Treatment options for chronic pancreatitis

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Abstract | This Review covers the latest developments in the treatment options for chronic pancreatitis. Pain is the most frequent and dominant symptom in patients with chronic pancreatitis, which ranges from severe disabling continuous pain to mild pain attacks and pain-free periods. Conventional treatment strategies and recent changes in the treatment of pain in patients with chronic pancreatitis are outlined. The different treatment options for pain consist of medical therapy, endoscopy or surgery. Their related merits and drawbacks are discussed. Finally, novel insights in the field of genetics and microbiota are summarized, and future perspectives are discussed.

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Introduction

Chronic pancreatitis is an inflammatory condition of the pancreas, in which development of fibrosis and loss of pancreatic parenchyma potentially leads to impaired endocrine and exocrine pancreatic function. The most frequent causal factor for developing chronic pancreatitis is alcohol, with less frequent causes being idiopathic, genetic predisposition, and autoimmunity.[1] Pain is the most frequent and dominant symptom and has a highly variable clinical presentation, differing in chronicity and severity.[2] Pain ranges from severe disabling continuous pain to mild pain attacks in between pain free periods.[3] The pathogenesis of pain in chronic pancreatitis is multifactorial and includes intra-pancreatic hypertension and ischaemia and neurogenic alterations of the pancreatic nerves or can be related to stenosis of the common bile duct or duodenum.[4–6] The goals of treatment of chronic pancreatitis can roughly be divided into three categories: pain management, management and prevention of complications of pancreatitis (for example pseudocysts, fistulae, duodenal or biliary obstruction, pancreatic ascites, splenic vein thrombosis, and pseudoaneurysms), and correction of pancreatic insufficiency (for example fat malabsorption and diabetes). In this Review, we provide an overview focused on the different treatment modalities of pain related to chronic pancreatitis.

Conventional concepts of pain therapy

Currently, no evidence-based protocols exist for the treatment of pain in patients with chronic pancreatitis. Owing to the complexity of the disease to enable optimal tailored treatment of patients with chronic pancreatitis, it is important to assess clinical data (for example, pain symptoms and risk factors), pancreatic function (endocrine and exocrine) and imaging data (for example, enlarged pancreatic head, ductal dilatation and local complications). A conservative step-wise treatment is advocated, starting with medical treatment (such as opioid analgesics) of the pain symptoms, followed by endoscopic or surgical therapy when feasible if morphological abnormalities are present, such as ductal abnormalities.[7]

Competing interests
The authors declare no competing interests.

Medical treatment

Medical treatment starts with lifestyle and dietary advice and efforts to achieve alcohol and smoking cessation, which is suggested to mitigate disease progression.[8] Patients with exocrine pancreatic insufficiency can be treated with pancreatic enzyme replacement therapy (PERT). For optimal treatment the dose and timing of PERT should depend on the fat content of the meal. Doses of 25,000–75,000 U of lipase per meal and 10,000–25,000 U for snacks have been recommended.[9] When symptoms of exocrine insufficiency persist, use of gastric secretion inhibition by means of a PPI is recommended.[10] However, the role of PERT in reducing pain is debatable. 10 small trials have been conducted, but study design and patient selection are so diverse that the results of the studies cannot be pooled to draw conclusions.[11]

The majority of patients require pain medication, including nonopioid and opioid analgesics, with a risk that some patients will develop opioid addiction and opioid-induced hyperalgesia.[12–17] Nusrat *et al.*[18] performed a large retrospective cohort study of 219 patients with chronic pancreatitis. Slightly more than half of the patients ($n = 112$) had opioid prescriptions.[18] Addiction and hyperalgesia were not assessed in these patients. The study highlights how often patients with chronic pancreatitis use opioids.

Patients with hyperalgesia become more sensitive to certain pain stimuli, eventually resulting in an autonomous pain perception independent of peripheral pain input.[19] This concept is fairly new, supported by earlier findings of alterations and damage of the pancreatic nerves, altered peripheral and central pain processing and central nervous

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Key points

- The treatment goals of chronic pancreatitis can roughly be divided into pain management, prevention and management of complications and improvement of pancreatic insufficiency
- Surgery outperforms endoscopic treatment in late-stage obstructive chronic pancreatitis
- Discoveries over the past few years in the fields of genetics and the microbiome have broadened our understanding of the pathogenesis of chronic and recurrent acute pancreatitis

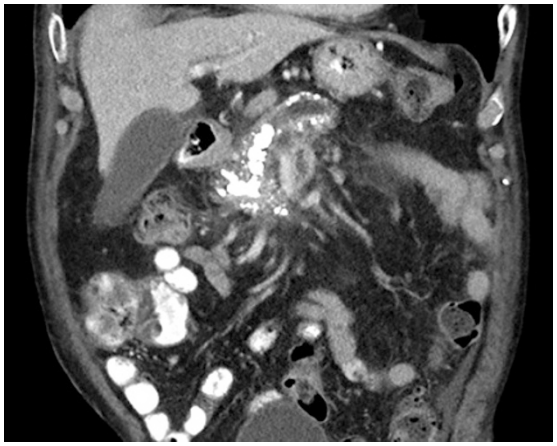

Figure 1 | Chronic pancreatitis. This CT image shows multiple calcifications in the head of the pancreas obstructing the main pancreatic duct, which is dilated.

system reorganization in patients with chronic pancreatitis.[20–22] These findings indicate that the pain processing in the nervous system of patients with chronic pancreatitis is abnormal, might be aggravated by use of opioid analgesics, and is similar to neuropathic pain disorders.[19,23] Pregabalin has been evaluated as an adjuvant analgesic in a randomized, double-blind, placebo-controlled trial in 64 patients with chronic pancreatitis with pain.[17] More effective pain relief was achieved after 3 weeks of treatment with pregabalin than placebo (36% versus 24%, $P = 0.02$). The findings of this study are certainly promising, but more research is needed to compare pregabalin with analgesics and/or interventional treatments.

Other medical options for pain management include antioxidant therapy. 10 randomized controlled trials have been conducted, in which many of the studies have small sample sizes and high drop-out rates. Overall, antioxidants might be effective in slowing the disease process and reducing pain in chronic pancreatitis, but the available data are not convincing.[24–27]

Endoscopic therapy for pain

Extracorporeal shock wave lithotripsy

Endoscopic therapy can be applied in different settings in the treatment of chronic pancreatitis, such as drainage of the pancreatic duct, treatment of biliary obstruction or pseudocyst drainage. The hypothesis of pancreatic duct drainage is that decompression of the duct will decrease intraductal pressure and thereby relieve pain. Extracorporeal shock wave lithotripsy (ESWL) can be applied in patients with large (>5 mm) and multiple (>4). stones. Usually ESWL is followed by stone extraction by endoscopic retrograde cholangiopancreatography (ERCP).[28] Pancreatic stones are found in 32–90% of patients with chronic pancreatitis and can cause outflow obstruction and dilation of the pancreatic duct (Figure 1).[29–31] After discussing the patient in a multidisciplinary team meeting, the clinical guideline of the European Society of Gastrointestinal Endoscopy (ESGE) recommends ESWL as a first-line therapy for patients with uncomplicated painful chronic pancreatitis and pancreatic (head) stones ≥5 mm obstructing the pancreatic duct, followed by endoscopic extraction of stone fragments.[32] Importantly, if no significant pain relief occurs after 6–8 weeks despite a technically successful treatment, the patient needs be re-discussed in a multidisciplinary team meeting and other treatments, including surgery, should be considered.

ESWL with endoscopic therapy achieves complete or partial pain relief in 48–91% of patients (follow-up of 6–77 months), a complete stone clearance rate of 39–76%, and a fragmentation rate of nearly 90%.[31,33–38] In the only randomized controlled trial comparing ESWL monotherapy ($n = 26$) with ESWL and endoscopic drainage ($n = 29$) in patients with obstructive chronic pancreatitis with calcifications, the intensity and number of pain relapses were comparable among groups after 2 years of follow-up (38% versus 45%, respectively OR 0.77; 95% CI 0.23 to 2.57).[39] Not surprisingly, the costs were three times higher in the ESWL plus endoscopy group ($P = 0.001$). Notably, in this study the patients were carefully selected, with 73–83% of the calcifications located at the pancreatic head; 42–69% reported pain symptoms at the time of study inclusion. ESWL treatment should only be carried out in centres with considerable experience and specialized equipment.[39]

Stenting

The aim of pancreatic duct stenting is to accomplish pain relief by primary drainage and dilatation of the pancreatic duct stricture to improve drainage after stent removal. Dilatation of the stricture alone might not be sufficient and at least one stent probably needs to be inserted across the stricture.[32] However, evidence-based guidelines for endoscopic treatment of the main pancreatic duct strictures (for example, sphincterotomy, dilatation and stenting) are lacking. About one-third of patients with obstructive chronic pancreatitis have pancreatic duct stones and strictures, and ~50% have pancreatic duct strictures without stones.[31] The technical success of pancreatic duct stenting varies between 85% and 98% long-term pain relief is experienced by 52–90% of patients after a follow-up of 14–69 months.[40–45] Costamagna *et al.*[46] applied multiple pancreatic stents for pancreatic duct strictures in patients with chronic pancreatitis: in a prospective study of 19 patients with pancreatic duct stricture in the pancreatic head with previous single stent therapy, a median of three simultaneous stents were inserted for a mean period of 7 months per stent. After stent removal, 84% of the patients were asymptomatic, 10.5% had stricture recurrence and one patient (5.5%) had persistent stricture after

a follow-up of 38 months. Self-expendable metal stents have been used, but so far with unsatisfactory results because of frequent stent dysfunction.[47,48]

Surgical therapy for pain

Different surgical procedures are available for the treatment of chronic pancreatitis. Selection is usually on the basis of the presence of morphological features of the pancreas and surrounding organs (for example, presence of an inflammatory mass, dilatation of the pancreatic duct or strictures of the common bile duct or duodenum) or experience of the surgeons.

Drainage

The longitudinal pancreaticojejunostomy (according to the Partington–Rochelle technique) is the most common treatment in patients with a dilated pancreatic duct (≥5 mm) and no enlarged pancreatic head (Figure 1).[49] A pancreaticojejunostomy has low morbidity (21%) and mortality rates (<1%), and immediate and lasting pain relief is reported in 80% (range 42–100%) of patients with a follow-up of 62 months (range 15–110).[50,51] In this procedure the pancreatic duct is opened from the pancreatic tail to the head along the anterior surface, as close to the duodenum as feasible. The open pancreatic duct is overlaid with a Roux-en-Y jejunal limb side-to-side to the pancreas. This procedure involves no resection of pancreatic parenchyma, which is important for the preservation of pancreatic function.[52]

Combined drainage and resection

For patients with an inflammed enlarged pancreatic head and a dilated pancreatic duct, a combined procedure of drainage and local resection of the inflamed tissue can be an effective treatment. Different variants of this technique have been compared head-to-head in randomized studies with comparable results for pain relief and quality of life.[53–55] The Frey procedure comprises a side-to-side pancreaticojejunostomy that incorporates a cored-out pancreatic head. The Beger procedure involves a complete resection of the pancreatic head (duodenum preserving) with an end-to-end pancreaticojejunostomy. The Berne and Izbicki procedures are modifications of the Frey and Beger procedures, with the principle idea to preserve as much pancreatic tissue as possible. The Berne procedure involves a local pancreatic head resection, without full transaction of the pancreas and without pancreaticojejunostomy; the reported mortality rate for this procedure is 0–1% and the morbidity rate is 16–23%.[55,56] Two randomized controlled trials have shown that the Berne procedure results in a shorter hospital stay and shorter operation time than the pylorus-preserving pancreaticoduodenectomy (PPPD; discussed later) and the Beger procedure in patients with chronic pancreatitis.[57,58] One of these trials demonstrated that the Berne procedure results in similar pain relief as the PPPD (85% versus 90% of patients, respectively; no *P* value was reported, but we calculated a *P* value of 0.63), and the other performed no head-to-head comparison with respect to pain relief.[57,58] The Izbicki modification involves a longitudinal V-shaped excision of the ventral aspect of the pancreas combined with a longitudinal pancreaticojejunostomy.[59] In a non-comparative series of 41 patients, long-term results show 0% mortality, ~20% perioperative morbidity, 43% newly developed endocrine insufficiency, 22% newly developed exocrine insufficiency, and 73% complete pain relief after a median follow-up of 83 months.[60]

The Frey and Beger procedures have been evaluated in several randomized trials.[61,62] Although both procedures have similar results in terms of pain relief, pancreatic endocrine and exocrine insufficiency and quality of life, the Frey procedure is associated with a lower postoperative morbidity rate than the Beger procedure.[61,62] This lower morbidity rate for the Frey procedure has been explained by the technically more demanding anastomoses that are part of the Beger procedure.[63] Izbicki *et al.*[64] randomly allocated 42 patients with chronic pancreatitis with an enlarged pancreatic head to either a Beger ($n = 20$) or a Frey procedure ($n = 22$) after a mean follow-up of 1.5 years. The Beger procedure is accompanied by 20% morbidity, whereas the Frey procedure has a significantly lower morbidity rate (9%).[64] In 2005, the long-term results of these 42 patients, plus 32 more patients (total of 74 patients) with a median follow-up of 104 months were reported.[65] No significant differences between the groups with regard to pain scores, global quality of life, late mortality, and pancreatic exocrine and endocrine insufficiency were found. Nowadays, the choice between either procedure depends largely on the surgeon's experience. Some surgeons have proposed the Frey procedure as the primary operation of choice because it is technically less demanding and easier to perform (especially when portal hypertension and inflammation make division of the neck of the pancreas difficult), has a reduced operation time (by 55 min), and has a low incidence of pancreatic anastomosis leakage.[63,66]

Resection

Pancreaticoduodenectomy and the pylorus-preserving variant (PPPD) provide long-term pain relief in 75–95% of patients, with a mortality rate <5% but a high complication rate of 20–40%.[66,67] A systematic review and meta-analysis of four randomized controlled trials comparing combined drainage/resection techniques with pancreaticoduodenectomy or PPPD for treatment of chronic pancreatitis demonstrated that the Frey procedure resulted in a higher quality of life and less exocrine pancreatic function impairment than pancreaticoduodenectomy.[67] In particular, the Frey procedure showed a significant reduction of operating time, delayed gastric emptying, and duration of hospital stay.[61,62,67–69] A meta-analysis of 15 studies has compared the pancreaticoduodenectomy with the Frey (seven retrospective studies) and the Beger procedures (eight retrospective studies). Quality of life, pancreatic exocrine function and delayed gastric emptying were better with the Frey and Beger procedures than with Pancreaticoduodenectomy.[70] The Beger procedure shows more postoperative pain relief compared with pancreaticoduodenectomy, whereas the Frey procedure has a better outcome in postoperative morbidity compared with pancreaticoduodenectomy and Beger procedures.

Table 1 | Most common genetic variants in recurrent acute pancreatitis and chronic pancreatitis

Gene	Product	Mutation(s)	Possible effects
Trypsin dependent			
PRSS1	Trypsinogen	p.R122H/p.R122C p.N29I/p.N29T p.D19A/p.D22G/p.K23R p.A16V p.E79K	Inhibits autolysis and increased auto-activation Increased stability and an enhanced auto-activation Enhanced auto-activation Accelerate trypsinogen activation Increased trypsinogen activation by transactivation of PRSS2
PRSS1	Trypsinogen	p.A121T	Increased trypsin cleavage rate
SPINK1	Trypsin inhibitor	p.N34S/p.N55S p.R65Q/p.D50E p.Y54H/p.R67C p.G48E	A complete or nearly loss-of-function of the SPINK1 protein; the mutations probably lower the threshold for developing pancreatitis from other genetic factors (for example, *CFTR*)
CTRC	Chymo-trypsinogen C	p.A73T/p.I64LfsX69	Reduces CTRC secretion and causes a near complete loss-of-function (the enzyme destroys prematurely activated trypsin)
CASR	Calcium-sensing receptor	R990G	Intracellular calcium dysregulation and recurrent trypsin activation or failed inhibition; in association with SPINK1 and CFTR variants effects duct cell function
CFTR	Transmembrane conductance regulator	F508-del R75Q	The manifestation of disease depends on the severity of the mutation and homo/heterozygosity; for example homozygotes (F508-del) have classic manifestations of cystic fibrosis and often develop chronic pancreatitis early in life, compared with heterozygotes (carriers) who have an increased risk for pancreatitis of 3–4-fold over the general population
Trypsin independent			
CLDN2	Claudin-2	rs12688220 C	Mechanism is independent of trypsin activation; more strongly associated with (alcoholic) chronic pancreatitis than recurrent acute pancreatitis (probably acts as a disease modifier)
CPA1	Carboxy-peptidase A1	MIM114850 (gene code)	Misfolding of the mutated peptides, causing stress inside of the endoplasmic reticulum; especially prevalent in paediatric idiopathic chronic pancreatitis
Protective variants against pancreatitis			
PRSS2	Trypsinogen	G191R	Mitigates trypsin activity and thereby protects against chronic pancreatitis
PRSS1-PRSS2	noncoding region PRSS1–PRSS2 locus	rs10273639T	Reduces expression of PRSS1; reduces the risk of pancreatitis

The review includes no head-to-head comparison of the Frey and Beger procedures.[70]

A distal pancreatectomy can be performed in patients with disease limited to the pancreatic tail and has a reported hospital mortality of 0–3.8% and a morbidity of 15–31%.[71,72] The results for pain relief after distal pancreatectomy differ in the literature between 57% and 90%.[73,74] Total pancreatectomy in combination with islet autotransplantation is rarely performed in patients with pain symptoms.[75] This operation has been considered a last resort for patients who have failed to respond to previous surgical therapies.[10] Alexakis *et al.*[76] reported complete pain relief in 81% of patients after a median follow-up of 8.5 months in 19 patients with chronic pancreatitis.[76] By contrast, a study that included >400 patients showed that 2 years after this major procedure 23% of patients had a similar pain score as before the procedure and 40% of patients were still using opioid analgesics.[77] A specific subset of patients with chronic pancreatitis and refractory pain despite maximal medical and endoscopic treatment and after other types of surgery for CP might benefit most from this procedure.

Celiac plexus block and splanchnicectomy

A less invasive treatment than resection is thoracoscopic splanchnicectomy and endoscopic ultrasonography or percutaneous celiac plexus blockade. Thoracoscopic splanchnicectomy is only performed rarely for patients with severe pain who have failed previous medical, endoscopic and surgical interventions. This procedure has a reported good short-term pain relief, with worsened outcome over time; the median success rate is 62% (free of opioids or significant pain reduction).[78,79] The celiac plexus blockade results in short-term pain relief in 50–60% of patients (often for several weeks to months), but with worsened outcome in the long term.[80] Endoscopic ultrasonography has become the favoured approach after two randomized trials demonstrated that the endoscopic-ultrasonography-guided approach was superior to CT guided celiac plexus block in terms of duration of pain relief.[81,82] These minimally invasive treatments are sometimes applied if all other therapies have failed.

Novel insights

Breakthroughs in genetics

Over the past few years, breakthroughs in the field of genetic variations have broadened our understanding of the pathogenesis of recurrent acute pancreatitis and chronic pancreatitis. Table 1 summarizes the identified more common genetic variants that are important to disease pathogenesis. Several genetic factors of rare

gain-of-function and loss-of-function mutations associated with chronic pancreatitis indicate an important role for trypsinogen expression, and its activation and degradation within the pancreas (for example mutations in *PRSS1*, *PRSS2*, *SPINK1*, *CFTR*, *CTRC*, *CASR*).[83,84] The central role of trypsinogen in the pathogenesis of chronic pancreatitis was confirmed in a genome-wide association study; a gene locus encoding both PRSS1 and PRSS2 can alter expression of the trypsinogen gene and thereby affect the susceptibility to develop recurrent acute pancreatitis and chronic pancreatitis.[85] However, genetic variations other than in the trypsinogen pathway have also been discovered. For example, an increase in risk of developing chronic pancreatitis was described through loss-of-function variations of the *CPA1* gene (which encodes carboxypeptidase A1) in patients not consuming excessive amounts of alcohol.[86] Likewise, a variant at the *CLDN2* locus (encodes claudin-2) has been strongly associated with chronic pancreatitis, and is thought to accelerate the progression from acute pancreatitis to chronic pancreatitis, particularly in patients with alcoholism.[87] This finding is important, given that about 15–20% of patients with acute pancreatitis develop chronic pancreatitis, especially when alcoholism seems to be the cause of the acute pancreatitis.[88] Furthermore, we now know that so called 'complex gene' mutations alone, such as mutations in *CTRC* and *CASR*, are not sufficient to cause recurrent acute pancreatitis or chronic pancreatitis. To increase the risk of developing recurrent acute pancreatitis or chronic pancreatitis a combination with mutations in *PRSS1*, *CFTR* or *SPINK1* is required.[89]

The microbiome

Notably, assessing microbiome composition is of increasing importance in unravelling the role of bacteria in disease development.[90,91] In pancreatic diseases, particular changes in (salivary) flora composition are associated with chronic pancreatitis and pancreatic cancer; these changes could act as a noninvasive biomarker in the future.[91] More research in the field of microbiomes and next-generation sequencing are needed to investigate the role that these and other potential risk factors (for example, gamma-glutamyltransferase 1 gene) have in the pathogenesis of chronic pancreatitis and might provide new targets for diagnosis and treatment.

Smoking

Genetic variations should always be considered in the context of other important environmental factors that have a major contribution to disease development and progression, such as alcohol consumption and tobacco smoking. Although smoking has been a known risk factor for chronic pancreatitis for more than three decades, in the past 5 years it has gained proper attention as an important contributing factor in the pathogenesis, development and progression of chronic pancreatitis.[92–94] Several studies have shown that smoking cigarettes doubles the risk of developing chronic pancreatitis compared with non-smokers, with an even stronger association in patients who also drink alcohol.[92,93] A large multicentre cohort study strengthens the evidence of smoking as a strong, independent and dose-dependent risk factor for chronic pancreatitis.[93] These findings are in line with studies from Denmark and a meta-analysis from Italy including 12 studies of >1,500 patients with chronic pancreatitis.[92,94] The results of the meta-analysis confirmed the dose-dependent effect of tobacco use for developing chronic pancreatitis: a pooled RR of 3.3 (95% CI 1.4–7.9) for smokers of one or more packs per day was reported compared with an RR of 2.4 (95% CI 0.9–6.6) for patients who smoked less than one pack per day. In addition, the authors showed that smoking cessation is helpful, as the risk in current smokers was higher than in former smokers, with pooled RR estimates of 2.8 (95% CI 1.8–4.2) and 1.4 (95% CI 1.1–1.9), respectively.[92] Smoking is also associated with an earlier diagnosis of chronic pancreatitis than non-smoking (~5 years), leading to an increased risk of developing calcifications and endocrine insufficiency.[95] Unfortunately, the mechanisms behind the pancreatic injury or how it influences the progression of the pancreatic inflammatory process are still poorly understood. Experimental studies show that cigarette smoke leads to or enhances fibrosis of pancreatic acinar cells (probably via reactive oxygen species), with an upregulation of trypsinogen and chymotrypsinogen genes. Nicotine causes further cellular injury as it results in high levels of intracellular calcium.[96–98] Similar to alcohol, smoking is an important risk factor in the development and progression to chronic pancreatitis, but is often underestimated by physicians and patients. Physicians should educate and counsel their patients to stop smoking as they do with alcohol consumption. Lifestyle advice is an important part of the treatment.

Risk of pancreatic cancer

A significant association exists between smoking and pancreatic cancer, with a 2–3 fold increased risk of pancreatic cancer for patients who smoke.[99] The cumulative risk of pancreatic cancer in patients with chronic pancreatitis after 10 years and 20 years is 2% and 4%, respectively.[100,101] Raimondi *et al.*[102] found an increased RR of developing pancreatic cancer of 5.1 in patients with unspecified pancreatitis, 13.3 in patients with chronic pancreatitis and 69.0 for patients with hereditary pancreatitis in a meta-analysis that included 22 studies.[102] Patients with hereditary pancreatitis have a high cumulative lifetime risk of developing pancreatic cancer of 40–55%.[103,104] Besides smoking, obesity and dietary factors (such as high intake of red meat) are associated with an increased risk of pancreatic cancer.[105–107] These environmental factors are important for future research—especially in combination with the rapidly developing field of next generation DNA sequencing, gut and oral microbiota analyses and microRNA testing—for creating more reliable screening tools to determine the subgroup of patients with chronic pancreatitis at high risk of developing pancreatic cancer.[91,108] In conclusion, patients with chronic pancreatitis have a small but increased risk of developing pancreatic cancer. Screening of patients with chronic pancreatitis for pancreatic cancer cannot be recommended yet, as cost-effectiveness data of surveillance are lacking.

Surgery outperforms endoscopic therapy

Two randomized trials have compared endoscopy with surgery in patients with late-stage chronic pancreatitis.[109,110] In both trials complete and partial pain relief was seen more frequently after surgery than after endoscopic treatment after 5–6 years of follow-up. A Cochrane review of endoscopic or surgical intervention for painful chronic pancreatitis pooled the data of both randomized trials (111 patients).[111] A higher proportion of patients in the surgical group achieved pain relief than in the endoscopic group (partial or complete pain relief: RR 1.62, CI 1.11–2.37; complete pain relief: RR 2.45, CI 1.18–5.09).

In the randomized trial by Dite *et al.*[109] surgery was superior to endoscopic therapy in terms of complete pain relief (34% versus 15%) after 5 years of follow-up in 72 patients with advanced chronic pancreatitis.[109] This trial was the first randomized trial to compare these procedures, but the results should be interpreted with caution. The endoscopic therapy was suboptimal, as ESWL and cumulative stenting was not applied. In the surgical group, different procedures were performed including drainage, resection and combined approaches altogether. Most of the patients in this study underwent a resection procedure. The trial by Cahen *et al.*[40] included 39 patients with advanced chronic pancreatitis with a follow-up of 79 months. Patients undergoing surgery had a higher rate of complete or partial pain relief, and required fewer procedures than patients undergoing endoscopic treatment. Furthermore, about half of the patients in the endoscopic group still needed surgery during follow-up. Quality of life, pancreatic function, hospital stay and costs are comparable between endoscopic and surgical treatment.[28,110,112]

Future perspectives

Early intervention

Currently, a conservative step-up approach is used for the treatment of chronic pancreatitis. Although conservative medical treatment might reduce symptoms in some patients, it does little to influence the progression of disease and symptoms in the long run. Besides smoking and alcohol cessation, various studies suggest that surgical intervention early in the disease process might mitigate disease progression, reduce pain symptoms more adequately than the conservative approach and slow down deterioration of pancreatic function in patients with chronic pancreatitis.[42,74,113–118] Different animal studies show better morphological features and pancreatic exocrine function when early surgical drainage is performed versus late drainage.[116] Various clinical cohort studies reported stabilization and postponement of both endocrine and exocrine insufficiency after surgical drainage procedures.[52,117,118] Furthermore, in a small randomized trial of 17 patients with chronic pancreatitis and dilated pancreatic duct and pain, patients who underwent early surgical intervention had markedly better pain relief as well as endocrine and exocrine pancreatic function compared with the conservatively treated group.[52]

The timing of intervention remains a dilemma for those involved in the treatment of patients with chronic pancreatitis. A large multicentre randomized trial is currently being conducted within the Dutch Pancreatitis Study Group: the ESCAPE trial (Early Surgery versus Optimal Current Step-Up Practice for Chronic Pancreatitis trial; ISRCTN45877994).[119] The ESCAPE trial will help to answer the question of whether early surgical intervention for chronic pancreatitis improves pain control and pancreatic function compared with the current step-up practice of medical, endoscopic and finally surgical treatment in patients with chronic pancreatitis.[119]

Need for evidence-based medicine

Although surgical drainage procedures have been shown to be more effective than endoscopic drainage procedures in patients with late-stage obstructive chronic pancreatitis, no consensus exists for the indications and timing of endoscopic or surgical intervention among gastroenterologists and surgeons. The treatment of chronic pancreatitis is for the most part still based on local expertise, beliefs and disbeliefs and not on evidence-based medicine principles. Furthermore, it tends to be country, intraspeciality and interspecialty dependent. Some physicians believe that endoscopic therapy in chronic pancreatitis should always be applied before surgical treatment in obstructive chronic pancreatitis;[120] whereas others believe that surgical drainage is more effective than endoscopic treatment in patients with obstruction of the pancreatic duct due to chronic pancreatitis as shown in two randomized controlled trials and should be the treatment of choice in these patients.[110,111,120] It is important that patients with complex cases should be treated in expert centres by multidisciplinary teams.

It has been suggested that there are differences in type of surgery and even in morphology of the pancreas in patients with chronic pancreatitis between countries.[66] Keck *et al.*[66] compared pancreatic morphology and type of operation in 93 consecutive patients with chronic pancreatitis operated in Freiburg, Germany and Boston, USA. Notably, the patients in Germany had a larger pancreatic head (4.5 cm versus 2.6 cm), more gastric outlet obstruction symptoms (9 of 48 and 1 of 45, respectively) and more splenic or portal vein thrombosis compared with the patients in Boston. These finding might be because patients in Germany had a longer period of conservative therapy compared with the patients in the USA (median 56 months versus 26 months). In the Boston group, ~90% of the procedures were a pancreatoduodenectomy and in Freiburg a duodenum preserving pancreatic head resection (DPPHR) was performed in about half of the patients. These variances might reflect differences in reference between centres or differences in thoughts about timing and type of surgery; the authors also suggest that the morphology of chronic pancreatitis differs between continents.[66] Even between surgeons there are different beliefs regarding the different surgical procedures for the treatment of chronic pancreatitis, such as in the pancreaticojejunostomy and Frey and Beger procedures. For example, it has been suggested that drainage procedures, such as the pancreaticojejunostomy, do not solve the problem of ongoing inflammation and therefore

does not provide adequate long-term pain relief in most patients, whereas the DPPHR is able to provide pain relief because it removes the root of the problem, namely the pancreatic head.

Similar to studies in the field of pancreatic cancer showing an inverse relationship between hospital volume and treatment outcome, patients with chronic pancreatitis should also be treated in expert centres, with multidisciplinary expertise, available facilities and a dedicated team.[121] The decision of which procedure to choose should be based on evidence-based medicine and the surgeon's experience. In patients in whom endoscopic and surgical treatments have failed to alleviate symptoms of pain, a multidisciplinary approach with consultation of pain specialists and psychologists is critical.

Conclusions

Surgery outperforms endoscopic treatment in late stage obstructive chronic pancreatitis, and in long-term outcome. Patients should be treated in a multidisciplinary team in centres of excellence with expertise in medical, endoscopic and surgical treatment in chronic pancreatitis. Recent breakthroughs in the field of genetics have improved our knowledge of the aetiology and pathogenesis of chronic pancreatitis. These new findings should be combined with our knowledge on metabolic and environmental (risk) factors, to achieve the most effective treatment for patients with chronic pancreatitis.

Review criteria

For this Review on chronic pancreatitis, we searched the PubMed database using the terms "chronic pancreatitis" combined with "pain", "endoscopy", "ESWL", "surgery", "genetics", "smoking", "pancreatic carcinoma" and "timing". We selected full-text articles in English from the past 10 years but exceptions were made for older highly cited papers. We aimed to describe results of randomised controlled trials but other study types are referenced. In addition, reference lists of articles were manually searched.

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Author contributions

All authors contributed equally to all aspects of this manuscript.