Open Access

OBM Hepatology and Gastroenterology

LIDSEN Publishing Inc.

Review

Hereditary Pancreatitis – A Review of Current Concepts and Management

Daniel Hughes [1, †, *], Alex Gordon-Weeks [2, †], Michael A Silva [1, †]

1. Department of Hepato-Pancreato-Biliary Surgery, Oxford University Hospitals NHS Foundation Trust, Oxford, UK; E-Mails: hughesdaniel32@yahoo.com; mikesilva10@gmail.com
2. Nuffield Department of Surgical Sciences, University of Oxford, UK; E-Mail: alexgordonweeks@gmail.com

† These authors contributed equally to this work.

* **Correspondence:** Daniel Hughes; E-Mail: hughesdaniel32@yahoo.com

Academic Editor: Prashanth Rawla

Special Issue: Pancreatitis: New Insights into Etiology, Pathogenesis, Diagnosis, Management and Complications

OBM Hepatology and Gastroenterology
2019, volume 3, issue 3
doi:10.21926/obm.hg.1903028

Received: April 30, 2019
Accepted: July 15, 2019
Published: July 19, 2019

Abstract

Background: Hereditary Pancreatitis is a rare cause of acute pancreatitis. These patients usually present at a young age with recurrent episodes of acute pancreatitis that usually progresses to chronic pancreatitis with associated endocrine and exocrine failure. Hereditary pancreatitis also carries an increased lifetime risk of pancreatic adenocarcinoma. These high risk patients need early intervention where appropriate by specialist multidisciplinary teams and tailored long term management.

***Methods*:** A review of the relevant literature regarding the epidemiology, the genetic mechanisms responsible for the disease and current management strategies for Hereditary Pancreatitis was performed.

***Results*:** Several underlying genetic driver mutations for Hereditary Pancreatitis have been identified, notably PRSS1, SPINK1, CFTR and CRTC mutations. Recurrent episodes of pancreatitis result in a progressive loss of normal pancreatic parenchyma, which is

eventually replaced with non-functioning fibrosis. High rates of diabetes and exocrine insufficiency is observed in this cohort of patients. The cumulative yearly risk of developing pancreatic cancer in patients with hereditary pancreatitis is significantly higher than the general population. Current indications for genetic testing for hereditary pancreatitis is based on low levels of evidence. Total pancreatectomy and auto islet transplantation is a definitive management strategy for hereditary pancreatitis. Early intervention may serve as an opportunity to improve islet cell yield, successful engraftment and long term endocrine function.

***Conclusions*:** Hereditary Pancreatitis is associated with a significant morbidity, risk of chronic pancreatitis and pancreatic cancer. Through combining early diagnosis and intervention with a greater understanding of not only of the genetic mutation the individual carries but their own personal risk of disease progression, allows for a personalised treatment strategy for these patients.

Keywords

Hereditary pancreatitis; management; surgery; total pancreatectomy and auto islet transplantation; genetic testing

1. Introduction

Hereditary pancreatitis (HP) is uncommon [1]. HP can induce both multiple episodes of acute pancreatitis and chronic pancreatitis. The diagnosis of HP usually follows a protracted course and patients are at times inappropriately labelled as idiopathic pancreatitis.

When a patient presents with a first episode of pancreatitis or with recurrent pancreatitis, it is essential therefore that a thorough diagnostic work up is undertaken in an attempt to identify or rule out any preventable causes of the pancreatitis. This serves not only to potentially remove any cause for recurrent disease but it will also influence future management strategies. HP should be considered when there is a family history of pancreatitis or if there are recurrent episodes with no identifiable cause especially in younger patients. Genetic screening in these individuals should be performed to assess for driving mutations. Early identification is crucial as epidemiological based studies have demonstrated that HP often has an earlier disease onset in addition to the yearly accumulating risk of developing pancreatic ductal adenocarcinoma [1, 2]. A robust and comprehensive follow up protocol is required for these patients. This article serves as a clinical review regarding the current knowledge and management strategies for HP.

2. Clinical Presentation

HP usually manifests with frequent and recurrent episodes of pancreatitis, and is associated with a gradual loss of pancreatic parenchyma which is subsequently replaced with nonfunctioning fibrosis [3]. When compared to other causes of pancreatitis, HP is associated with much higher rates of diabetes and exocrine failure over time [1]. Published HP case series illustrate that exocrine failure is prevalent in up to 37% of patients and endocrine insufficiency in 32% [1, 3, 4].

3. Genetic Predisposition and Pattern of Inheritance

Hereditary pancreatitis often presents early in childhood. These patients are often diagnosed with their first episode of pancreatitis before 10 years of age [5, 6]. The inherited mutations in HP results in a disequilibrium between the secretion of the proteolytic protease enzymes and their regulatory inhibitor proteins. This imbalance causes an unopposed proteolytic enzyme activity which results in destructive autodigestion of the pancreatic parenchyma. HP is mostly inherited through an autosomal dominant pattern, however additional (rarer) patterns of inheritance have been described [7].

The most common germline mutation in patients with HP is within the PRSS1 gene which encodes for cationic trypsin [4, 8]. Following food stimulation, inactivate trypsin (trypsinogen) is activated by cationic trypsin, however in HP, premature activation within the pancreatic gland prior to excretion results in autodigestion. The PRSS1 gene has been thoroughly investigated and there are now 20 documented mutations of the gene that can cause HP [9, 10]. These mutations result in alterations to the cellular mechanism that govern the regulation of trypsin. There is either a loss of autolysis of trypsin as a regulatory mechanism that results in high levels of activated trypsin (as noted with the R122H mutation), or a gain in inappropriate activation of trypsin (as described in the N29I mutation) [11, 12]. The SPINK1 gene has also been linked with HP. SPINK1 encodes for a protein that negatively regulates the activation of protease enzymes. A mutation in the SPINK1 gene itself causes a global reduction in the availability of the inhibitor protein [13]. Evidence has since emerged that the mutation burden in the systemic disease that is cystic fibrosis can also cause HP [14]. The mutation in the cystic fibrosis transmembrane receptor (CFTR) causes an abnormally thick and viscus gastrointestinal tract secretion, as a consequence there is a failure in local mucocilliary clearance and a global reduction in the volume of pancreatic secretions [3]. The pH of the pancreatic duct becomes more acidic which results in precipitation of protein and subsequent ductal obstruction. There are in excess of 2,000 CFTR mutations reported in the literature [3]. The R75Q mutation variant of the CFTR is associated with a significantly higher risk of developing pancreatitis [15]. Recent genotyping of the CFTR gene through DNA sequencing has identified nine mutations that result in an impairment of bicarbonate conductance, whereby increasing the individual's risk of recurrent pancreatitis [16]. Another gene that has been described in the context of HP is the Chymotrypsin C (CTRC) gene[17]. This gene encodes a protease that disrupts and degrades both trypsinogen and trypsin, with mutation leading to reduced secretion [18]. Although a mutation in CTRC gene may not necessarily induce HP, its interaction with environmental factors (smoking, alcohol etc) or other mutated genes (CFTR or SPINK1) significantly increases the risk of HP [18].

4. Genetic Testing in HP

Alongside a better understanding of the genes implicated with HP, technological advances have made available rapid and cost effective genetic tests for its diagnosis. There is however a lack of robust data to guide clinicians as to who should undergo screening for HP in addition to the ethical implications involved with such a diagnosis.

Where there is sufficient clinical concern regarding the possibility of HP, a genetic screen should be considered in that individual to assess for the most common genetic mutations

predisposing to HP (notably PRSS1, SPINK1, CTRC and CFTR mutations). While there are no definitive guidelines with regard to whom to screen, there is an identifiable subgroup of high risk patients who may or may not have a family history where genetic screening is indicated (Figure 1) [19-21]. If genetic screening is to be undertaken this must also include suitable genetic counseling for the patient and family. [20]. Such a diagnosis can have a significant effect on an individual, especially in the context of future family planning [22]. The situation is less clear in the setting of screening for genetic mutations in asymptomatic individuals. Individuals with a family history of a PRSS1 mutation who are asymptomatic may request a genetic assessment only once they understand what information can or cannot be obtained [20]. From what is already known only a small proportion of patients with either a CFTR or a SPINK1 mutation will develop pancreatitis, therefore screening asymptomatic individuals where there is a family history of HP is not recommended. Screening of asymptomatic children too is not advocated either [20]. Identifying asymptotic children with a predisposing HP mutation at a young age does not deliver any medical advantage, in addition from an ethical stand point this deprives them from being able to make an autonomous decision whether they wish to pursue genetic screening when they are an adult [23]. This could also have an adverse effect on their psychosocial wellbeing [24]. However as our understanding of the genetic mechanism that drives HP increases, screening may translate into reliable risk prediction that can be utilised to tailor treatments specifically to each individual patient.

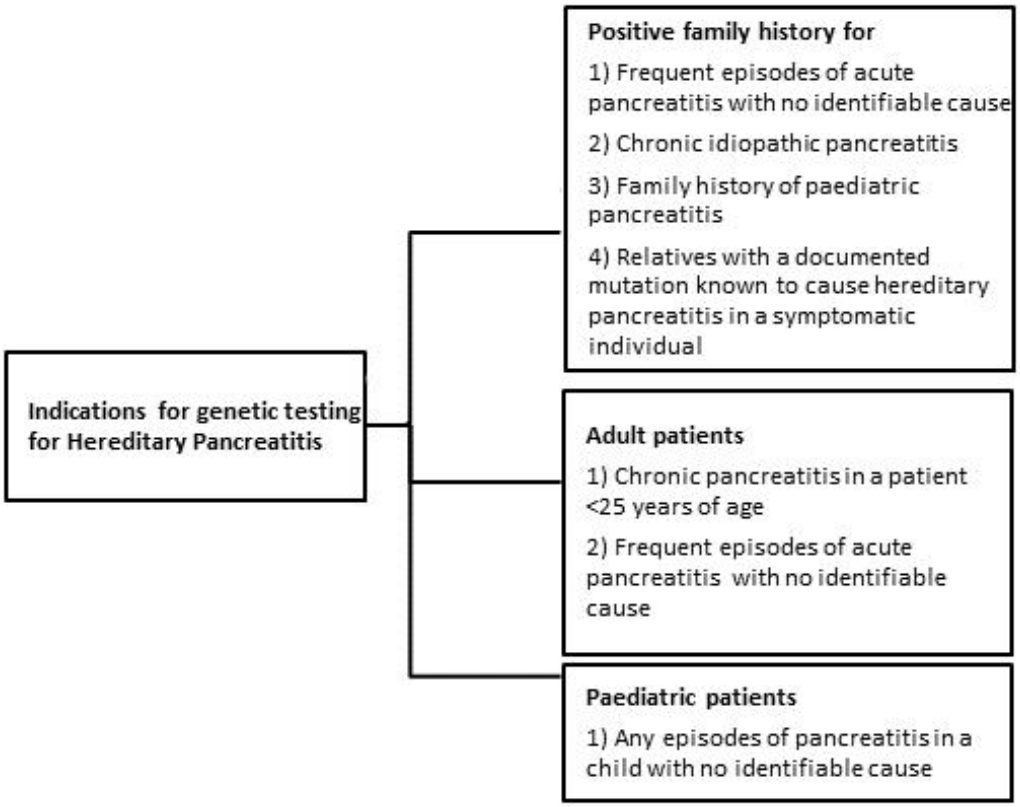

Figure 1 Clinical indications for performing genetic testing to identify hereditary pancreatitis [19, 20].

5. Hereditary Pancreatitis and Pancreatic Carcinogenesis: Genetic Predisposition or Inflammation Driven?

HP induces serial episodes of inflammation, which invariably results in gross structural and morphological changes throughout the gland. Healthy pancreatic parenchyma is replaced with non-functioning fibrosis. This cyclical injury results in irreversible loss of cellular function. Longitudinal population based studies clearly demonstrate higher incidence rates of pancreatic cancer in patients with HP compared to the general population [25]. A combination of factors is likely to be responsible. What is difficult to ascertain is whether the genetic mutations linked with HP are oncogenic drivers for sporadic cancer development or whether carcinogenesis is a result of recurrent inflammation.

Repeated and prolonged episodes of inflammation invariably causes DNA damage [26]. Injury repair mechanisms become compromised and there is a gradual accumulation of genetic mutations. Our understanding of the inflammatory cascade associated with carcinogenesis has significantly improved over the last decade. One of the main signalling pathways involved with pancreatic cancer development from pancreatic inflammation is the cyclooxygenase 2 (COX-2) signalling pathway [27, 28]. COX-2 induces prostaglandin synthesis, which in turn drives cell proliferation and cytokine mass production and release [29]. A clear correlation has been demonstrated between a poor prognosis and high levels of COX-2 [30, 31].

The abundance of cytokine release in HP may also contribute to cancer development. Tissue inflammation may up regulate pro inflammatory cytokines, notably Interlukin-6 (IL-6) [32]. IL-6 induces the development of pre-neoplastic lesions (pancreatic intraepithelial neoplasia) through activation of Stat3/Socs3 signalling [33]. Aberrant IL-6 signalling can induce an aggressive phenotype through activating GTPase signalling [34]. Tumour necrosis factor-α (TNF-α) is another inflammatory cytokine that enhances tumour growth though manipulating the tumour micro-environment [35]. Inflammatory cytokines not only initiates tumour development, but also influence the phenotype of the tumour. Over expression of the chemokine CXCL-12 promotes epithelial–mesenchymal transition, which promotes invasiveness and metastatic dissemination of pancreatic cancer [36]. Several different inflammation based signalling pathways have now been identified as being involved with cancer development in HP. However most to date do not have drug amenable targets. With further research and pharmacological intervention, it may be possible to prevent patients with HP from developing malignancy through manipulating the inflammatory response produced by HP and preventing the inflammation-carcinoma sequence.

6. Pancreatic Cancer Surveillance

It has previously been argued that routine screening of the general population for pancreatic cancer is not indicated [37]. This is based upon the fact that the overall lifetime risk of developing pancreatic cancer for the general population is low (approximately 1.3%), thus a screening programme would be inefficient [37]. However, the International Cancer of the Pancreas Screening (CAPS) Consortium has advocated that screening should be performed in high-risk individuals [37]. These high-risk individuals are defined as patients with a greater that 5% lifetime risk or five folds increased relative risk of developing pancreatic cancer [37]. Patients with HP fall within this cohort. The optimal screening regime is yet to be determined. Several different

surveillance protocols have been described, however the diagnostic yield varies significantly [38, 39]. Both Endoscopic Ultrasound and MRI are preferred radiological screening modalities, in light of the fact there is no radiation burden and higher sensitivity for pancreatic lesions [37]. ERCP currently has no role in disease screening due the associated pancreatitis risk [40]. The age at which screening should be commenced remains another controversial topic. It has been suggested that a starting age of 50 is recommended for patients with familial pancreatic cancer, where as a much younger age of 40 is suggested as a staring point for patients with HP carrying a PRSS1 gene mutation in light of the younger age of onset of pancreatic cancer [37]. An area of current interest is combining surveillance regimes to detect multiple cancers. It is well documented that mutations in BRCA1 and BRCA2 not only predisposes to breast cancer , but also to a range of other cancers including pancreatic cancer [41]. BRCA positive individuals represent another high risk patient cohort, the current recommendation for these patients is a yearly MRI should be performed for screening [42]. A recently published study clearly demonstrated the benefit of combining screening for pancreatic cancer and breast cancer in BRCA positive patients [43]. The authors' published a novel rapid screening MR protocol for this high-risk cohort [43]. The rapid screen MR was successfully completed in all patients in addition to achieving high quality images for analysis [43]. Pancreatic pathology was detected in 5 patients (one neuroendocrine tumour and 4 pancreatic cystic lesions) [43]. Further research is required to determine the optimal surveillance strategy for genetic syndromes that predispose to a number of cancers.

7. Management

There is no uniform management algorithm for patients with hereditary pancreatitis. Treatment strategies should be tailored to each individual, with emphasis on preventative measures where possible, management of acute episodes of pancreatitis in addition to strategies to reduce impact of the sequelae of recurrent inflammation. Recent advances in both surgical and endoscopic therapies have also broadened the treatment options for these patients.

8. Lifestyle Modifications

Patients with HP represent a sub set of patients who are inherently at higher risk of recurrent episodes of pancreatitis. The underlying genetic predisposition to inflammation is the fundamental driver of this risk. To date there is no gene based therapy to reduce this risk. However precautionary measures can be implemented in order to prevent patients from exposure to and also acquiring cumulative risk factors. Risk reduction can be achieved through lifestyle modifications. Smoking tobacco should be strictly avoided by patients with HP. Previous studies in the context of chronic alcoholic pancreatitis have shown that cigarette smoking rapidly accelerated the disease process with chronic pancreatitis diagnosed much earlier [44]. Additionally a recent meta-analysis demonstrated that smoking increases the risk of both acute and chronic pancreatitis [45]. Inhaled smoke also carried numerous carcinogens that are also associated with the development pancreatic cancer, as highlighted by a population based case-control study from the Netherlands, where smoking doubled the risk of pancreatic cancer [46]. Lowenfels, et al. undertook a review of patients with HP who were smokers (current and ex smokers). This study showed that HP patients who smoked developed pancreatic cancer 20 years earlier when compared to their non smoker counterparts [47].

Alcohol is a known etiological cause for pancreatitis and is of greater significance in HP [48]. It is well established that alcohol could trigger the onset of pancreatitis or a recurrence in patients with HP. Therefore it is paramount that HP patients are educated regarding this significant and avoidable risk. Other lifestyle measures such as a low fat and low protein diet may also help prevent the onset of pancreatitis [49]. Polypharmacy should be avoided in patients with HP. Extra care should be taken to ensure that common medications that are known to cause pancreatitis such as selective serotonin reuptake inhibitors and ACE inhibitors are avoided if possible. They should not be prescribed routinely without a structured evaluation of the intended benefits and potential risks in addition to involving the patient with this decision [50].

9. Endoscopic Management

As the disease progresses, the main pancreatic duct is often obstructed either secondary to stone impaction or inflammatory stricture. Obstruction of the main pancreatic duct in itself can also induce recurrent pancreatitis [51]. As the main pancreatic outflow channel is occluded, it is hypothesized that this induces ductal hypertension [52]. This initiates a cascade of events that decreases the blood supply to the acinar cells whereby propagating the inflammatory process and promoting further development of fibrosis [52]. Pancreatic duct decompression can be achieved with endoscopic intervention with stent placement to alleviate ductal obstruction [3]. This is an effective intervention that can significantly improve the chronic abdominal pain associated with recurrent pancreatitis. In patients with chronic pancreatitis and main duct stricture, stent placement achieves resolution of pain in 52%–95% of patients [3, 53-55]. In addition to achieving pain control, these studies also illustrated a reduction in pancreatitis related hospital admissions along with improved nutrition and reduction in the severity of exocrine failure [52]. Similar results of pain alleviation with endoscopic stenting of the main pancreatic duct have been reproduced in paediatric patients with recurrent pancreatitis. Li et al published their experience of endoscopic management of children with chronic pancreatitis [56]. They reported at that at a mean follow-up of 61 months, 64% of patients experienced complete relief of abdominal pain [56].

However, endoscopic therapy is not without complication. Reported rates of ERCP induced pancreatitis and duodenal perforation are 5%–10% and 1% respectively [55]. Stent related complications include occlusion and distal migration [36]. Stenting is also not a long-term solution for young patients presenting with HP. Therefore current recommended practice is to remove endoscopically-placed stents after a duration of stability. Stent insertion also carries a risk of infection and possible bacterial colonization of the pancreatic ductal system [57]. This poses a risk of post operative infective complications such as sepsis or liver abscesses if the patient was to later undergo a total pancreatectomy and autologous islet transplant [58]. The main limitation of stent decompression however is that upon removal of the stent, there is a possibility of a persistent stricture and recurrence of all the issues related to this [59]. Endoscopic stent placement is however an acceptable 'bridging therapy' especially in very young patients instead of major surgical procedures which may be more suitable at a later stage.

Surgery provides definitive management of hereditary pancreatitis. A meta analyses on the subject has demonstrated that surgical management is superior to endoscopic decompression of the main pancreatic duct for the long-term management of chronic pancreatitis pain [60]. Therefore endoscopic therapy is typically utilized as an initial management strategies in a

personalised, step-up approach for patients with HP. More recently the combination of endoscopic intervention for obstructing pancreatic ductal stones with Extracorporeal Shock Wave Lithotripsy (ESWL) has been described. To this effect the European Society of Gastrointestinal Endoscopy guidelines on the endoscopic management of chronic pancreatitis concluded that both endoscopcic therapy and ESWL should be first line treatment strategies for patients with main pancreatic duct obstruction due to ductal stones [61]. ESWL can be used to manage obstructing main duct stones that are radiopaque and are greater than 5mm in size [61]. Subsequent endoscopic clearance of the duct should only be performed in the context of failure of spontaneous clearance following ESWL stone fragmentation [61]. However the lack of availability and access to ESWL may limit its use within some centres and further results from larger studies on this treatment option is awaited.

10. Surgical Management

When considering surgical management of HP, it is important to differentiate between the varied indications for surgery. Surgery may be required for the management of a complication of recurrent pancreatitis or could be performed with prophylactic intent. In the context of pancreatitis complications (infected necrosis or pseudocyst formation), current evidence supports utilising a minimally invasive approach to allow adequate drainage and sepsis control [62, 63]. Published results from the PANTER trial (minimally invasive step-up approach versus open necrosectomy) highlighted a lower overall major complication rate with a stepwise minimally invasive when compared to open necrosectomy (40% vs 69%) [64]. The study defined a major complication as multiorgan failure or multiple systemic complications, the formation of an enterocutaneous fistula, visceral perforation or haemorrhage [64]. As a consequence, we have observed a paradigm shift in clinical practice , moving away from early aggressive open surgery through open necrosectomy (a procedure associated with a mortality rate of up to 40%) to a minimally invasive approach [65]. Walled off necrosis and pancreatic pseudocysts can be effectively managed with endoscopic cyst gastrostomy formation [44].

The primary indication for surgical management of chronic pancreatitis is chronic pain[66]. Disease distribution, the morphology of the main pancreatic duct and the presence of an inflammatory mass are all factors that influence the nature of the surgical intervention [66, 67]. It is possible to broadly categorize the type of surgical interventions for chronic pancreatitis into 3 groups: drainage procedures, resection and a combination of resection and drainage [66]. When the main pancreatic duct is obstructed, duct decompression may provide symptomatic relief. Several techniques of duct decompression procedures have been described. However the most frequently used is the Puestow–Gillesby procedure, which consisted of a longitudinal pancreaticojejunostomy [68]. This technique permitted full length duct decompression even in the presence of multiple strictures or stones [69]. Procedures that resected the diseased pancreas include a Kausch-Whipple pancreaticoduodenecomy, pylorus-preserving pancreaticoduodenecomy and Beger's procedure (duodenum preserving pancreatic head resection) [66]. The indications for resection include the presence of an inflammatory mass in the pancreatic head with subsequent biliary/pancreatic duct or duodenal obstruction. Indications for pancreatic head resection include the presence of an inflammatory mass causing biliary/pancreatic duct or duodenal obstruction. It is hypothesized that the pancreatic head serves as the pacemaker region for pain in patients with

chronic pancreatitis [70]. Greater rates of long-term pain control following resection of the pancreatic head are observed when compared to pancreatic duct drainage alone [51].

The significant morbidity and mortality rates associated with standard pancreatic head resections resulted in the development of hybrid procedures to reduce overall morbidity. These procedures combined resection and drainage of the pancreatic ductal system. Most notably the Frey's procedure (de-bulking the disease burden in the pancreatic head combined with a lateral panceatico-jejunostomy) [71]. The literature is rich with a number of other surgical procedures that have been described for chronic pancreatitis [66].

Whilst resectional procedures may provide symptomatic relief, it is important to highlight that they may complicate any further pancreatic interventions, notably total pancreatectomy and autologous islet transplant. Wang, et al (2013) demonstrated that there was a significant reduction in the beta islet cell yield in patients undergoing autologous islet transplant where prior surgery for chronic pancreatitis had been performed [72].

Over recent years, much interest has been drawn towards combining total pancreatectomy and autologous islet transplantation [73]. Initially described in 1977, it was proposed as a treatment strategy for chronic pancreatitis [74]. Total pancreatectomy enables the removal of the pancreas in its entirety, thus removing the source of focal recurrent inflammation and also risk of malignancy. Epidemiological based studies reviewing cohorts of patients with hereditary or chronic pancreatitis illustrate that approximately 90% of their respective patients suffer from chronic abdominal pain [75, 76]. This has been demonstrated to have significant adverse effects on patients' quality of life [77]. Symptom management is difficult and often results in a high dose, long term prescription of opiates [78]. Total pancreatectomy serves as an opportunity to alleviate chronic abdominal pain and reduce opiate usage. Published rates of successful withdrawal of opiates following total pancreatectomy vary (Table 1) [79-86]. The highest rates are observed in the younger patient cohort [87]. Therefore early intervention in this specific cohort may prevent long term opiate use and ensure that these patients are able to integrate and function within society. Initial clinical concerns with the procedure revolved around the possibility of rendering patients with refractory diabetes. However subsequent analyses of total pancreatectomy have noted HbA1c results ranging between 5.8%–7.5% at 6 months post operatively [88, 89]. Endocrinological outcomes may be influenced by the quantity and quality of islets cells isolated, in addition to the success rate of islet cell engraftment. An atrophic, fibrotic pancreas with extensive calcification may reduce the successful yield of the islets cell harvest [3]. Some would argue that intervention for hereditary pancreatitis should be undertaken earlier within the disease course, prior to the development of extensive fibrosis in order to obtain an adequate islet cell mass for auto-transplantation [80]. Following islet cell infusion and throughout the early post operative period, close glucose control is paramount. Glucose homeostasis should be maintained with an intravenous infusion of insulin in order to alleviate any metabolic functional stress on the Beta cell islets during engraftment [90]. Failure to minimize the metabolic stress to the beta islet cells prior to engraftment will result in cell death and ultimately failure of the autotransplant of the islet cells. Current attempts at establishing a predictive model for endocrine function following islet auto transplantation have been unsuccessful. Most patients will require insulin therapy, albeit at low doses. A positive correlation has been noted between a greater total quantity yield of islets cells for auto transplantation in non insulin dependent patients when compared to insulin dependent patients [79, 80, 83]. This therefore potentially reinforces the need for an earlier

intervention in this cohort of patients [79]. Published patient outcomes following total pancreatectomy and islet autotransplant highlight resolution of symptoms in addition to a good quality of life and functional capacity [80, 82].

Table 1 Functional Outcomes following total pancreatectomy and auto islet transplantation.

Authors	**Patient cohort and genetic mutation profile**	**Intervention**	**Functional Outcome**
Fan et al, 2017 [81]	Total cohort (20) Hereditary pancreatitis = 9 patients PRSS1 mutation (2) SPINK1 (2) CFTR (2) SPINK1 and CFTR 2 SPINK1 and PRSS1 (1)	LTP & AIT	60% of patients opiate independent at 6 months
Chinnakotla et al, 2014 [80]	Total cohort (75) Hereditary pancreatitis = 37 patients	Open TP & AIT	At 1 year >80% opiate independent
Wilson et al, 2013 [86]	Total cohort (14) Hereditary pancreatitis = 6 patients Mutation profile: CFTR (4) SPINK (1) PRSS1 (1)	Open TP & AIT	79% of patients independent of opiates at the endo of the follow up (medial follow up 9 months)
Sutherland 2012 [83]	Total cohort (409) Hereditary pancreatitis = 58 patients [&]	Open TP & AIT	59%* of patients opiate independent at 24 months
Morgan et al, 2012 [82]	Total cohort (33) Hereditary pancreatitis = 3 patients [&]	Open TP & AIT	23%* of patients opiate independent at 12 months, 64% decrease in opiate requirement
Walsh et al, 2012 [85]	Total cohort (20) Hereditary pancreatitis = 2 patients [&]	Open TP & AIT	23%* of patients opiate independent at 12 months
Ahmad et al, 2005 [79]	Total cohort (45) Hereditary pancreatitis = 1 patient [&]	Open TP & AIT	72%* of patients opiate independent at 23 months
Sutton et al, 2010 [84]	Total cohort (188) Hereditary pancreatitis = 16 patients Mutation profile: CFTR (10) PRSS1 (4) SPINK1 (2)	Open TP & AIT	63%* patients opiate independent at documented last follow up

LTP = Laparoscopic Total Pancreatectomy, AIT = Auto-Islet Transplantation, TP = Total Pancreatectomy, * = of the total study cohort, £ = genetic mutation profile not recorded, & sub cohort of patients with > 5months of follow up (n=32).

The current guideline recommendations for total pancreatectomy and auto islet transplantations are based on low levels of evidence [87]. The consensus statement from Pancreas Fest 2014 specified that the main indication for surgery was chronic pain that was refractory to analgesia and was severe enough to adversely impact quality of life. Where pain was caused by either chronic pancreatitis or recurrent acute pancreatitis in which previous interventions (medical, endoscopic and or surgical) had failed [87]. In addition, surgery is indicated for patients with HP who are at higher risk of pancreatic cancer. Despite the potential therapeutic benefits that total pancreatectomy and auto islet transplantation provides, patient selection is crucial. Both active substance dependence and pre-existing poorly controlled psychiatric illness are considered contraindications for surgery [73, 79]. Post operatively patients are commenced on a complex regime of pancreatic exocrine supplementation, where needed insulin and appropriate analgesia. Performing a total pancreatectomy on a patient, will commit that patient to life long pancreatic exocrine replacement therapy [91]. Higher doses of enzyme replacement therapy are often indicated in this cohort of patients, however normal digestive function may not be achieved [92]. Malabsorption through steatorrhea may also complicate the concurrent management of diabetes [92]. Long term use of opiates may result in opiate associated bowel dysfunction. Early intervention with total pancreatectomy and auto islet transplantations may reduce opiate related complications. Patient compliance with therapy is essential. A tapering dose of analgesia may be required if there is a history of opiate dependence [79]. Patients need to be engaged with their management and long term follow up. Evidence has merged from the literature highlighting that optimal long-term outcomes in quality of life, pain control and islet function is achieved at much higher rates when patients with genetic pancreatitis who are non smokers and who also have a shorter duration of their disease undergo total pancreatectomy and auto islet transplantation [93]. These specific patient demographics should be incorporated into the selection process of identifying suitable patients for surgical intervention.

Another important aspect that should be emphasised regarding total pancreatectomy, is that is serves as a prophylactic procedure in the context of reducing risk of the development of pancreatic cancer. It is now well acknowledged that patients with hereditary pancreatitis are at a significantly higher risk of developing pancreatic cancer when compared to the general population [80]. The risk is cumulative over time [1]. The International Hereditary Pancreatitis Study Group demonstrated that the cumulative risk of pancreatic cancer development was 40% by the age of 70 [94].This aspect should be considered in the patient's treatment planning algorithm, balancing definitive surgery against the need for lifelong, frequent screening for cancer development. To date, there is a lack of data regarding prophylactic surgery in individuals with genetic mutations associated with hereditary pancreatitis with no clinical phenotype of recurrent pancreatitis. Therefore total pancreatectomy and auto islet transplantation should not be recommended for asymptomatic individuals. Total pancreatectomy and islet auto transplantation for definitive management of HP, should only be undertaken following a multi-disciplinary team evaluation. Additionally further work is required in order to develop and optimise a treatment algorithm for patients with HP, especially in the context of timing of surgery.

11. Conclusion

HP is a rare cause of recurrent or chronic pancreatitis. Since it was first described, several aetiological genetic mutations have been identified (notably PRSS1, SPINK1, CTRC and CFTR). However the penetrance of these genes varies and results a varied risk of developing chronic disease. What is difficult to analyse is the affect of the interaction between genetic predisposition and exposure to environmental factors known to be causative of pancreatic inflammation. This combination may alter pathophysiological mechanisms of the disease and may influence rate of progression, the development of endocrine and exocrine failure or even malignancy. What is clear is that patients with HP present earlier in life. Thus a lifetime exposure of recurrent inflammation predisposes to pancreatic cancer development. These individuals must be identified early in order to ensure appropriate management (risk reduction and preservation of endocrine function) is instigated. Through combining early diagnosis and intervention with a greater understanding of not only the genetic mutation the individual carries but their own personal risk of disease progression, will allow a unique and personalised treatment strategy for patients with HP.

Author Contributions

All authors significantly contributed to this manuscript.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Howes N, Lerch MM, Greenhalf W, Stocken DD, Ellis I, Simon P, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clin Gastroenterol Hepatol. 2004; 2: 252-261.
2. Brand RE, Lerch MM, Rubinstein WS, Neoptolemos JP, Whitcomb DC, Hruban RH, et al. Advances in counselling and surveillance of patients at risk for pancreatic cancer. Gut. 2007; 56: 1460-1469.
3. Raphael KL, Willingham FF. Hereditary pancreatitis: Current perspectives. Clin Exp Gastroenterol. 2016; 9: 197-207.
4. Rebours V, Boutron-Ruault MC, Schnee M, Ferec C, Le Marechal C, Hentic O, et al. The natural history of hereditary pancreatitis: A national series. Gut. 2009; 58: 97-103.
5. Oracz G, Kolodziejczyk E, Sobczynska-Tomaszewska A, Wejnarska K, Dadalski M, Grabarczyk AM, et al. The clinical course of hereditary pancreatitis in children - A comprehensive analysis of 41 cases. Pancreatology. 2016; 16: 535-541.
6. Schmitt F, Le Henaff G, Piloquet H, Leclair MD, David A, Heloury Y, et al. Hereditary pancreatitis in children: Surgical implications with special regard to genetic background. J Pediatr Surg. 2009; 44: 2078-2082.
7. LaRusch J, Barmada MM, Solomon S, Whitcomb DC. Whole exome sequencing identifies multiple, complex etiologies in an idiopathic hereditary pancreatitis kindred. JOP. 2012; 13: 258-262.

8. Howes N, Greenhalf W, Stocken DD, Neoptolemos JP. Cationic trypsinogen mutations and pancreatitis. Clin Lab Med. 2005; 25: 39-59.
9. Kereszturi E, Szmola R, Kukor Z, Simon P, Weiss FU, Lerch MM, et al. Hereditary pancreatitis caused by mutation-induced misfolding of human cationic trypsinogen: A novel disease mechanism. Hum Mutat. 2009; 30: 575-582.
10. Rygiel AM, Beer S, Simon P, Wertheim-Tysarowska K, Oracz G, Kucharzik T, et al. Gene conversion between cationic trypsinogen (PRSS1) and the pseudogene trypsinogen 6 (PRSS3P2) in patients with chronic pancreatitis. Hum Mutat. 2015; 36: 350-356.
11. Sahin-Toth M. Human cationic trypsinogen. Role of Asn-21 in zymogen activation and implications in hereditary pancreatitis. J Biol Chem. 2000; 275: 22750-22755.
12. Sahin-Toth M, Toth M. Gain-of-function mutations associated with hereditary pancreatitis enhance autoactivation of human cationic trypsinogen. Biochem Biophys Res Commun. 2000; 278: 286-289.
13. DiMagno MJ, DiMagno EP. Chronic pancreatitis. Curr Opin Gastroenterol. 2012; 28: 523-531.
14. Ooi CY, Durie PR. Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations in pancreatitis. J Cyst Fibros. 2012; 11: 355-362.
15. Cohn JA, Mitchell RM, Jowell PS. The impact of cystic fibrosis and PSTI/SPINK1 gene mutations on susceptibility to chronic pancreatitis. Clin Lab Med. 2005; 25: 79-100.
16. LaRusch J, Jung J, General IJ, Lewis MD, Park HW, Brand RE, et al. Mechanisms of CFTR functional variants that impair regulated bicarbonate permeation and increase risk for pancreatitis but not for cystic fibrosis. PLoS Genet. 2014; 10: e1004376.
17. Nemoda Z, Sahin-Toth M. Chymotrypsin C (caldecrin) stimulates autoactivation of human cationic trypsinogen. J Biol Chem. 2006; 281: 11879-11886.
18. Beer S, Zhou J, Szabo A, Keiles S, Chandak GR, Witt H, et al. Comprehensive functional analysis of chymotrypsin C (CTRC) variants reveals distinct loss-of-function mechanisms associated with pancreatitis risk. Gut. 2013; 62: 1616-1624.
19. Ellis I, Lerch MM, Whitcomb DC, Consensus Committees of the European Registry of Hereditary Pancreatic Diseases MM-CPSGIAoP. Genetic testing for hereditary pancreatitis: Guidelines for indications, counselling, consent and privacy issues. Pancreatology. 2001; 1: 405-415.
20. Fink EN, Kant JA, Whitcomb DC. Genetic counseling for nonsyndromic pancreatitis. Gastroenterol Clin North Am. 2007; 36: 325-333.
21. Patel MR, Eppolito AL, Willingham FF. Hereditary pancreatitis for the endoscopist. Therap Adv Gastroenterol. 2013; 6: 169-179.
22. Solomon S, Whitcomb DC. Genetics of pancreatitis: An update for clinicians and genetic counselors. Curr Gastroenterol Rep. 2012; 14: 112-117.
23. Applebaum-Shapiro SE, Peters JA, O'Connell JA, Aston CE, Whitcomb DC. Motivations and concerns of patients with access to genetic testing for hereditary pancreatitis. Am J Gastroenterol. 2001; 96: 1610-1617.
24. Botkin JR, Belmont JW, Berg JS, Berkman BE, Bombard Y, Holm IA, et al. Points to consider: Ethical, legal, and psychosocial implications of genetic testing in children and adolescents. Am J Hum Genet. 2015; 97: 6-21.
25. Bansal P, Sonnenberg A. Pancreatitis is a risk factor for pancreatic cancer. Gastroenterology. 1995; 109: 247-251.

26. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002; 420: 860-867.
27. Hamada S, Masamune A, Shimosegawa T. Novel therapeutic strategies targeting tumor-stromal interactions in pancreatic cancer. Front Physiol. 2013; 4: 331.
28. Maitra A, Ashfaq R, Gunn CR, Rahman A, Yeo CJ, Sohn TA, et al. Cyclooxygenase 2 expression in pancreatic adenocarcinoma and pancreatic intraepithelial neoplasia: An immunohistochemical analysis with automated cellular imaging. Am J Clin Pathol. 2002; 118: 194-201.
29. Weiss FU. Pancreatic cancer risk in hereditary pancreatitis. Front Physiol. 2014; 5: 70.
30. Kondo M, Yamamoto H, Nagano H, Okami J, Ito Y, Shimizu J, et al. Increased expression of COX-2 in nontumor liver tissue is associated with shorter disease-free survival in patients with hepatocellular carcinoma. Clin Cancer Res. 1999; 5: 4005-4012.
31. Rawla P, Sunkara T, Gaduputi V. Epidemiology of pancreatic cancer: Global trends, etiology and risk factors. World J Oncol. 2019; 10: 10-27.
32. Ikeda O, Egami H, Ishiko T, Ishikawa S, Kamohara H, Hidaka H, et al. Signal of proteinase-activated receptor-2 contributes to highly malignant potential of human pancreatic cancer by up-regulation of interleukin-8 release. Int J Oncol. 2006; 28: 939-946.
33. Lesina M, Kurkowski MU, Ludes K, Rose-John S, Treiber M, Kloppel G, et al. Stat3/Socs3 activation by IL-6 transsignaling promotes progression of pancreatic intraepithelial neoplasia and development of pancreatic cancer. Cancer Cell. 2011; 19: 456-469.
34. Razidlo GL, Burton KM, McNiven MA. Interleukin-6 promotes pancreatic cancer cell migration by rapidly activating the small GTPase CDC42. J Biol Chem. 2018; 293: 11143-11153.
35. Balkwill F. Tumour necrosis factor and cancer. Nat Rev Cancer. 2009; 9: 361-371.
36. Shen B, Zheng MQ, Lu JW, Jiang Q, Wang TH, Huang XE. CXCL12-CXCR4 promotes proliferation and invasion of pancreatic cancer cells. Asian Pac J Cancer Prev. 2013; 14: 5403-5408.
37. Canto MI, Harinck F, Hruban RH, Offerhaus GJ, Poley JW, Kamel I, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut. 2013; 62: 339-347.
38. Langer P, Kann PH, Fendrich V, Habbe N, Schneider M, Sina M, et al. Five years of prospective screening of high-risk individuals from families with familial pancreatic cancer. Gut. 2009; 58: 1410-1418.
39. Ludwig E, Olson SH, Bayuga S, Simon J, Schattner MA, Gerdes H, et al. Feasibility and yield of screening in relatives from familial pancreatic cancer families. Am J Gastroenterol. 2011; 106: 946-954.
40. Canto MI, Goggins M, Hruban RH, Petersen GM, Giardiello FM, Yeo C, et al. Screening for early pancreatic neoplasia in high-risk individuals: A prospective controlled study. Clin Gastroenterol Hepatol. 2006; 4: 766-781.
41. Greer JB, Whitcomb DC. Role of BRCA1 and BRCA2 mutations in pancreatic cancer. Gut. 2007; 56: 601-605.
42. Lee MV, Katabathina VS, Bowerson ML, Mityul MI, Shetty AS, Elsayes KM, et al. BRCA-associated cancers: Role of imaging in screening, diagnosis, and management. Radiographics. 2017; 37: 1005-1023.
43. Corrias G, Raeside MC, Agostini A, Huicochea-Castellanos S, Aramburu-Nunez D, Paudyal R, et al. Pilot study of rapid MR pancreas screening for patients with BRCA mutation. Eur Radiol. 2019; 29: 3976-3985.

44. Maisonneuve P, Lowenfels AB, Mullhaupt B, Cavallini G, Lankisch PG, Andersen JR, et al. Cigarette smoking accelerates progression of alcoholic chronic pancreatitis. Gut. 2005; 54: 510-514.
45. Ye X, Lu G, Huai J, Ding J. Impact of smoking on the risk of pancreatitis: A systematic review and meta-analysis. PLoS One. 2015; 10: e0124075.
46. Bueno de Mesquita HB, Maisonneuve P, Moerman CJ, Runia S, Boyle P. Life-time history of smoking and exocrine carcinoma of the pancreas: A population-based case-control study in The Netherlands. Int J Cancer. 1991; 49: 816-822.
47. Lowenfels AB, Maisonneuve P, Whitcomb DC, Lerch MM, DiMagno EP. Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. JAMA. 2001; 286: 169-170.
48. Chowdhury P, Gupta P. Pathophysiology of alcoholic pancreatitis: An overview. World J Gastroenterol. 2006; 12: 7421-7427.
49. Pitchumoni CS. Pathogenesis of alcohol-induced chronic pancreatitis: Facts, perceptions, and misperceptions. Surg Clin North Am. 2001; 81: 379-390.
50. Jones MR, Hall OM, Kaye AM, Kaye AD. Drug-induced acute pancreatitis: A review. Ochsner J. 2015; 15: 45-51.
51. Delhaye M, Matos C, Arvanitakis M, Deviere J. Pancreatic ductal system obstruction and acute recurrent pancreatitis. World J Gastroenterol. 2008; 14: 1027-1033.
52. Testoni PA. Endoscopic pancreatic duct stent placement for inflammatory pancreatic diseases. World J Gastroenterol. 2007; 13: 5971-5978.
53. Cremer M, Deviere J, Delhaye M, Baize M, Vandermeeren A. Stenting in severe chronic pancreatitis: Results of medium-term follow-up in seventy-six patients. Endoscopy. 1991; 23: 171-176.
54. Rosch T, Daniel S, Scholz M, Huibregtse K, Smits M, Schneider T, et al. Endoscopic treatment of chronic pancreatitis: A multicenter study of 1000 patients with long-term follow-up. Endoscopy. 2002; 34: 765-771.
55. Topazian M, Aslanian H, Andersen D. Outcome following endoscopic stenting of pancreatic duct strictures in chronic pancreatitis. J Clin Gastroenterol. 2005; 39: 908-911.
56. Li ZS, Wang W, Liao Z, Zou DW, Jin ZD, Chen J, et al. A long-term follow-up study on endoscopic management of children and adolescents with chronic pancreatitis. Am J Gastroenterol. 2010; 105: 1884-1892.
57. Gregg JA, De Girolami P, Carr-Locke DL. Effects of sphincteroplasty and endoscopic sphincterotomy on the bacteriologic characteristics of the common bile duct. Am J Surg. 1985; 149: 668-671.
58. Colling KP, Blondet JJ, Balamurugan AN, Wilhelm JJ, Dunn T, Pruett TL, et al. Positive sterility cultures of transplant solutions during pancreatic islet autotransplantation are associated infrequently with clinical infection. Surg Infect. 2015; 16: 115-123.
59. Smits ME, Badiga SM, Rauws EA, Tytgat GN, Huibregtse K. Long-term results of pancreatic stents in chronic pancreatitis. Gastrointest Endosc. 1995; 42: 461-467.
60. Ahmed Ali U, Pahlplatz JM, Nealon WH, van Goor H, Gooszen HG, Boermeester MA. Endoscopic or surgical intervention for painful obstructive chronic pancreatitis. Cochrane Database Syst Rev. 2012; 1: CD007884.

61. Dumonceau JM, Delhaye M, Tringali A, Arvanitakis M, Sanchez-Yague A, Vaysse T, et al. Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Updated August 2018. Endoscopy. 2019; 51: 179-193.
62. Cirocchi R, Trastulli S, Desiderio J, Boselli C, Parisi A, Noya G, et al. Minimally invasive necrosectomy versus conventional surgery in the treatment of infected pancreatic necrosis: A systematic review and a meta-analysis of comparative studies. Surg Laparosc Endosc Percutan Tech. 2013; 23: 8-20.
63. Puli SR, Graumlich JF, Pamulaparthy SR, Kalva N. Endoscopic transmural necrosectomy for walled-off pancreatic necrosis: A systematic review and meta-analysis. Can J Gastroenterol Hepatol. 2014; 28: 50-53.
64. van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med. 2010; 362: 1491-1502.
65. Makris GC, See T, Winterbottom A, Jah A, Shaida N. Minimally invasive pancreatic necrosectomy; a technical pictorial review. Br J Radiol. 2018; 91: 20170435.
66. Perwaiz A, Singh A, Chaudhary A. Surgery for chronic pancreatitis. Indian J Surg. 2012; 74: 47-54.
67. Parekh D, Natarajan S. Surgical management of chronic pancreatitis. Indian J Surg. 2015; 77: 453-469.
68. Puestow CB, Gillesby WJ. Retrograde surgical drainage of pancreas for chronic relapsing pancreatitis. AMA Arch Surg. 1958; 76: 898-907.
69. Partington PF, Rochelle RE. Modified Puestow procedure for retrograde drainage of the pancreatic duct. Ann Surg. 1960; 152: 1037-1043.
70. Izbicki JR, Bloechle C, Knoefel WT, Rogiers X, Kuechler T. Surgical treatment of chronic pancreatitis and quality of life after operation. Surg Clin North Am. 1999; 79: 913-944.
71. Frey CF, Amikura K. Local resection of the head of the pancreas combined with longitudinal pancreaticojejunostomy in the management of patients with chronic pancreatitis. Ann Surg. 1994; 220: 492-504; discussion 504-497.
72. Wang H, Desai KD, Dong H, Owzarski S, Romagnuolo J, Morgan KA, et al. Prior surgery determines islet yield and insulin requirement in patients with chronic pancreatitis. Transplantation. 2013; 95: 1051-1057.
73. Kesseli SJ, Smith KA, Gardner TB. Total pancreatectomy with islet autologous transplantation: The cure for chronic pancreatitis? Clin Transl Gastroenterol. 2015; 6: e73.
74. Sutherland DE, Matas AJ, Najarian JS. Pancreatic islet cell transplantation. Surg Clin North Am. 1978; 58: 365-382.
75. Yang CJ, Bliss LA, Schapira EF, Freedman SD, Ng SC, Windsor JA, et al. Systematic review of early surgery for chronic pancreatitis: Impact on pain, pancreatic function, and re-intervention. J Gastrointest Surg. 2014; 18: 1863-1869.
76. Mullady DK, Yadav D, Amann ST, O'Connell MR, Barmada MM, Elta GH, et al. Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: A prospective cohort study. Gut. 2011; 60: 77-84.
77. Wehler M, Nichterlein R, Fischer B, Farnbacher M, Reulbach U, Hahn EG, et al. Factors associated with health-related quality of life in chronic pancreatitis. Am J Gastroenterol. 2004; 99: 138-146.

78. Wilder-Smith OH, Schreyer T, Scheffer GJ, Arendt-Nielsen L. Patients with chronic pain after abdominal surgery show less preoperative endogenous pain inhibition and more postoperative hyperalgesia: A pilot study. J Pain Palliat Care Pharmacother. 2010; 24: 119-128.
79. Ahmad SA, Lowy AM, Wray CJ, D'Alessio D, Choe KA, James LE, et al. Factors associated with insulin and narcotic independence after islet autotransplantation in patients with severe chronic pancreatitis. J Am Coll Surg. 2005; 201: 680-687.
80. Chinnakotla S, Radosevich DM, Dunn TB, Bellin MD, Freeman ML, Schwarzenberg SJ, et al. Long-term outcomes of total pancreatectomy and islet auto transplantation for hereditary/genetic pancreatitis. J Am Coll Surg. 2014; 218: 530-543.
81. Fan CJ, Hirose K, Walsh CM, Quartuccio M, Desai NM, Singh VK, et al. Laparoscopic total pancreatectomy with islet autotransplantation and intraoperative islet separation as a treatment for patients with chronic pancreatitis. JAMA Surg. 2017; 152: 550-556.
82. Morgan K, Owczarski SM, Borckardt J, Madan A, Nishimura M, Adams DB. Pain control and quality of life after pancreatectomy with islet autotransplantation for chronic pancreatitis. J Gastrointest Surg. 2012; 16: 129-133; discussion 133-124.
83. Sutherland DE, Radosevich DM, Bellin MD, Hering BJ, Beilman GJ, Dunn TB, et al. Total pancreatectomy and islet autotransplantation for chronic pancreatitis. J Am Coll Surg. 2012; 214: 409-424; discussion 424-406.
84. Sutton JM, Schmulewitz N, Sussman JJ, Smith M, Kurland JE, Brunner JE, et al. Total pancreatectomy and islet cell autotransplantation as a means of treating patients with genetically linked pancreatitis. Surgery. 2010; 148: 676-685; discussion 685-676.
85. Walsh RM, Saavedra JR, Lentz G, Guerron AD, Scheman J, Stevens T, et al. Improved quality of life following total pancreatectomy and auto-islet transplantation for chronic pancreatitis. J Gastrointest Surg. 2012; 16: 1469-1477.
86. Wilson GC, Sutton JM, Salehi M, Schmulewitz N, Smith MT, Kucera S, et al. Surgical outcomes after total pancreatectomy and islet cell autotransplantation in pediatric patients. Surgery. 2013; 154: 777-783; discussion 783-774.
87. Bellin MD, Freeman ML, Gelrud A, Slivka A, Clavel A, Humar A, et al. Total pancreatectomy and islet autotransplantation in chronic pancreatitis: Recommendations from PancreasFest. Pancreatology. 2014; 14: 27-35.
88. Oberholzer J, Triponez F, Mage R, Andereggen E, Buhler L, Cretin N, et al. Human islet transplantation: Lessons from 13 autologous and 13 allogeneic transplantations. Transplantation. 2000; 69: 1115-1123.
89. Dorlon M, Owczarski S, Wang H, Adams D, Morgan K. Increase in postoperative insulin requirements does not lead to decreased quality of life after total pancreatectomy with islet cell autotransplantation for chronic pancreatitis. Am Surg. 2013; 79: 676-680.
90. Biarnes M, Montolio M, Nacher V, Raurell M, Soler J, Montanya E. Beta-cell death and mass in syngeneically transplanted islets exposed to short- and long-term hyperglycemia. Diabetes. 2002; 51: 66-72.
91. Bellin MD, Gelrud A, Arreaza-Rubin G, Dunn TB, Humar A, Morgan KA, et al. Total pancreatectomy with islet autotransplantation: Summary of an NIDDK workshop. Ann Surg. 2015; 261: 21-29.
92. Del Chiaro M, Rangelova E, Segersvard R, Arnelo U. Are there still indications for total pancreatectomy? Updates Surg. 2016; 68: 257-263.

93. Morgan KA, Lancaster WP, Owczarski SM, Wang H, Borckardt J, Adams DB. Patient Selection for Total Pancreatectomy with islet autotransplantation in the surgical management of chronic pancreatitis. J Am Coll Surg. 2018; 226: 446-451.
94. Lowenfels AB, Maisonneuve P, DiMagno EP, Elitsur Y, Gates LK, Jr., Perrault J, et al. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst. 1997; 89: 442-446.