic pancreatitis.[13] Type 1 autoimmune pancreatitis is mainly manifest as multiorgan fibroinflammatory syndrome, highly correlate to immunoglobulin G4 (IgG4), characterized by increase serum IgG4 concentration, multiorgan involvement, typical histologic findings, and responsive to corticosteroid and B cell depletion therapy. IgG4 related disease affect several organs, including pancreas, biliary duct, salivary duct, kidney, and lymph nodes.[14] Histologically, this disease marked as lymphoplasmacytic infiltration around duct, storiform fibrosis, heavy inflammation on vein that could spread to adjacent rteries, and abundance of IgG4 positive plasma cell (>10/high power field).[12] Common form of type 1 autoimmune chronic pancreatitis is an obstructive jaundice. Pain is not dominant and relieved after steroid administration. Unfortunately,

relaps rate was high in this condition.[15] On the other hand, ductal idiopathic chronic pancreatitis (type 2 autoimmune pancreatitis) was substantially differ to type 1 autoimmune pancreatitis. Histologically, duct obliteration in type 2 autoimmune pancreatitis was resulted from neutrophil infiltration in duct epithelial layer.

Table 2. Characteristic of chronic autoimmune pancreatitis[12]

	Type 1	Type 2
Median age	7th decade	3rd decade
Gender	Male predominant	Equal
Other organ involvment	Frequent (60%)	None
Inflammatory bowel disease	< 10%	30%
Increase serum IgG4	> 80%	< 10%
Histologic findings:		
Granulocyte epithelial lesion	Not present	Present
IgG4 (+) staining	Prominent	Rarely
Response to steroid therapy	Universal	Universal
Relapse after steroid therapy	30-60%	< 10%

Risk Factors

Alcohol

Traditionally, alcohol was known as main risk factor of chronic pancreatitis. Epidemiologic study in US reported that almost 50% of chronic pancreatitis was caused by alcoholism.[17] Alcoholism was risk factor for chronic pancreatitis, both alone (34%) or as a combination to ductal obstruction (9%) and higher proportion in male (59% vs. 28%).[18] Recently, a locus gen CLDN2 was identified and related to alcoholism as risk factor of pancreatitis.[19] Homozygosity frequency were higher in male (0.26 vs. 0.07) thus strengthen the evidence and role of gender to alcoholism and chronic pancreatitis.

The risk of chronic pancreatitis was correlate to alcohol intake dose. Recent case control and meta analysis showed that 2-3 times higher risk to develop pancreatitis if consuming 4-5 portion of alcohol everyday.[20,21] No exact threshold of alcohol consumption that increase the risk of chronic pancreatitis. Alcohol increase acinar cell damage by interfering its defence mechanism against tissue oxidative stress.[23]

Cigarette Smoking

Cigarrete smoking is an independent risk factor of chronic pancreatitis. In a meta analysis, estimate risk of chronic pancreatitis among smoker was 2.5 (95% CI: 1.3-4.6) compared to non-smoker (after alcohol consumption adjustment).[20. 24] Relationship between cigarette smoking and chronic pancreatitis was dose-dependent, estimate about 3.3 (95% CI: 1.4-7.9) in smoker more than 1 pack everyday, compared to 2.4 (95% CI: 0.9-9.6) in non-heavy smokers. People who have been smoking in the past also had higher risk to develop chronic pancreatitis (HR = 1.59; 95% CI: 1.1.9 -2.12).[24] In vitro study showed that nicotine and its metabolite induce oxidative stress in pancreatic acinar cell.[25,26]

Genetic

In the last two decades, several studies have identified specific gen that increase the predisposition to develop chronic pancreatitis, by premature trypsinogen activation ot by failure to inactivate trypsin during inflammation process. Previous research identified mutation in cationic trypsin gene (PRSS1) that prematurely activate trypsinogen, lead to hereditary pancreatitis.[27] This was autosomal dominant trait with high penetration rate, as affected individual showed clinical symptoms. Inhibitor of serum protease, SPINK1, expressed by acinar cell during inflammatory response also encode trypsin inhibitor. Although SPINK1 mutation was not an independent risk factor, it could modify disease and involve in transformation from acute to chronic pancreatitis.[28] This mutation was highly related to trophic calficic pancreatitis.[29] Mutation in CFTR (cause of cystic fibrosis) was also found in chronic idiopathic pancreatitis.[30,31] CTRC, CASR, and CLDN1 gene in X chromocome were also highly correlate to chronic pancreatitis.[12,32-34] Hereditary pancreatitis secondary to PRSS1 mutation increase the risk of adenocarcinoma development in pancreatis tissue.[35]

Ductal Obstruction

Ductal obstruction caused by inflamed stricture, benign tumor, or malignancy could lead to chronic obstructive pancreatitis. Patient with CFTR mutation have higher risk of divisum pancreas.[36,37] Patophysiology of those phenomena is still unknown.

Idiopathic

In most cases, the etiology of chronic pancreatitis is unknown. Before classified as idiopathic, all examination panel should be done. Tropical pancreatitis, known as fibrocalculous diabetic pancreatitis, is an early form of idiopathic pancreatitis in tropical region. South India has the highest prevalence of this chronic pancreatitis, marked as early onset of pain, calcification in main pancreatic duct, and rapid-onset ketosis that

resistant to diabetes treatment. Even genetic (SPINK1), nutrition, and inflammatory factors have implication in this condition, the basic pathogenesis is still questionable.[38]

PATHOGENESIS

Underlying mechanism of chronic pancreatitis begin with pancreatic stellate cell (PCS) activity. Triggering factor (alcohol and toxic metabolic strees) initiate the spontaneous acute pancreatitis episode (SAPE). This inflammation could be suppressed if triggering factor present only in a short time. On the other hand, repeat exposure to triggering factor would lead to persisten recurrent acute pancreatitis (RAP), and lately activate PCS. TNF-related apoptosis-inducin ligand = proinflammatory cytokine (TRAIL) and other chemokine from inflammatory process and PCS activation would induce parenchymal damage, later develop to fibrosis, that finally manifest as ductal obstruction, dilatation, or increase in pressure. This long-term remodeling of duct could activate signaling pathway (e.g Notch and Hedgehog) that lead to cellular transformation, resulting in acinoductal metaplasia (ADM), pancreatic intraepithelial neoplasia (PanIN), and pancreatic ductal adenocarcinoma.[39] Under influence of IFN-gamma released by lymphocyte CD4+ and CD8+, this acinar cell would express CD95, TRAIL R1, and TRAIL R2 which related to intracellular death. Therefore, pancreatic acinar cell was considered as susceptible to apoptosis by T cell that express CD95L and TRAIL, locally produced by PSC. Acinar cell death in chronic pancreatitis also related to perforin granzim B. Otherwise, pancreatic island maintains CD95L (+) status and negative status (death receptor) and neoexpression of TRAIL R4. NF-kB is expressed in islet cell that activate inhibitor apoptosis proteins (IAPs) to protect islet cell. At the end of obstruction process, dilatation and increase of intraductal pressure in chronic pancreatitis would activate Notch and Hedgehog signaling pathway that further increase the risk of ADM and PanIN development.[39]

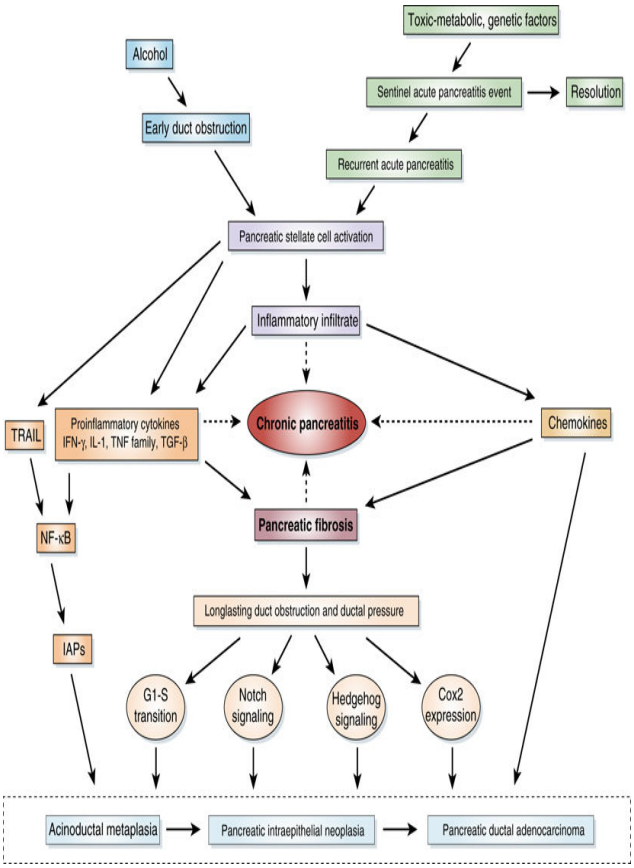

Figure 1. Pathogenesis of chronic pancreatitis[39]

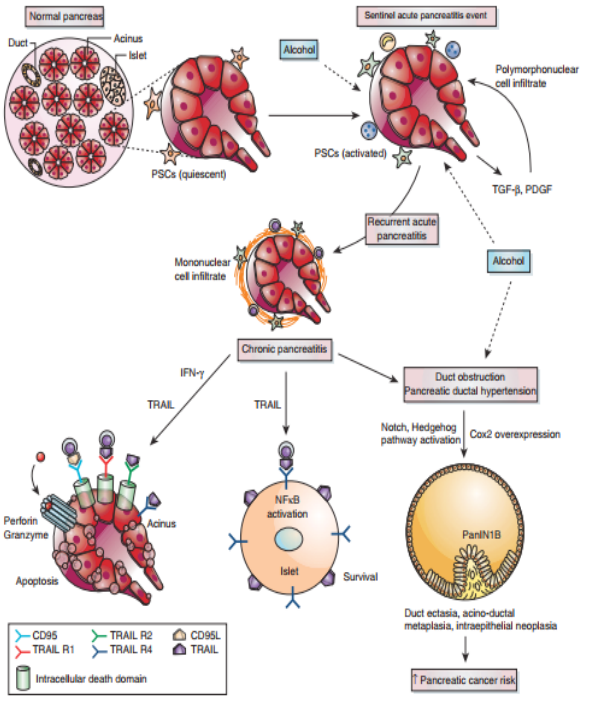

Figure 2. Concept of novel integration in cellular, genetic, and molecular mechanism in chronic pancreatitis[39]

CLINICAL MANIFESTATION

Chronic pancreatitis main characteristic is progressive damage of pancreatic tissue. After subclinical phase that have various duration, recurrent acute abdominal pain is often and followed by insufficiency of both endocrine and exocrine secretion function.[40] Predominant complaint are abdominal pain, maldigestion, or unintended weight loss. Abdominal pain varies according to location, severity, or frequency, could be constant or intermittent. Food intake would propagate abdominal pain, so that most patient refuse

to eat, leading to weight loss. Maldigestion shown as chronic diarrhea, steatorrhea, weight loss, and fatigue. Patient with chronic abdominal pain was not always progress to maldigestion, and about 20% patient with maldigestion do not complain abdominal pain. Steatorrhea do not correlate to deficiency of lipid-soluble vitamin. Patient with chronic pancreatitis have

Table 3. Clinical manifestation, complication, and comorbidities among chronic pancreatitis patient[42]

Findings	n (%)
Weight loss	45 (43.3)
Steatorrhea	14 (13.5)
Pancreatitic *Diabetes melitus*	31 (29.8)
Calcification	11 (10.6)
Pancreatitic pseudocyst	28 (26.9)
Dyspepsia	45 (43.3)
Jaundice	10 (9.6)
Splenomegaly	10 (9.6)
Pancreatitic Ascites	10 (9.6)
Esophagogastric varices	1 (1.0)
Portal vein thrombosis	1 (1.0)
Variceal colon	1 (1.0)
Duodenal stenosis	1 (1.0)
Erotion or ulcer in gastroduodenal mucosa	8 (7.7)
Anemia	30 (28.8)
Hypoproteinemia	22 (21.2)
Alcoholic cirrhosis	1 (1.0)
Tuberculosis	1 (1.0)
Pancreatititc carcinoma	3 (2.9)
Other malignancy	
Gastric carcinoma	2 (1.9)
Cholangioma	1 (1.0)
Carcinoma of ampulla	2 (1.9)
Sjogren syndrome	1 (1.0)
Hypothyroidsm	1 (1.0)
Diabetes Mellitus type 1	2 (1.9)

high social impairment.[41]

CONFIRMATORY WORKUP

Transabdominal ultrasonography (USG) and computed tomography scan (CT Scan) play an important role in diagnosis confirmation. Diagnosis using USG and CT Scan rely on morphological changes which is less seen in early-stage of chronic pancreatitis. Diagnosis establishment even getting harder since histological confirmation is unusual in clinical practice. The main findings are glandular atrophy, chronic inflammation, and fibrosis in pancreatis tissue. Others are main and branches pancreatic duct dilatation and intraductal calcification.[1]

Abdominal USG

Abdominal USG has been used in recent year to evaluate pancreas, yet no new study to investigate the role of high-end USG in chronic pancreatitis diagnosis. Even with good visualization, USG was less sensitive and specific in chronic pancreatitis examination. Common findings during abdominal USG is calcification of pancreas, shown as multiple ecogenic focus (found in 40% patients). Otherwise, no correlation between pancreatic function and the size of calcification. Other findings during USG are change in size and echogeneity of pancreatic gland, dilatation, and irregularity of pancreatic duct. USG also

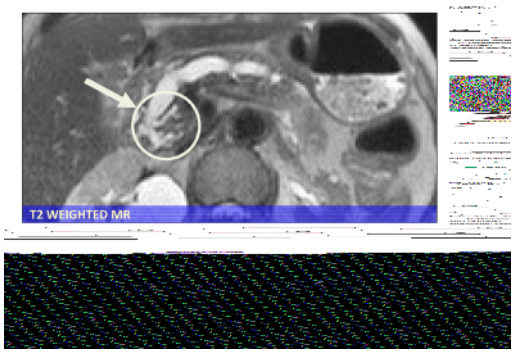

Figure 3. Pancreatic calcification in USG[1]

could examine pseudocyst, biliary duct dilatation, and splenic vein thrombosis, as a complication of chronic pancreatitis.[1]

CT Scan

CT scan is the best imaging study in chronic pancreatitis. Classic finding is pancreatic duct dilatation, calcification, and parenchymal atrophy. Of chronic pancreatitis cases, about 68% have pancreatic duct dilatation and 50% having intraductal calcification, both focal or diffuse. Other findings are parenchymal atrophy (54%), enlarging pancreas (30%), or even normal pancreas (7%). CT scan could also detect any complication such as pseudocyst, portosplenic vein thrombosis, pseudoaneurysm, and fistula pancreaticopleura. At some point, CT

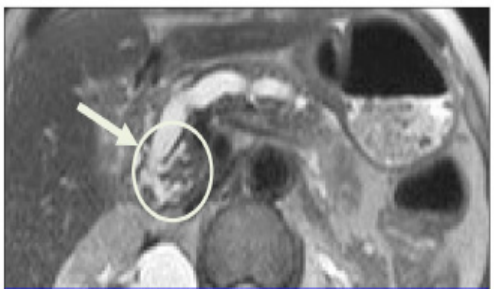

Figure 4. "Duct-penetrating sign" in chronic pancreatitis[1]

scan evaluation can differ chronic pancreatitis with pancreatic cancer by finding obstruction related to tumor, pancreatic tissue atrophy, vascular invasion, or any sign of metastasis.[1]

Magnetic Resonance Imaging (MRI)

MRI is another imaging modality that possible to detect early-stage disease, so that early intervention to prevent progressivity can be planned. MRI has high sensitivity and specificity to evaluate any changes in pancreatic tissue. Parenchym evaluation in MRI showed low intensity at duct in chronic pancreatitis cases. By injecting intravenous secretin, MRI can also diagnose chronic pancreatitis by evaluating exocrine secretion response. The focus was in pancreatic duct compliance (PDC) defined as normal duct distention ± 1 mm after secretin stimulation and reversal to baseline diameter 10 minutes after injection.[1] Sometimes, parenchymal abnormalities precede ductal abnormalities. Cambridge classification is used to evaluate any abnormalities in duct, stricture, cyst formation, or intraductal stone.

Endoscopic Ultasound (EUS)

Endoscopic ultrasound (EUS) is a common diagnostic tool for chronic pancreatitis because of its ability in evaluating minimal changes in pancreatic structure before able to detect by other modalities. Diagnosis using EUS based on ducatal and parenchymal criteria established by International Working Group with Minimum Standard Terminology (MST). Chronic pancreatitis morphology in EUS is: (1) hyperechoic and strand foci; (2) Lobular pancreas; (3) irregular and dilated pancreatic duct; (4) marginal duct hyperechoic; (5) calcification or shadowing stones. Although EUS was recently developed well in other disease evaluation, the use of this tools in chronic pancreatitis diagnosis is stagnant in the last decade. [1]

Endoscopic retrograde cholangiopancreatography (ERCP)

Because chronic pancreatitis mainly diagnosed by finding changes in main and branch pancreatic duct, a high-quality pancreatogram is needed to accurately visualize duct anatomy. Contrast injected along duct to caudal, including secondary branches to avoid contrast acinarization. The widely accepted criteria in pancreatogram is Cambridge criteria:[1]

Table 4. Cambridge criteria[1]

Grade	Main pancreatic duct	Duct branches
Normal	Normal	Normal
Equivocal	Normal	<3 Abnormal
Ringan	Normal	≥3 Abnormal
Sedang	Abnormal	>3 Abnormal
Berat*	Abnormal	> 3 Abnormal

*including: large cavity > 10 mm, intraductal filling defect, duct obstruction (stricture), duct dilatation and iregularity, pancreatic calficication/stone, adjacent organ invasion

In general, ERCP gave an important additional diagnostic information although it rarely uses in chronic pancreatitis. Correlation between pancreatogram abnormalities and histological findings is found higher in late-stage disease rather dan early-stage. Weakness of this modalities is its invasiveness and having a risk of postprocedural complication, such as acute pancreatitis. ERCP also only visualize duct anatomy, but not for parrenchym.[1]

Indirect Pancreatic Function Testing

Indirect pancreatic testing such as serum trypsinogen, fecal elastase, and fecal fat do not need direct hormonal stimulation. This testing only sensitive to patinet with steatorrhea and use if direct testing unavailable or intolareated by patient. Indirect pancreatitis function testing should minimally examine two parameters. For example, a serum trypsin with < 20 pg/dL and fecal elastase < 50 ug/dL is suggestive of chronic pancreatitis. Unfortunately, fecal fat level is not specific for chronic pancreatitis and fecal chymotrypsin only available in US.[1]

Direct Pancreatic Function Testing (PFT)

This testing could detect secretion problem in 30% damaged pancreatic tissue, with high sensitivity mainly in late-stage chronic pancreatitis. Secretin stimulated direct PFT using traditional dreiling tube is accurate to estimate pancreatic duct function.[43] Weakness of this examination is uncomfortable for patient, need fluoroscopy, and the availability of the traditional dreiling tube. Patient with gastroparesis and pyloric stenosis also not compatible with this examination. Other direct PFT is CCK that measure acinar cell function. Weakness of this test is tube availability, fluoroscopy, PEG/mannitol marker, and CCK continuous infusion during examination. No advantage of combining secretin and CCK testing.[1]

Endoscopic Pancreatic Function Test (ePFT)

This test is developed by Cleveland Clinic. After sedated, patient injected by secretin bolus (0,2 mcg/kg) and followed with duodenal fluid aspiration and analysis. This test is simpler and do not need fluoroscopy. ePFT and dreiling tube test is the gold standard of non-histologic examination in early-stage chronic pancreatitis. In daily clinical practice, suspected chronic pancreatitis patient benefits more with combination of EUS and ePFT test, mainly to detect any structural and functional abnormalities in pancreas.[1]

CORRELATION BETWEEN RADIOLOGIC, FUNCTION TEST, AND HISTOLOGIC FINDINGS

Mild exocrine insufficiency is commonly found in mild to severe pancreatitis, while structural fibrosis reflects pancreas exocrine function. But, no linier relation between radiologic, function test, and histological findings. Previous study showed suboptimal concordation of ERCP result and PFT, mostly in early-stage disease. Concordation level of secretin PFT and ERCP in chronic non-calcifying pancreatitis is less than 47%. Nowadays, EUS is preferred because of its safety and ability to evaluate, although still suboptimal.[1]

DIAGNOSTIC ALGORITHM

In establishing chronic pancreatitis diagnosis, definitive diagnostic findings should be present, supported with risk factors above. Longitudinal follow-up of serial radiologic examination and functional test is recommended in undetermined. Diagnostic algoritm can be seen in Figure 5.

TREATMENT

Treatment of chronic pancreatitis depend on the etiology, calcification, severity, and staging. Lifestyle such as alcohol consumption also a consideration in treatment.[42] This disease classified into compensated, transitional, and uncompensated phase. Because of possible exocrine disfunction, both pharmacological and nutritional treatment is important.[42]

In compensated phase, the main goal is to control relaps and pain. Main approach in this phase is nutritional dietary and pharmacotherapy with protease inhibitor. In uncompensated phase, along with digestion and absorption dysfunction, patient should avoid low fat diet. Steatorrhea should be controlled with adequate fat intake (50-70 g/day) followed by digestive enzyme administration. Available oral pancreatic enzyme is pancrelipase. Other consideration in this phase is low bicarbonate secretion that lower proximal duodenal pH. If duodenal pH lower than 4, bile and several digestive enzymes could be coagulating. Therefore, antacid, H_2 receptor agonist, or proton pump inhibitor can be added to increase pH.[42] Pancreatic diabetes is a complication in uncompensated phase, so that glucose level should

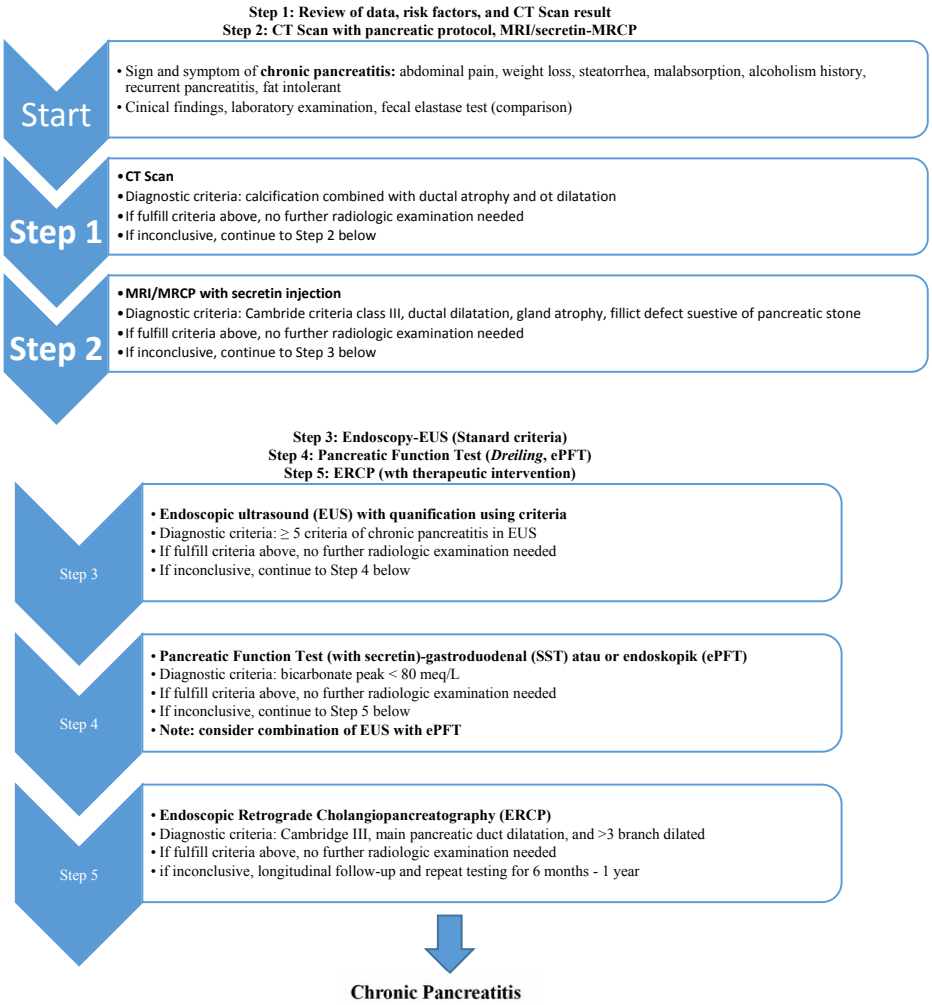

Figure 5. Diagnostic algorithm

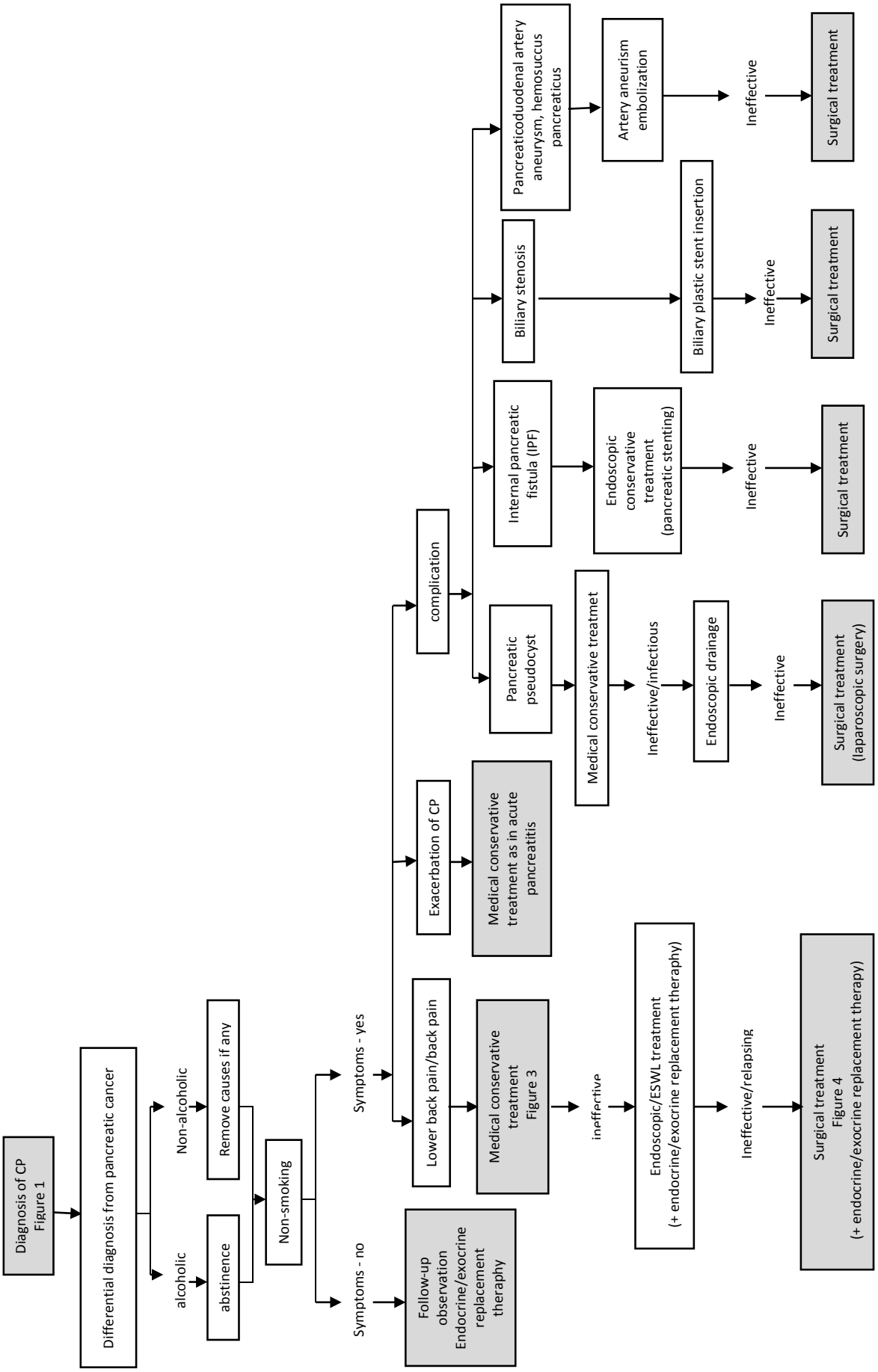

Figure 6. Chronic pancreatitis treatment algorithm[42]

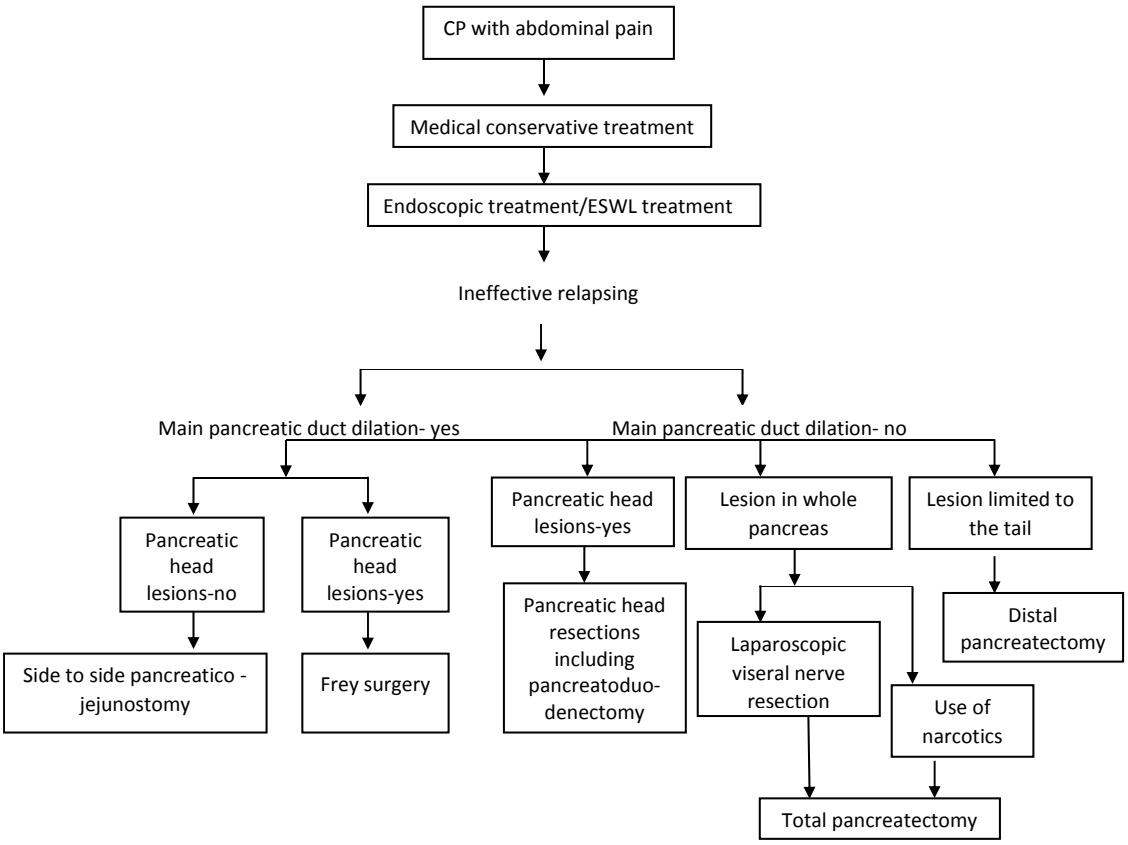

Figure 7. Surgical approach in chronic pancreatitis[42]

be monitored closely. Algorithm of chronic pancreatitis treatment is shown in Figure 6 and Figure 7.

Lifestyle Modification

If chronic pancreatitis etiology is alcoholism, abstinence is the main treatment. Besides, stop smoking also help to relieve chronic pancreatitis since it triggers the development of calcification in pancreas parenchym. A deep consultation is needed to ensure patient compliance in stop alcohol consumption and smoking.[42] Abdominal and back pain is the main contributor to low quality of life in chronic pancreatitis patient. Social impairment and nutritional problem related to inability in food digestion is the most serious problem faced by both patient and treating physician. Dietary management is the key success of chronic pancreatitis patient, especially with abdominal pain as dominant symptom.[42]

ROLE OF ENDOSCOPY IN CHRONIC PANCREATITIS TREATMENT

European Society of Gastroenterology (ESGE) recommend endoscopic approach as first line in chronic pancreatitis without severe complication that have severe pain complaint.[43]

Pancreatic duct decompression is the first line therapy in patient with intraductal obstruction and hypertension via sphincterotomy, litotripsy, extraction, or stent placement. ESGE recommend extracorporeal shockwave lithotripsy (ESWL) in chronic pancreatitis with pancreatic stone $\geq$ 5 mm, continued with stone extraction (stone size should < 5 mm). Intraductal lithotripsy is suggested if ESWL approach failed.[43] For stricture, dilatation using balloon or catheter is the best approach, continued by plastic stent placement. If success, this decompression would lead to pain relieve. EUS-guided drainage in main pancreatic duct that punctured via gaster or duodenum to make a fistula for drainage is the second line.[43] EUS-guided celiac plexus block is another approach to relieve pain. Chemical sympathectomy using absolute alcohol injection will result in anesthesia for 8-12 months. Pain exacerbation 48 hours after procedure occur in 9% patients.[43]

Endoscopic approach is the first line in chronic pseudocyst formation without complication. Drainage method consist of transpapillary/transductal endoscopic drainage and EUS-guided drainage.[43] Transpapillary/transductal endoscopic drainage for 4-6 weeks period is recommended in small pseudocyst which connect to main pancreatic duct. Otherwise, EUS-guided drainage

is indicated in portal hypertension or absent of luminal bulging cases. Complication rate is 18%, mainly about bleeding, infection, perforation, and stent migration.[43]

PROGNOSIS

In general, chronic pancreatitis is a progressive inflammatory disease. Observation and evaluation of clinical symptoms such as pain, enzymatic changes overtime, pancreas morphology, and exocrine-endocrine function is important in prognostication. Chronic pancreatitis patient has more risk to develop pancreatic cancer, supported by their lifestyle which is carcinogenic (alcohol, smoking).[42]

CONCLUSION

Diagnosis of chronic pancreatitis is still challenging, especially patient in early-stage disease. Risk factor assessment is important in evaluating patient with abdominal pain as chief complaint. Diagnosis should only establish if definite diagnostic findings is found. Several workup for chronic pancreatitis patient are CT Scan, MRI, or MRCP. Management of chronic pancreatitis consist of counseling and multidisciplinary approach in pain management, enzyme replacement therapy, endoscopic intervention, or surgery. Appropriate management of chronic pancreatitis would reduce its mortality and recurrence in the future.

REFERENCES

1. 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;43:1143-62.
2. Lankisch PG, Assmus C, Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic diseases in Luneburg County. A study in a defined german population. Pancreatology 2002;2:469-77.
3. Dite P, Stary K, Novotny I, Precechtelová M, Dolina J, Lata J, et al. Incidence of chronic pancreatitis in the Czech Republic. Eur J Gastroenterol Hepatol 2001;13:749–50.
4. Yadav D, Timmons L, Benson JT, Dierkhising RA, Chari ST. Incidence, prevalence, and survival of chronic pancreatitis: a population-based study. Am J Gastroenterol 2011;106:2192–9.
5. Lin Y, Tamakoshi A, Matsuno S, Takeda K, Hayakawa T, Kitagawa M , et al. Nationwide epidemiological survey of chronic pancreatitis in Japan. J Gastroenterol 2000;35:136–41.
6. Tinto A, Lloyd DA, Kang JY, Majeed A, Ellis C, Williamson RC, et al. Acute and chronic pancreatitis-diseases on the rise: a study of hospital admissions in England 1989/90–1999/2000. Aliment Pharmacol Ther 2002;16:2097-105.
7. Yang AL, Vadhavkar S, Singh G, Omary MB. Epidemiology of alcohol-related liver and pancreatic disease in the United States. Arch Intern Med 2008;168:649–56.
8. Spanier BW, Dijkgraaf MG, Bruno MJ. Trends and forecasts of hospital admissions for acute and chronic pancreatitis in the Netherlands. Eur J Gastroenterol Hepatol 2008;20:653–8.
9. Yadav D, Muddana V, O'Connell M. Hospitalizations for chronic pancreatitis in allegheny county, pennsylvania, USA. Pancreatology: official journal of the International Association of Pancreatology 2011;11:546–52.
10. Seicean A, Tantau M, Grigorescu M, Mocan T, Seicean R, Pop T. Mortality risk factors in chronic pancreatitis. J Gastrointestin Liver Dis 2006;15:21-6.
11. Forsmark CE. Management of chronic pancreatitis. Gastroenterology 2013;144:1282-91.
12. Majumder S, Chari ST. Chronic pancreatitis [serial online] [cited: 2017 Sept 23]. Available from:URL:http://www.thelanset.com.
13. Hart PA, Zen Y, Chari ST. Recent advances in autoimmune pancreatitis. Gastroenterology 2015;149:39–51.
14. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. Lancet 2015;385:1460–71.
15. Hart PA, Kamisawa T, Brugge WR, Chung JB, Culver EL, Czakó L, et al. Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis. Gut 2013;62:1771–76.
16. Kamisawa T, Chari ST, Giday SA, Kim MH, Chung JB, Lee KT, et al. Clinical profile of autoimmune pancreatitis and its histological subtypes: an international multicenter survey. Pancreas 2011;40:809–14.
17. Yadav D, Timmons L, Benson JT, Dierkhising RA, Chari ST. Incidence, prevalence, and survival of chronic pancreatitis: a population-based study. Am J Gastroenterol 2011;106:2192–99.
18. Frulloni L, Gabbrielli A, Pezzilli R, Zerbi A, Cavestro GM, Marotta F, et al. Chronic pancreatitis: report from a multicenter Italian survey (PanCroInfAISP) on 893 patients. Dig Liver Dis 2009;41:311–17.
19. 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;44:1349–54.
20. 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;169:1035–45.
21. Irving HM, Samokhvalov AV, Rehm J. Alcohol as a risk factor for pancreatitis. A systematic review and meta-analysis. JOP 2009;10:387–92.
22. Muniraj T, Aslanian HR, Farrell J, Jamidar PA. Chronic pancreatitis, a comprehensive review and update. Part I: epidemiology, etiology, risk factors, genetics, pathophysiology, and clinical features. Dis Mon 2014;60:530–50.
23. Pandol SJ, Gorelick FS, Gerloff A, Lugea A. Alcohol abuse, endoplasmic reticulum stress and pancreatitis. Dig Dis 2010;28:776–82.
24. Andriulli A, Botteri E, Almasio PL, Vantini I, Uomo G, Maisonneuve P. Smoking as a cofactor for causation of chronic pancreatitis: a meta-analysis. Pancreas 2010;39:1205–10.
25. Chowdhury P, Walker A. A cell-based approach to study changes in the pancreas following nicotine exposure in an animal model of injury. Langenbecks Arch Surg 2008; 393:547–55.

26. Alexandre M, Uduman AK, Minervini S, Raoof A, Shugrue CA, Akinbiyi EO, et al. Tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone initiates and enhances pancreatitis responses. Am J Physiol Gastrointest Liver Physiol 2012;303:G696-704.
27. Whitcomb DC, Preston RA, Aston CE, Sossenheimer MJ, Barua PS, Zhang Y, et al. A gene for hereditary pancreatitis maps to chromosome 7q35. Gastroenterology 1996;110:1975–80.
28. 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:e2003
29. 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:e2003.
30. Schneider A, Larusch J, Sun X, Aloe A, Lamb J, Hawes R, et al. Combined bicarbonate conductance-impairing variants in CFTR and SPINK1 variants are associated with chronic pancreatitis in patients without cystic fi brosis. Gastroenterology 2011;140:162–71.
31. Cohn JA, Friedman KJ, Noone PG, Knowles MR, Silverman LM, Jowell PS. Relation between mutations of the cystic fi brosis gene and idiopathic pancreatitis. N Engl J Med 1998;339:653–58.
32. Rosendah J, Witt H, Szmola R, Bhatia E, Ozsvári B, Landt O, et al. Chymotrypsin C (CTRC) variants that diminish activity or secretion are associated with chronic pancreatitis. Nat Genet 2008;40:78–82.
33. Masson E, Chen JM, Scotet V, Le Maréchal C, Férec C. Association of rare chymotrypsinogen C (CTRC) gene variations in patients with idiopathic chronic pancreatitis. Hum Genet 2008;123:83–91.
34. Felderbauer P, Klein W, Bulut K, Ansorge N, Dekomien G, Werner I, et al. Mutations in the calcium-sensing receptor: a new genetic risk factor for chronic pancreatitis? Scand J Gastroenterol 2006;41:343–48.
35. Weiss FU. Pancreatic cancer risk in hereditary pancreatitis. Front Physiol 2014;5:70.
36. Warshaw AL, Richter JM, Schapiro RH. The cause and treatment of pancreatitis associated with pancreas divisum. Ann Surg 1983;198:443–52.
37. Bertin C, Pelletier AL, Vullierme MP, Bienvenu T, Rebours V, Hentic O, et al. Pancreas divisum is not a cause of pancreatitis by itself but acts as a partner of genetic mutations. Am J Gastroenterol 2012;107:311–17.
38. Unnikrishnan R, Mohan V. Fibrocalculous pancreatic diabetes (FCPD). Acta Diabetol 2015;52:1–9.
39. Bhanot UK, Moller P. Mechanisms of parenchymal injury and signaling pathways in ectatic ducts of chronic pancreatitis: implications for pancreatitic carcinogenesis. Lab Invest 2009;89:489-07.
40. Chen WX, Zhang WF, Lin HJ, Zhang X, Chen HT, Gu ZY, et al. Clinical manifestations of patients with chronic pancreatitis. Hepatobilliary Pancreat Dis Int 2006;5:133-7.
41. Conwell DL, Banks P, Greenberger NJ. Acute and chronic pancreatitis. In: Braunwald, eds. Harrison's Principal of Internal Medicine 19th ed. New York: Mc Graw Hill 2015.p.2090-01.
42. Ito T, Ishiguro H, Ohara H, Kamisawa T, Sakagami J, Sata N, et al. Evidence-based clinical practice guidelines for chronic pancreatitis 2015. J Gastroenterol 2016;51:85-92.
43. Seicean A, Vultur S. Endoscopic therapy in chronic pancreatitis: current perspectives . Clinical and Experimental Gastroenterology 2015;8:1-11.