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Complications of Chronic Pancreatitis

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Abstract

Chronic pancreatitis is a disease that leads to irreversible changes in the pancreatic morphology and function. The loss of function can lead to diabetes mellitus and exocrine pancreatic insufficiency. The inflammation and fibrosis can also lead to other complications including a chronic abdominal pain syndrome, metabolic bone disease, and pancreatic cancer. This article reviews our current understanding of the mechanisms and management of these complications of chronic pancreatitis.

Keywords

Type 3c diabetes mellitus; Pancreatogenic diabetes; Pancreatic pseudocyst; Pancreatic cancer; Splenic vein thrombus

Introduction

Chronic pancreatitis (CP) is a fibro-inflammatory disease characterized by a low-grade inflammatory state [1]. Over time, chronic inflammation promotes the development of parenchymal fibrosis, which leads to loss of pancreatic endocrine and exocrine function. In general, the development of end-stage disease occurs irrespective of the CP etiology, and there are some scenarios in which the risk of a particular complication is exceptionally high. The end stage of CP is characterized by multiple complications including pain, pancreatic insufficiency (endocrine and/or exocrine), metabolic bone disease, and pancreatic ductal adenocarcinoma (PDAC); the mechanisms and management of CP-associated pain are discussed in detail in other articles within this issue. As there are currently no treatments to reverse or delay disease progression in CP, the clinical management primarily consists of screening for and treating complications.

Endocrine Insufficiency

Endocrine dysfunction and the subsequent insufficiency associated with CP lead to the development of diabetes mellitus (DM). Currently, the diabetes subtypes associated with

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Compliance with ethical standards

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exocrine disease of the pancreas (including CP) are collectively referred to as pancreatogenic or type 3c diabetes mellitus (T3cDM) [2]. Although T3cDM is a common name for the various subtypes, the mechanisms of hyperglycemia can differ substantially among the various types of pancreatic disease. Importantly, CP represents the most common and best characterized etiology of T3cDM.

It is estimated that approximately 5% of all DM is attributable to T3cDM, but the true prevalence has not been elucidated [2]. For example, in the largest single-center study to assess the prevalence of T3cDM among a cohort of diabetics, the prevalence was approximately 9%; however, the presence of pancreatic disease was determined based on an abnormal fecal elastase level, which is only fairly accurate for the diagnosis of mild CP [3, 4]. The most common etiologic sources of T3cDM were CP (80%), pancreatic cancer (8%), and hereditary hemochromatosis (7%) [3]. These estimates require further epidemiologic study following the development of more accurate diagnostic markers for T3cDM.

Among those with established CP, DM is highly prevalent; previous studies estimate up to 80% of those with CP will develop DM, which generally does not develop until a couple decades after the onset of symptoms [5]. There are no standardized diagnostic criteria for T3cDM secondary to CP; however, in essence, this requires meeting three parameters: (1) fulfillment of the diagnostic criteria for DM, (2) fulfillment of diagnostic criteria for CP, and (3) exclusion of other potential sources of DM. Previously proposed criteria for T3cDM align with these criteria, which are considered as major criteria [6]. In addition to these three criteria, minor criteria were proposed, including: impaired beta cell function, absence of insulin resistance, impaired incretin secretion, and low serum concentrations of fat-soluble vitamins. These criteria require further validation to differentiate T3cDM from type 2 DM, but encompass our current understanding of key clinical differences between these DM subtypes.

The pathophysiology of hyperglycemia in T3cDM secondary to CP appears to be primarily a consequence of insulin deficiency secondary to acinar cell fibrosis, which results in reduced insulin production. However, there are also likely other contributing mechanisms promoting hyperglycemia prior to the development of end-stage disease. For example, in one study, subjects were noted to have decreased insulin secretion (estimated by the disposition index) prior to the onset of overt diabetes [7]. Hypotheses for these changes include beta cell dysfunction mediated by pro-inflammatory cytokines and development of both hepatic and peripheral insulin resistance. Although the cause of the resistance is unclear, it has been recognized that a deficient pancreatic polypeptide (PP) response plays an important role in the hepatic insulin resistance. A series of studies have demonstrated that administration of PP can reverse the hepatic insulin resistance [8]. Lastly, it has been proposed that maldigestion of nutrients secondary to EPI associated with CP may lead to an impaired effect of two key incretin hormones [glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1)]. Whether or not this impairment in the incretin hormone response is a cause or a result of the hyperglycemia remains uncertain.

Due to the high prevalence of DM in patients with CP, frequent screening has been recommended by a multidisciplinary consensus group [9]. In those diagnosed with T3cDM

secondary to CP, treatment decisions are primarily based on an understanding of the underlying pathophysiology rather than evidence from clinical trials. Since the primary mechanism of hyperglycemia is related to insulin deficiency, insulin therapy is often considered as first-line therapy for these patients. However, in those with mild severity of DM, metformin is another reasonable consideration. In addition to the convenience of using an oral agent, data supporting a potential chemoprotective for the development of PDAC make this an attractive medication [10]. The use of thiazolidinediones (TZD) is potentially of interest as these have been shown to improve the hepatic and peripheral insulin sensitivities in rats with CP [11]. However, TZDs are also associated with an increased risk of bone fracture which is a major drawback in this patient population. Otherwise, the use of incretin-based therapies (including GLP-1 analogues and DPP4-inhibitors) is generally not used in those with underlying pancreatic disorders due to possible increased risk of acute pancreatitis or PDAC, even though these risks have not been confirmed in recent studies [12].

Exocrine Pancreatic Insufficiency

Exocrine pancreatic insufficiency (EPI) develops as a consequence of inadequate production and/or secretion of pancreatic enzymes. Symptoms of mild EPI are mostly related to fat malabsorption and include abdominal bloating, cramping, and gas, while symptoms of severe EPI include unexplained weight loss and steatorrhea [4]. Seminal work from DiMagno and colleagues demonstrated that steatorrhea, indicating clinically significant fat malabsorption, does not develop until approximately 90% of the exocrine pancreatic function is lost [13]. Accordingly, EPI does not typically develop until more than 10 years after symptom onset [14]. It is important to recognize EPI, when present, as it can lead to other nutritional consequences and is easily treated with pancreatic enzyme replacement therapy (PERT).

EPI develops due to disruption of the normal production, storage, and/or secretion of pancreatic enzymes. The majority of the proteins synthesized in the pancreas are digestive enzymes, including amylase and a variety of lipases and proteases. All proteases and several lipases (specifically, phospholipase and colipase) are produced as inactive proenzymes and are activated by trypsin, which is itself activated by enterokinase, an enzyme secreted by brush border cells in the duodenum. The release of these enzymes from acinar cells is primarily directed through stimulation from cholecystokinin (CCK). The enzymes subsequently mix with electrolytes and water secreted from the pancreatic ductal cells, which facilitates transit into the duodenal lumen.

Exocrine pancreatic function can be assessed with pancreatic function testing (PFTs), which is broadly classified as “direct” (involves collection and analysis of pancreas secretions following hormonal stimulation) and “indirect” (most commonly involves analysis of analytes from a stool or breath test) [4]. Direct PFTs have evolved over time. Initial tests consisted of measuring pancreas enzyme output after stimulation with CCK and were considered the gold standard for diagnosis of EPI. The more commonly used endoscopic PFT (ePFT) at this time involves measurement of the bicarbonate concentration in the fluid following stimulation with secretin [15]. This current version of direct PFT is more precisely

a measurement of pancreatic duct cell function and does not diagnose EPI per se. Nevertheless, the ePFT remains clinically valuable to rule out chronic pancreatitis as well as to collect pancreatic fluid for translational research [15]. The most commonly used indirect PFTs involve assessment of the stool, including qualitative and quantitative fat, and fecal elastase measurements. European centers also have access to the ^{13}C -mixed triglyceride breath test, which estimates fat lipolysis following ingestion of a standardized test meal. In general, indirect PFTs are most useful when the pretest probability for EPI is high, since the accuracy of the tests is lower than for direct PFTs [4].

One of the challenges with existing data regarding EPI is the lack of a standardized diagnostic test. Thus, many studies use tests that suffer from suboptimal diagnostic accuracy. Therefore, data regarding the prevalence of EPI in CP is dependent not only on the clinical stage of disease, but also the method of diagnosing EPI. Recognizing these limitations, it is estimated that EPI develops in approximately 30–80% of those with CP [4]. Patients with recurrent episodes of acute pancreatitis may have a further increased risk [16]. Fat-soluble vitamin deficiencies are an important secondary nutritional consequence of EPI that commonly develop. A recent meta-analysis estimated the prevalence of deficiencies in vitamins A, D, and E in CP as 16.8, 57.6, and 29.2%, respectively; there were inadequate data to provide an estimate for vitamin K deficiency [17]. Due to the high prevalence of EPI and the increased prevalence of fat-soluble vitamin deficiencies in CP, routine diagnostic testing for vitamin deficiencies should be considered.

For CP patients diagnosed with EPI, initiation of PERT is recommended to reduce symptoms and normalize nutrient absorption. There is variation in recommendations regarding PERT, but most suggest a starting dose of 25,000–50,000 units of lipase per meal with titration based on resolution of symptoms and nutritional deficiencies [18, 19]. It is often recommended that patients take 50% of their mealtime dose with snacks. For those with EPI that is not responsive to PERT, several other steps in management may be considered, including further titration of PERT dosage, addition of a proton pump inhibitor, or empiric therapy for bacterial overgrowth or bile salt diarrhea [20]. Unfortunately, there is currently no convenient and accurate marker for EPI to assess the effectiveness of PERT, which leads to substantial variations in clinical practice [21].

Metabolic Bone Disease

Another common complication in CP is metabolic bone disease, which is occasionally termed CP-associated osteopathy. The pooled prevalence of CP-associated osteopathy, which includes either osteopenia or osteoporosis, is approximately 66% [22]. Similarly, large studies have demonstrated an increased risk of low trauma fractures in patients with CP [23, 24]. There are multiple factors that help explain this markedly increased risk, including shared risk factors (e.g., cigarette smoking, excessive alcohol usage), vitamin D deficiency, female gender, and chronic inflammation, which promotes an imbalance of bone production and resorption that favors bone loss. At this time, there are no societal guidelines to recommend screening for metabolic bone disease in CP. Nevertheless, baseline screening for patients with CP can be justified, as the odds of developing a fragility fracture (which is the primary clinical endpoint of metabolic bone disease) in this group is similar to other

commonly recognized indications for screening, including inflammatory bowel disease, celiac disease, and cholestatic liver disease [23].

In those diagnosed with CP-associated osteopathy, clinical management is similar to the management of metabolic bone disease in the general population, including abstinence from alcohol and tobacco, and increased weight-bearing physical activity. A diet rich in calcium and vitamin D is recommended to achieve a normal serum concentration of 25-hydroxyvitamin D, with pharmacologic supplementation reserved for those unable to attain adequate levels with diet alone. Importantly, those with EPI should be appropriately managed to avoid vitamin D deficiency. Additional pharmacotherapy, including antiresorptive agents like bisphosphonates, and bone-anabolic medications (such as parathyroid hormone and teriparatide) have not been specifically studied in CP, but may also be considered. Additional research is needed to better understand the prevention, screening, and management of CP-associated osteopathy.

Pancreatic Cancer

There is an increased risk of PDAC in those with an underlying diagnosis of CP, which is affected by multiple variables, including shared risk factors for cigarette smoking, alcohol use, and diabetes mellitus [25]. The increased risk compared in CP is believed to be influenced by chronic inflammation and over-proliferation of pancreatic stellate cells [26]. Early studies reported a cumulative risk of developing PDAC of 4.0% (95% CI 2.0–5.9%) in CP [27]. A subsequent meta-analysis also showed an increased risk of PDAC for CP (pooled RR = 13.3, 95% CI 6.1–28.9); however, there are several factors that may further increase the risk [28]. There are two important CP subtypes associated with a markedly increased risk of PDAC. First, those with PRSS1 hereditary pancreatitis have a substantially increased risk of PDAC (RR = 69). In these patients, the cumulative lifetime risk is approximately 40%, and the risk is even higher in cigarette smokers [25]. Tropical pancreatitis, a form of calcific CP primarily described in Asia, has also been associated with a dramatically increased risk of PDAC (RR = 100); however, recent risk estimates are not available [29].

Although there are multiple shared risk factors for CP and PDAC, the presence of DM in the context of CP appears to accelerate progression to PDAC. Database studies have shown an increased risk of PDAC in patients with CP and DM (RR = 4.7 and HR = 12.1) [30, 31]. Additional efforts are needed to further understand the pathophysiology of T3cDM secondary to CP to characterize the underlying mechanisms promoting cancer development.

Miscellaneous Complications of CP

There are other consequences of acute and chronic inflammation related to CP on the adjacent vascular and luminal anatomy. The prevalence of these problems and management are not as well described as the preceding complications, but remain clinically relevant.

Splenic Vein Thrombosis

Splanchnic venous thromboses can occur in the context of both acute pancreatitis and chronic pancreatitis. Due to the lower levels of inflammation typically observed in CP, the

splenic vein is more commonly affected than the portal or superior mesenteric veins. It is estimated that splenic vein thrombosis (SVT) develops in approximately 10–20% of patients with CP [32, 33]. Although the majority of patients with SVT are asymptomatic, an important subset develops gastric varices, which are at high risk of gastrointestinal bleeding. Splenomegaly is an inconsistent indicator of SVT, so when the diagnosis is suspected, diagnosis should be evaluated by ultrasound with Doppler evaluation or cross-sectional imaging with IV contrast. The management of SVT is largely conservative, with monitoring for signs of bleeding from gastric varices. One small study suggested that anticoagulation does not increase the odds of recanalization of the splenic vein in the setting of acute pancreatitis, so it is doubtful this would be possible in those with CP-associated SVT, but has not been directly examined [34]. In patients with clinically significant bleeding from gastric varices, splenectomy was previously considered the treatment of choice; however, endoscopic therapies have evolved and may be considered prior to surgical intervention depending on local expertise [35].

Pseudocysts

The prevalence of pseudocysts in those with CP has been estimated to at approximately 20–40%; however, this may be overestimated due to changes in nomenclature of peripancreatic fluid collections. The development of symptoms associated with a pseudocyst depends on the cyst size and anatomic location. Potential symptoms include abdominal pain, early satiety, nausea/vomiting, jaundice, and weight loss. Secondary complications that may occur due to pseudocysts include duodenal and/or biliary obstruction, SVT, and rarely infection. Management strategies for pancreatic pseudocysts have evolved, with previous intervention primarily involving either surgical resection (e.g., distal pancreatectomy) or surgical cystogastrostomy. The technique of endoscopic cystogastrostomy has been borrowed from the management of walled off necrosis, to address symptomatic pancreatic pseudocysts. One randomized controlled trial involving 40 subjects demonstrated endoscopic therapy has similar efficacy to surgical drainage and was associated with improved quality of life and decreased healthcare utilization [36]. A recent meta-analysis showed similar results favoring an endoscopic approach; however, these findings were based on low quality evidence and should be interpreted cautiously [37].

Duodenal Obstruction

Duodenal obstruction is another local complication associated with CP. Among hospitalized patients with acute or chronic pancreatitis, the incidence of duodenal obstruction is approximately 1% [38]. When it develops duodenal obstruction may be transient or fixed. Transient swelling occurs in the setting of an acute pancreatitis flare, whereas fixed obstructions occur secondary to compression from a peripancreatic fluid collection (namely pseudocysts) or fibrotic changes in the head of the pancreas. Groove pancreatitis describes an anatomic subtype of CP that primarily involves the head of the pancreas near the pancreaticoduodenal groove; this subtype is frequently complicated by duodenal obstruction [39]. Obstructive symptoms including nausea and emesis shortly after eating should raise consideration of this potential complication in those with known CP. Evaluation typically consists of both direct endoscopic visualization and cross-sectional imaging. Patients with compression from a pancreatic pseudocyst can often be managed with endoscopic therapy

(as discussed above). Although endoscopic stenting of the duodenal lumen is technically feasible, this is generally not pursued for benign indications due to the risk of delayed perforation. Therefore, management of duodenal obstruction from CP due to fibrotic changes is primarily surgical, with options including a palliative gastrojejunostomy, duodenum-preserving pancreatic head resection, or pancreaticoduodenectomy.

Biliary Obstruction

Patients with CP are at increased risk of developing fibrotic strictures of the intrapancreatic portion of the common bile duct, which may occur in up to 25% of those with calcific CP [40]. In general, patients with biliary dilation on imaging, but normal liver tests are followed clinically, whereas intervention is recommended for those with marked, unexplained elevation of the serum alkaline phosphatase and/or bilirubin levels. Previously, there was little enthusiasm for endoscopic stenting of CP-related biliary strictures, because the fibrotic nature of the strictures limited the durability of the therapeutic dilation. However, recent studies have demonstrated the use of self-expanding metal stents or multiple plastic stents may permit effective endoscopic therapy [41, 42]. Patients with clinically significant biliary obstruction that is resistant to biliary stenting warrant consideration for surgical intervention, which may consist of a hepaticojejunostomy or pancreaticoduodenectomy (which may be favored in patients with concurrent duodenal obstruction).

Conclusions

Chronic pancreatitis is a fibro-inflammatory disease that can produce complications through loss of endocrine function, loss of exocrine function, and compromise of the local vascular and luminal anatomy. The primary complications include abdominal pain, diabetes mellitus, exocrine pancreatic insufficiency (namely fat malabsorption), metabolic bone disease, and pancreatic cancer. Additional anatomic complications can include pseudocysts, splanchnic venous thrombosis, and duodenal or biliary obstruction. These complications are primarily the consequence of chronic inflammation and fibrosis, and management primarily consists of screening for and treating complications after they develop. Additional efforts are needed to further understand the pathophysiology of disease progression and study therapeutic interventions to prevent the development of these end-stage complications.

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Abbreviations

BMD	Bone mineral density
CP	Chronic pancreatitis
CCK	Cholecystokinin

EPI	Exocrine pancreatic insufficiency
PDAC	Pancreatic ductal adenocarcinoma
PERT	Pancreatic enzyme replacement therapy
DM	Diabetes mellitus
T3cDM	Type 3c diabetes mellitus
PFT	Pancreatic function testing
TZD	Thiazolidinediones
GLP-1	Glucagon-like peptide-1
GIP	Glucose-dependent insulinotropic polypeptide
SVT	Splenic vein thrombosis

References

1. Majumder S, Chari ST. Chronic pancreatitis. *Lancet*. 2016; 387:1957–1966. [PubMed: 26948434]
2. Hart PA, Bellin M, Andersen DK. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. *Lancet Gastroenterol Hepatol*. 2016; 1:226–237. [PubMed: 28404095]
3. Ewald N, Kaufmann C, Raspe A, et al. Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c). *Diabetes Metab Res Rev*. 2012; 28:338–342. [PubMed: 22121010]
4. Hart PA, Conwell DL. Diagnosis of exocrine pancreatic insufficiency. *Curr Treat Options Gastroenterol*. 2015; 13:347–353. [PubMed: 26077487]
5. Malka D, Hammel P, Sauvanet A, et al. Risk factors for diabetes mellitus in chronic pancreatitis. *Gastroenterology*. 2000; 119:1324–1332. [PubMed: 11054391]
6. Ewald N, Hardt PD. Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. *World J Gastroenterol*. 2013; 19:7276–7281. [PubMed: 24259958]
7. Lundberg R, Beilman GJ, Dunn TB, et al. Early alterations in glycemic control and pancreatic endocrine function in nondiabetic patients with chronic pancreatitis. *Pancreas*. 2016; 45:565–571. [PubMed: 26918872]
8. Brunicaudi FC, Chaiken RL, Ryan AS, et al. Pancreatic polypeptide administration improves abnormal glucose metabolism in patients with chronic pancreatitis. *J Clin Endocrinol Metab*. 1996; 81:3566–3572. [PubMed: 8855802]
9. Rickels MR, Bellin M, Toledo FG, et al. Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: recommendations from PancreasFest 2012. *Pancreatol*. 2013; 13:336–342. [PubMed: 23890130]
10. Li D, Yeung SC, Hassan MM, et al. Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology*. 2009; 137:482–488. [PubMed: 19375425]
11. Zhou X, You S. Rosiglitazone inhibits hepatic insulin resistance induced by chronic pancreatitis and IKK-beta/NF-kappaB expression in liver. *Pancreas*. 2014; 43:1291–1298. [PubMed: 25036911]
12. Forsmark CE. Incretins, diabetes, pancreatitis and pancreatic cancer: what the GI specialist needs to know. *Pancreatol*. 2016; 16:10–13. [PubMed: 26795258]
13. DiMagno EP, Go VL, Summerskill WH. Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. *N Engl J Med*. 1973; 288:813–815. [PubMed: 4693931]

14. Lacer P, Yamamoto H, Kalthoff L, et al. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. *Gastroenterology*. 1994; 107:1481–1487. [PubMed: 7926511]
15. Hart PA, Topazian M, Raimondo M, et al. Endoscopic pancreas fluid collection: methods and relevance for clinical care and translational science. *Am J Gastroenterol*. 2016; 111:1258–1266. [PubMed: 27481304]
16. Sandhu BS, Hackworth WA, Stevens S, et al. Recurrent flares of pancreatitis predict development of exocrine insufficiency in chronic pancreatitis. *Clin Gastroenterol Hepatol*. 2007; 5:1085–1091. (quiz 1007). [PubMed: 17588823]
17. Martinez-Moneo E, Stigliano S, Hedstrom A, et al. Deficiency of fat-soluble vitamins in chronic pancreatitis: a systematic review and meta-analysis. *Pancreatol*. 2016; 16:988–994. [PubMed: 27681502]
18. Forsmark CE. Management of chronic pancreatitis. *Gastroenterology*. 2013; 144:e3.
19. Frulloni L, Falconi M, Gabbriellini A, et al. Italian consensus guidelines for chronic pancreatitis. *Dig Liver Dis*. 2010; 42:S381–S406. [PubMed: 21078490]
20. Dominguez-Munoz JE. Pancreatic exocrine insufficiency: diagnosis and treatment. *J Gastroenterol Hepatol*. 2011; 26:12–16.
21. Hart PA, Conwell DL. Challenges and updates in the management of exocrine pancreatic insufficiency. *Pancreas*. 2016; 45:1–4. [PubMed: 26658035]
22. Duggan SN, Smyth ND, Murphy A, et al. High prevalence of osteoporosis in patients with chronic pancreatitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2014; 12:219–228. [PubMed: 23856359]
23. Tignor AS, Wu BU, Whitlock TL, et al. High prevalence of low-trauma fracture in chronic pancreatitis. *Am J Gastroenterol*. 2010; 105:2680–2686. [PubMed: 20736937]
24. Munigala S, Agarwal B, Gelrud A, et al. Chronic pancreatitis and fracture: a retrospective, population-based veterans administration study. *Pancreas*. 2016; 45:355–361. [PubMed: 26199986]
25. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology*. 2013; 144:1252–1261. [PubMed: 23622135]
26. Algul H, Treiber M, Lesina M, et al. Mechanisms of disease: chronic inflammation and cancer in the pancreas—a potential role for pancreatic stellate cells? *Nat Clin Pract Gastroenterol Hepatol*. 2007; 4:454–462. [PubMed: 17667994]
27. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. *N Engl J Med*. 1993; 328:1433–1437. [PubMed: 8479461]
28. Raimondi S, Lowenfels AB, Morselli-Labate AM, et al. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. *Best Pract Res Clin Gastroenterol*. 2010; 24:349–358. [PubMed: 20510834]
29. Chari ST, Mohan V, Pitchumoni CS, et al. Risk of pancreatic carcinoma in tropical calcifying pancreatitis: an epidemiologic study. *Pancreas*. 1994; 9:62–66. [PubMed: 8108373]
30. Brodovicz KG, Kou TD, Alexander CM, et al. Impact of diabetes duration and chronic pancreatitis on the association between type 2 diabetes and pancreatic cancer risk. *Diabetes Obes Metab*. 2012; 14:1123–1128. [PubMed: 22831166]
31. Munigala S, Singh A, Gelrud A, et al. Predictors for pancreatic cancer diagnosis following new-onset diabetes mellitus. *Clin Transl Gastroenterol*. 2015; 6:e118. [PubMed: 26492440]
32. Agarwal AK, Raj Kumar K, Agarwal S, et al. Significance of splenic vein thrombosis in chronic pancreatitis. *Am J Surg*. 2008; 196:149–154. [PubMed: 18585674]
33. Butler JR, Eckert GJ, Zyromski NJ, et al. Natural history of pancreatitis-induced splenic vein thrombosis: a systematic review and meta-analysis of its incidence and rate of gastrointestinal bleeding. *HPB (Oxford)*. 2011; 13:839–845. [PubMed: 22081918]
34. Harris S, Nadkarni NA, Naina HV, et al. Splanchnic vein thrombosis in acute pancreatitis: a single-center experience. *Pancreas*. 2013; 42:1251–1254. [PubMed: 24152951]
35. Levy MJ, Wong Kee Song LM. EUS-guided angiotherapy for gastric varices: coil, glue, and sticky issues. *Gastrointest Endosc*. 2013; 78:722–725. [PubMed: 24120335]

36. Varadarajulu S, Bang JY, Sutton BS, et al. Equal efficacy of endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in a randomized trial. *Gastroenterology*. 2013; 145:e1.
37. Gurusamy KS, Pallari E, Hawkins N, et al. Management strategies for pancreatic pseudocysts. *Cochrane Database Syst Rev*. 2016; 4:CD011392. [PubMed: 27075711]
38. Vijungco JD, Prinz RA. Management of biliary and duodenal complications of chronic pancreatitis. *World J Surg*. 2003; 1270
39. Oza VM, Skeans JM, Muscarella P, et al. Groove pancreatitis, a masquerading yet distinct clinicopathological entity: analysis of risk factors and differentiation. *Pancreas*. 2015; 44:901–908. [PubMed: 25899649]
40. Costamagna G, Boskoski I. Current treatment of benign biliary strictures. *Ann Gastroenterol*. 2013; 26:37–40. [PubMed: 24714594]
41. Deviere J, Nageshwar Reddy D, Puspok A, et al. Successful management of benign biliary strictures with fully covered self-expanding metal stents. *Gastroenterology*. 2014; 147:385–395. (quiz e15). [PubMed: 24801350]
42. Haapamaki C, Kylanpaa L, Udd M, et al. Randomized multicenter study of multiple plastic stents vs. covered self-expandable metallic stent in the treatment of biliary stricture in chronic pancreatitis. *Endoscopy*. 2015; 47:605–610. [PubMed: 25590182]

Key Findings

- Chronic pancreatitis is a fibro-inflammatory disease that can lead to a variety of complications due to loss of function or compromise of the adjacent vascular or luminal anatomy.

Future Unmet Needs

- Better understanding of type 3c diabetes secondary to chronic pancreatitis is needed to provide optimal diabetes treatment and understand the accelerated risk of pancreatic cancer in those with chronic pancreatitis and diabetes.
- The development and validation of an accurate and easily repeatable test for assessment of exocrine pancreatic insufficiency is needed.
- Additional studies are needed to examine preventative strategies for the development of metabolic bone disease and pancreatic cancer in chronic pancreatitis.

Implications for the Clinician

- There are several potential complications of chronic pancreatitis which require active surveillance by clinicians, including diabetes, exocrine pancreatic insufficiency, metabolic bone disease, and pancreatic cancer.