



## PRACTICE

## CLINICAL UPDATE

## Chronic pancreatitis

Anand Gupte *assistant professor of medicine*<sup>1</sup>, Dianne Goede *assistant professor of medicine*<sup>2</sup>, Robert Tuite *Florida Chapter Chair*<sup>3</sup>, Chris E Forsmark *professor of medicine*<sup>1</sup>

<sup>1</sup>Department of Gastroenterology, Hepatology, and Nutrition, University of Florida, Gainesville, FL, USA; <sup>2</sup>Division of General Internal Medicine, University of Florida, Gainesville, FL, USA; <sup>3</sup>Florida Chapter Chair, National Pancreas Foundation, FL, USA

## What you need to know

- Although alcohol consumption is the most common cause of chronic pancreatitis, smoking and genetic mutations are also risk factors
- Older people, those with diabetes, and those who smoke or drink to excess can have changes on imaging that mimic pancreatitis
- Pancreatic insufficiency typically takes 10 years to develop and is best managed with replacement therapy
- If abdominal pain is disproportionate, consider whether there is a complication such as a pseudocyst, obstruction, malignancy, or hyperalgesia
- Monitor for the development of secondary diabetes

Although chronic pancreatitis is commonly attributed to alcohol consumption, it is now clear that newly discovered genetic mutations and smoking are also important risk factors, and idiopathic chronic pancreatitis is much more common than appreciated. The diagnosis rests on cross-sectional imaging, or endoscopic ultrasound, but these tests might be non-diagnostic early in the clinical course. Avoiding further exposure to toxins like alcohol and tobacco can moderate the disease course and reduce the risk of secondary pancreatic cancer and other non-pancreatic complications. Abdominal pain remains difficult to manage, but a good patient-doctor relationship allows reasonable goals to be set. Malabsorption—exocrine insufficiency—can occur, and requires appropriate dosage of pancreatic enzyme replacement therapy (PERT) and monitoring for osteoporosis. Secondary diabetes—endocrine insufficiency—can occur and can be difficult to manage, requiring an understanding of the unique mechanisms of diabetes in patients with chronic pancreatitis. Effective collaboration between primary care doctors and specialists in pain management, diabetes, gastroenterology, surgery, and radiology is important and often essential in these complex patients.

In this article, we review the causes, consequences, and management of chronic pancreatitis and its complications. The available therapeutic options, with very few exceptions, are not

supported by randomised trials or high quality evidence, but are instead supported by guidelines<sup>1</sup> and expert opinion.

## Search strategy

We searched Medline and Embase for English language papers using a combination of MeSH and text words to search “chronic pancreatitis,” as well as personal references and reference lists. The search was limited to English language publications.

## What is chronic pancreatitis?

Chronic pancreatitis is characterised by inflammation, fibrosis, and loss of exocrine (acinar cells) and endocrine (islets) tissue<sup>2</sup> in people with genetic or environmental risk factors. The mechanisms and pathways to chronic pancreatitis are complex, but recurrent episodes of acute pancreatitis are a central feature.

## What causes it?

It is a common misconception that almost all patients with chronic pancreatitis develop it from alcohol abuse. In one large study of the causes of chronic pancreatitis, alcohol accounted for around 60% of all cases of chronic pancreatitis in men, but only 28% in women, who were much more likely to have an idiopathic diagnosis.<sup>3,4</sup> The aetiology of chronic pancreatitis varies by sex, based on both differences in environmental exposure (alcohol and smoking)<sup>5</sup> and genetic factors.<sup>6</sup>

Longstanding alcohol consumption is an important risk factor for chronic pancreatitis, although less than 5% of heavy drinkers develop the syndrome.<sup>3</sup> On average, around five alcoholic drinks daily for more than five years carries increased risk; while moderate alcohol intake (<1 drink/day) may be protective against all types of pancreatitis.<sup>5,7</sup> Smoking is now known to be an independent and equally potent risk factor in the development of chronic pancreatitis, and alcohol and smoking tobacco appear to work synergistically.<sup>5</sup>

Numerous genetic mutations and polymorphisms are also risk factors for chronic pancreatitis.<sup>8</sup> Genetic mutations are important

as they also increase the risk of secondary pancreatic cancer.<sup>9,10</sup> The role of genetic testing is evolving, but is most widely used in the evaluation of younger patients with unexplained chronic pancreatitis.

Autoimmune pancreatitis occurs in two forms, one of which is a systemic disease associated with increased levels of IgG4. Both forms can present as acute or chronic pancreatitis, but more commonly mimic pancreatic cancer with obstructive jaundice.<sup>11</sup> The condition usually responds to steroid therapy but will often relapse when steroids are tapered.<sup>12</sup>

Additional risk factors for chronic pancreatitis include long term pancreatic duct obstruction (eg, stricture), repeated attacks of acute pancreatitis, and even single episodes of severe necrotising acute pancreatitis. Obesity and longstanding diabetes also predispose to chronic pancreatitis. Many cases remain idiopathic.<sup>13</sup>

## How common is it?

Chronic pancreatitis affects around 50/100 000 people across the world. Recent research has focused on exploring its complex relationship with diabetes and pancreatic cancer.

## How do patients with chronic pancreatitis present?

In the early stages of chronic pancreatitis, patients may present with relapsing acute pancreatitis or with chronic or recurrent pancreatic-type pain. Exocrine insufficiency (steatorrhea) and endocrine insufficiency (diabetes) are late consequences of chronic pancreatitis, usually occurring years or even decades after the onset of chronic pancreatitis (fig 1).

## How is chronic pancreatitis diagnosed?

### A clinical diagnosis

Chronic pancreatitis is usually suspected based on clinical features: chronic or relapsing pancreatic-type pain (epigastric pain radiating to the back), or evidence of steatorrhea or diabetes. There is no “gold standard” diagnostic test, since chronic pancreatitis is a syndrome.

### Supportive imaging

Guidelines<sup>14</sup> and expert opinion generally recommend starting with a computed tomography scan or ultrasound as first line imaging to detect those with more obvious disease: features such as calcifications or a dilated duct. However, magnetic resonance imaging (MRI) (with secretin stimulation if available) is becoming the diagnostic modality of choice as no radiation risk is involved. EUS (endoscopic ultrasonography) or pancreatic function testing can also be used, if available, as a final diagnostic test, and if previous testing is negative or equivocal.

In the early stages of chronic pancreatitis, the pancreas may appear relatively normal. As the disease progresses, pancreatic atrophy, calcifications, and pancreatic duct abnormalities usually develop; along with the development of exocrine and/or endocrine insufficiency.

Chronic pancreatitis can be difficult to diagnose in the early phases, when pancreatic function is preserved and laboratory and imaging studies may be only minimally abnormal. This can lead to a delay in diagnosis. Furthermore, certain groups—older people, those with longstanding diabetes, people who drink alcohol moderately, and those who smoke—can develop changes in the pancreas (radiological and histological) that mimic the

features of chronic pancreatitis. This pancreatic damage has been termed “pancreatopathy,” to distinguish it from chronic pancreatitis.<sup>15</sup> Later in the clinical course of chronic pancreatitis, imaging tests become more reliable diagnostic tools.<sup>14,16</sup>

### Ultrasonography

Ultrasound has low sensitivity (60%-70%),<sup>17</sup> and visualisation can be affected by overlying intestinal gas.

### Cross-sectional imaging

Computed tomography and MRI (often with magnetic resonance cholangiopancreatography, or MRCP) are most commonly used. There are no high quality or randomised comparative studies that determine the relative accuracy of these imaging tests for chronic pancreatitis. Secretin enhanced MRCP, which allows for improved visualisation of the pancreatic ductal system in response to stimulation with the hormone secretin, does appear to improve sensitivity and specificity for early chronic pancreatitis.<sup>14</sup>

### Endoscopic approaches

EUS enables a detailed examination of the pancreatic parenchyma and duct, and assigns a score to several of these ductal and parenchymal changes; this scoring system is utilised to assess the likelihood of chronic pancreatitis.<sup>14,16,18</sup> EUS is widely used and highly sensitive (reaching 100% in some reports), but with a lower specificity for chronic pancreatitis.<sup>19</sup> In some analyses, EUS is less accurate than MRI in the earlier stages of chronic pancreatitis.<sup>20</sup> Endoscopic evaluation with endoscopic retrograde cholangiopancreatography (ERCP) should not be used for diagnosis because of its invasive nature but might be useful for therapy in patients with intraductal stones or strictures, which are recognised sequelae of chronic pancreatitis.

### Pancreatic function tests

Pancreatic function tests (PFTs) measure enzyme or bicarbonate output from the pancreas in response to hormonal stimulation. These direct PFTs are not widely available but can be used in the diagnosis of early chronic pancreatitis before the development of radiologic features.<sup>1</sup>

## How is chronic pancreatitis managed?

In general, there are a few small trials of medical therapy (antioxidants, enzymes, and gabapentoids) and surgical therapy (comparing surgical with endoscopic therapy) for the management of pain. But very few randomised trials exist to guide management decisions in chronic pancreatitis; much of the clinical guidance comes from expert opinion and guidelines.

### Explain the diagnosis

Chronic pancreatitis is not curable, and most patients will experience longstanding symptoms, such as abdominal pain or steatorrhea, which detract from their quality of life. Patients will likely eventually need treatment for abdominal pain, exocrine insufficiency with maldigestion, and endocrine insufficiency with diabetes. In all patients with pancreatitis, explain that alcohol and tobacco are associated with worse outcomes, as such patients are generally encouraged to abstain from both. Offer support and referral to those who would like help with abstinence. Patients often need the involvement of other specialists in caring for the consequences of chronic pancreatitis.

## Manage abdominal pain

Pain is the most common problem for patients and has the most negative impact on both quality of life and use of healthcare resources.<sup>21,22</sup> The mechanisms of pain are complex, and although driven by pancreatic damage often also involve changes in nociceptive function and central pain perception.<sup>1,22-25</sup> If pain is out of proportion, or worsens unexpectedly, clinicians should look for complications such as pseudocyst, duodenal obstruction, bile duct obstruction, or a secondary pancreatic malignancy (see below).

Patients with chronic pancreatitis can develop hyperalgesia (a centrally sensitised pain state), in which interventions directed at the pancreas (endoscopic or surgical therapy, or nerve block) fail to relieve pain. This makes treating pain in these patients very difficult. Pain patterns are variable in character, severity, and temporal evolution.

Using the World Health Organization pain relief “ladder” is a reasonable approach to pain management in chronic pancreatitis, as there is no specific analgesic contraindicated in chronic pancreatitis.<sup>26</sup> Pain is, unfortunately, difficult to eliminate; a multidisciplinary approach that involves the patient and pain management team may help establish shared goals and expectations regarding pain relief.

Several adjunctive agents are frequently utilised, including selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), or gabapentoids.<sup>24,27</sup> Of these, only pregabalin has been directly studied in patients with chronic pancreatitis by randomised controlled trial. Of 64 enrolled patients, the pregabalin treated group exhibited a 36% pain reduction score at 3 weeks compared with placebo group, which reported a 24% pain reduction score.<sup>27</sup> These adjunctive agents may be used alone, but are commonly used in conjunction with analgesics.

Abstinence from alcohol and smoking cessation slow the progression of chronic pancreatitis and reduce the risk of malignancy, with unpredictable but generally positive effects on pain.<sup>28</sup>

Although a low fat diet is frequently recommended, randomised studies have not been performed to provide an evidence base for this intervention, and adequate nutrition is very important to avoid loss of muscle mass or vitamin deficiency. Pancreatic enzyme supplementation is used to treat maldigestion and has been studied in several very small randomised controlled trials, but might also have some benefit for pain relief.<sup>1,22,29</sup>

Coeliac plexus blockade (either computed tomography-guided or by EUS) with injection of an anaesthetic and a steroid into the coeliac plexus is largely ineffective for pain relief in chronic pancreatitis.<sup>18</sup> Pancreatic duct dilation and strictures are often the consequence of chronic pancreatitis and not the cause of ongoing pain. Some patients may be candidates for endoscopic (stenting or stone removal) or surgical treatment (drainage of pancreatic duct or resection), particularly those with a dilated pancreatic duct and a pancreatic ductal stricture or stone.

## Monitor for and manage malabsorption (exocrine insufficiency)

Pancreatic enzyme insufficiency (PEI) leads to maldigestion of carbohydrates, proteins, and fat, and occurs on average 10-15 years after diagnosis of chronic pancreatitis. Fat maldigestion is most common and most severe, and has nutritional consequences. Steatorrhea develops when more than 90% of the enzyme output is lost, and can also occur when there is a blockage of the pancreatic duct, preventing the enzymes from

reaching the duodenum. Malabsorption of fat soluble vitamins (A, D, E, and K) is frequent,<sup>30</sup> while osteopenia or osteoporosis are found in two thirds of patients with PEI.<sup>31</sup> Indirect evidence of PEI includes the clinical features noted above, along with measurement of faecal elastase (<200 ug/g stool=mild PEI and <100 ug/g stool=severe PEI) or serum trypsin (levels below 20 ng/mL are also suggestive of PEI). The use of breath tests to document PEI is promising, but these remain largely unavailable.<sup>32</sup>

A diagnosis of chronic pancreatitis should prompt measurement of baseline levels of fat soluble vitamins and bone density, with subsequent testing based on the initial results. Patients should receive routine supplementation with vitamin D and calcium.<sup>33</sup>

Treatment of PEI involves pancreatic enzyme replacement therapy (PERT). The aim of PERT is to achieve sufficient concentration of pancreatic enzymes in the duodenal lumen for digestion. In general, 10% of this amount is needed to correct steatorrhea. There is often some residual pancreatic secretion, so an appropriate dose for adults is a dose of at least 40 000-50 000 USP lipase units/meal (half dose for snacks), but this dose often needs to be increased based on response.<sup>1,18</sup> The normal pancreas produces at least 900 000 USP units of lipase per meal.<sup>34</sup> Pancreatic enzyme replacement products are comprised of porcine pancreatic extracts of lipase, amylase, and proteases (table 1). The capsules or tablets should be taken with the meal. In patients on the non-enteric coated preparation, it is necessary to co-administer an acid suppressant to prevent acid inactivation of lipase. In some patients on an enteric coated preparation, adding an acid suppressing agent can improve effectiveness.<sup>35</sup>

Response is measured by assessing steatorrhea, weight gain, and fat soluble vitamin levels (A, D, E, K). If the response is poor, the most likely explanation is inadequate dosage (prescribed by the clinician or taken by the patient). If the response remains poor despite dose escalation, look for other causes of malabsorption (such as coeliac disease or small bowel bacterial overgrowth).

## Monitor for and manage secondary diabetes (endocrine insufficiency)

Some patients develop secondary diabetes. Pancreatogenic diabetes (also termed type 3c diabetes) can be caused by chronic pancreatitis, pancreatic resection, or pancreatic cancer.<sup>36</sup> It is characterised by loss of the  $\beta$ -cells, leading to impaired insulin secretion and the loss of counter-regulatory hormones (eg, glucagon). Patients may have a brittle diabetes, may be malnourished with unpredictable dietary intake, and are at particular risk of treatment induced hypoglycaemia. Diagnosis of type 3c diabetes is the same as for type 1 or 2 diabetes, using HbA1c fasting glucose measurement or glucose tolerance testing. Expert guidance suggests screening patients with chronic pancreatitis annually for development of diabetes with fasting glucose measurement or HbA1c testing.<sup>36</sup>

Management of patients with type 3c diabetes is challenging, and patients may benefit from formal nutritional counselling and consultation with an endocrine specialist. Therapy may be effective with oral agents, but insulin is needed in most patients. Additionally, optimal management of PEI with PERT is crucial in providing predictable absorption in patients with type 3c diabetes.<sup>37</sup>

## Other complications

Patients with chronic pancreatitis can develop obstruction of the duodenum or bile duct, producing gastric outlet obstruction or jaundice. Importantly, these features may indicate the

presence of a secondary pancreatic cancer (see below). Obstruction of a nearby vascular structure—the splenic vein or portal vein—can produce gastric or oesophageal varices, and may be complicated by gastrointestinal bleeding.

## Risk for pancreatic cancer

Patients with chronic pancreatitis are at increased risk of pancreatic malignancy.<sup>3,38</sup> Overall, patients with chronic pancreatitis have a relative risk of 13 for the development of pancreatic cancer<sup>39,40</sup>; those with genetic forms of pancreatitis (hereditary pancreatitis) and those who smoke or drink to excess are at particular risk.<sup>3,39</sup> There are no general recommendations for surveillance in these patients. Patients with chronic pancreatitis who develop a change in their symptoms—weight loss, protracted abdominal pain, or functional decline—should be evaluated for secondary pancreatic cancer (with serum measurements of CA19-9, computed tomography, and/or EUS, for example). Consider underlying pancreatic cancer especially in an older lean patient with new-onset diabetes, typically without a family history of diabetes.<sup>38</sup> Pancreatic cancer may sometimes be mistaken for chronic pancreatitis. No specific biomarkers or clinical features allow secondary pancreatic cancer to be identified, so clinical recognition of new or worrisome symptoms is critical.

## What treatments can we expect in future?

Current treatments in chronic pancreatitis are limited to supportive and palliative care. Patients with advanced disease are managed with endoscopic or surgical methods.

## Medicines

Drugs that can stop the death of pancreatic cells when they are exposed to bile acids are currently being studied. Natural products such as polyphenols, curcumin, and vitamin A are also being studied for their antioxidant, anti-inflammatory, and anti-fibrotic properties.

## Gene therapy

Therapy targeting pancreatic fibrosis is being evaluated to potentially alter the course of chronic pancreatitis. However, because of the nature of the disease, long term outcomes are still not clear.

### How patients were involved in the creation of this article:

A patient with chronic pancreatitis is a co-author of the paper, and suggested areas of emphasis such as effective management of pain and exocrine insufficiency. Patients who participate in a support forum through the National Pancreas Foundation provided additional comments for inclusion or emphasis, most commonly on pain and its negative effect on quality of life.

### Additional educational resources

Pancreas Foundation <https://pancreasfoundation.org/patient-information/chronic-pancreatitis/>  
 American Family Physician <https://www.aafp.org/afp/2018/0315/p385.html>  
 National Library of Medicine <https://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0022862/>

### Education into practice

- Can you give an overview of how chronic pancreatitis is diagnosed?
- How will you discuss pain management options with a patient with abdominal pain suspected to be pancreatic in origin?
- How will you monitor and manage pancreatic insufficiency?

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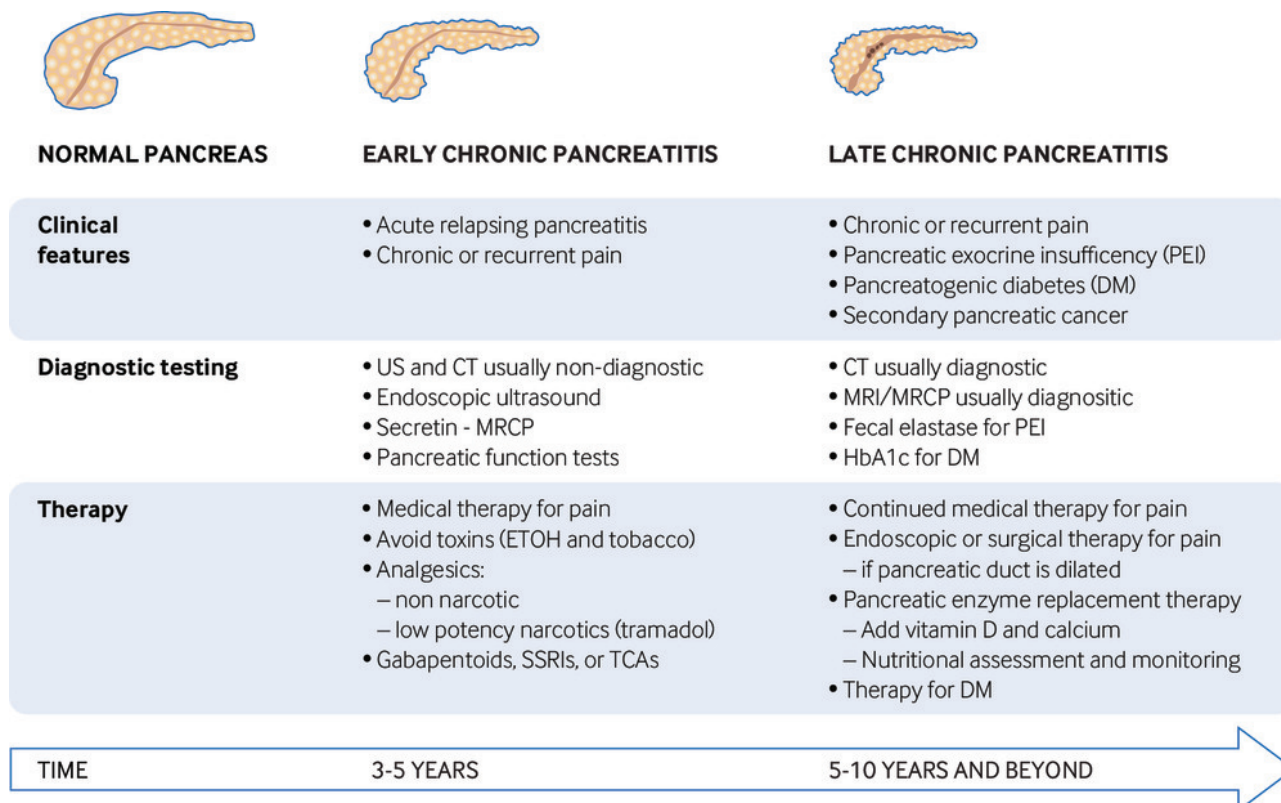
## Table

**Table 1 | Currently available enzyme products in the US and UK**

Product	Formulation	Country	Lipase content per capsule of pill (USP)
Zenpep	Enteric-coated porcine	US	3000, 5000, 10 000, 15 000, 20 000, 25 000, 40 000
Creon	Enteric-coated porcine	US and UK	3000, 6000, 10 000, 12 000, 24 000, 25 000, 36 000, 40 000
Pancreaze	Enteric-coated porcine	US	2600, 4200, 10 500, 16 800, 21 000
Viokace	Non-enteric coated tablet	US	10 440, 20 880
Pertzye	Enteric-coated porcine with bicarbonate	US	4000, 8000, 16 000
Nutrizym <sup>25</sup>	Enteric-coated porcine	UK	22 000
Pancrease HL	Enteric-coated porcine	UK	25 000

\* The 10 000 and 25 000 strength dosages of Creon are available only in the UK. US dosages are 3000, 6000, 12 000, 24 000, 36 000, and 40 000

## Figure



**Fig 1** The typical natural history and timeline of chronic pancreatitis, with associated diagnostic testing and therapeutic options. US: ultrasonography. CT: computed tomography. MRCP: magnetic resonance cholangiopancreatography. SSRI: Selective serotonin reuptake inhibitors. TCI: tricyclic antidepressant. DM: diabetes mellitus