Tampere University

MIKAEL PARHIALA

Treatment of Chronic Pancreatitis

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ACADEMIC DISSERTATION
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PREFACE

"The conquest of health is not enough…for the quality of life is more important than life itself." Nobel prize winning surgeon Alexis Carrel (Reflections of life). The World Health Organization has a broad definition of quality of life (QoL): "Defined as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns." In this thesis we focus on a more specific aspect of QoL, namely the preservation of functioning and the treatment of symptoms. We focus on patients suffering from chronic pancreatitis, an often poorly understood long-term disease. This thesis hopes to contribute to a better more holistic understanding of the quality of life of patients suffering from chronic pancreatitis and inspire clinicians to find new ways to approach, study and treat this disease.

“It's the job that's never started as takes longest to finish.”

Professor J.R.R. Tolkien, The Lord of the Rings: The Fellowship of the Ring, Samwise Gamgee

ABSTRACT

Chronic pancreatitis (CP) is defined as an ongoing inflammatory process where the pancreatic tissue is replaced with fibrotic tissue leading to pancreatic insufficiency. CP may cause intra-abdominal complications and constant pain. There are several risk factors for CP, alcohol and smoking being the most common, but a significant proportion is idiopathic. Treatment of CP is primally conservative treatment of pain and pancreatic insufficiency, but invasive endoscopic or surgical procedures may be needed. This thesis focuses on the surgical and endoscopic treatment and quality of life of patients suffering from CP.

The first study was a population-based study on CP patients from a tertiary care hospital. We investigated the current epidemiological and behavioural data on CP patients in Finland. We ascertained the burden CP causes for patients and for the healthcare system, especially patients consuming alcohol and smoking, who are at higher risk of developing complications. Half of CP patients continue smoking and drinking after their diagnosis but on the other hand there is more alcohol abstinence among CP patients than in Finnish general population. In one in five CP patients the aetiology remains unknown. CP patients have a poorer quality of life and lower survival rate than compared to the normative population.

It is known that CP is associated with osteoporosis. From the patients in the first study, we examined the prevalence of osteoporosis and sarcopenia among CP patients in Finland. Half of CP patients had previously unknown abnormal bone density and sarcopenia and one in five had osteoporosis. Patients with pancreatic exocrine insufficiency (PEI), especially without adequate treatment, were at risk for osteoporosis and sarcopenia. Disease duration seems to be a risk factor for sarcopenia. More care should be taken with this patient population in the basic treatment of PEI. Vitamin status and bone density should be measured in CP patients with PEI.

In the second study our aim was to determine the long-term outcomes and symptoms in CP patients operated on for CP in a nationwide Finnish cohort study.

Surgery seems to give good long-term pain relief and reduces opiate usage. Quality of life (QoL) was the same as in the rest of CP population. The rate of idiopathic CP is higher in patients undergoing surgery. Most of the surgical interventions in CP involve treatment for complications or procedures due to suspicion of malignancy. Under one percent of CP patients have pancreatic surgery for pain. Patients undergoing surgery for pain reported less pain than before surgery and good QoL in 14-year follow-up.

Our third and fourth studies were both cross-sectional multicentre studies intended to ascertain the optimal treatment in surgical and endoscopic treatment strategies of CP in the Scandinavian and Baltic countries. Study III focused on patients requiring surgical intervention and in Study IV we studied patients undergoing endoscopic procedures. The surgical group most likely differ from endoscopically treated group in disease severity. We found that pancreatic surgery rates are low (7%) in the Scandinavian and Baltic countries while one out of five (20%) CP patients undergo endoscopic procedures. CP patients undergoing endoscopic procedures had better QoL than the rest of the CP population. CP patients with no prior endoscopic procedures before surgery also had better QoL than patients who underwent endoscopic procedures before surgery. Patients with longer disease duration had worse outcome.

Based on these studies we conclude that CP patients have poor QoL and survival and are at risk for sarcopenia and osteoporosis. Patient follow-ups and education are necessary to prevent malnutrition and disease progression. CP patients often need invasive interventions but surgery for CP pain is rare and may provide good long-term results. Prospective trials are needed to determine which patients benefit from early surgery, endoscopy or medical management.

TIIVISTELMÄ

Pitkäaikainen haimatulehdus eli krooninen pankreatiitti on jatkuva haiman inflammatorinen prosessi, jossa haimakudos korvautuu sidekudoksella johtaen vähitellen haiman entsyymituotannon vajaatoimintaan ja diabetekseen. Krooninen pankreatiitti voi aiheuttaa komplikaatioita, kuten jatkuvaa vatsan alueen kipua ja pseudokystiä. Krooniselle pankreatiitille on useita riskitekijöitä, joista yleisimmät ovat alkoholin käyttö ja tupakointi, mutta merkittävällä osalla potilaista taudinaiheuttaja ei ole tiedossa. Kroonisen pankreatiitin hoito on ensisijaisesti konservatiivista kivun ja vajaatoiminnan hoitoa, sekä toisaalta riskitekijöiden välttämistä. Sairaus saattaa kuitenkin vaatia myös kajoavia endoskooppisia tai kirurgisia toimenpiteitä. Tämä väitöskirja keskittyy kroonista pankreatiittia sairastavien potilaiden hoitoon ja elämänlaatuun.

Ensimmäisessä tutkimuksessa selvitimme Tampereen yliopistollisessa sairaalassa hoidettujen kroonista pankreatiittia sairastavien potilaiden epidemiologiaa ja elämänlaatua. Tässä tutkimuksessa puolet potilaista jatkoi diagnoosin jälkeen tupakointia ja alkoholin käyttöä. Totesimme, että krooninen pankreatiitti aiheutti kuormitusta potilaille ja terveydenhuollolle erityisesti näiden potilaiden kohdalla. Kaikilla kroonista pankreatiittia sairastavilla potilailla oli alentunut elämänlaatu ja suurentunut kuolleisuus. Yhdellä viidestä taudinaiheuttaja oli tuntematon.

Kroonisen pankreatiitin tiedetään aiheuttavan osteoporoosia. Selvitimme myös sarkopenian ja osteoporoosin esiintyvyyttä ensimmäisen tutkimuksen potilailla.

Puolella potilaista oli ennestään toteamaton poikkeava luuntiheys ja sarkopenia ja yhdellä viidestä oli osteoporoosi. Ne potilaat, joilla oli eksokriininen haiman vajaatoiminta, etenkin ilman adekvaattia lääkitystä, saattoivat olla riskissä sairastua osteoporoosiin ja sarkopeniaan. Pidempi taudin kesto vaikutti lisäävän sarkopenian riskiä. Tämän perusteella kroonista pankreatiittia sairastavien potilaiden haiman eksokriinisen vajaatoiminnan hoitoon ja seurantaan pitäisi panostaa.

Toisessa osatyössä tutkimme kroonisen pankreatiitin vuoksi leikattujen potilaiden pitkäaikaistuloksia ja elämänlaatua. Suurin osa krooniseen pankreatiitiin liittyvistä leikkauksista tehtiin komplikaatioiden tai syöpäepäilyn vuoksi ja alle prosentti kaikista kroonista pankreatiittia sairastavista potilaista leikattiin oireiden vuoksi. Tähän tutkimukseen otimme mukaan kaikki kroonisen pankreatiitin aiheuttamien oireiden vuoksi tietyllä ajanjaksolla leikatut potilaat Suomessa. Oireiden vuoksi leikatut potilaat raportoivat leikkauksen jälkeen vähemmän kipua kuin ennen leikkausta. Totesimme, että kirurgia vaikuttaa antavan hyviä pitkäaikaistuloksia kroonisen pankreatiitin kivun hoidossa ja esimerkiksi vähentää opiaatti-kipulääkkeiden käyttöä. Leikattujen potilaiden elämänlaatu oli samanlainen kuin leikkaamattomilla kroonista pankreatiittia sairastavilla potilailla.

Kolmannessa ja neljännessä tutkimuksessa tavoitteenamme oli selvittää optimaalista lähestymistapaa kroonisen pankreatiitin kirurgiselle ja endoskooppiselle hoidolle Pohjoismaiden ja Baltian maiden monikeskusrekisterin pohjalta. Kirurgista hoitoa vaativilla potilailla taudinkuva on todennäköisesti vaikeampi kuin endoskooppisilla toimenpiteillä hoidetuilla potilailla. Totesimme, että kroonisen pankreatiitin vuoksi tehdyt leikkaukset olivat harvinaisia (7 %). Sen sijaan yksi viidestä potilaista (20 %) hoidettiin endoskooppisesti. Endoskooppisen toimenpiteen läpikäyneillä potilailla oli parempi elämänlaatu verrattuna potilaisiin, jotka eivät tarvinneet toimenpiteitä. Lisäksi elämänlaatu oli parempi niillä leikatuilla potilailla, joille ei tehty endoskooppista toimenpidettä ennen leikkausta. Pitempi taudin kesto heikensi leikkaustuloksen vaikutusta elämänlaatuun.

Johtopäätöksinä toteamme, että kroonista pankreatiittia sairastavien potilaiden elämänlaatu ja elinajanodote ovat alentuneita. Potilailla on riski sairastua sarkopeniaan ja osteoporoosiin. Kroonista pankreatiittia sairastavien potilaiden seuranta ja neuvonta on tarpeellista, jotta voidaan ehkäistä aliravitsemusta ja taudin etenemistä. Potilaat tarvitsevat usein kajoavia toimenpiteitä. Oireiden vuoksi tehtävät leikkaukset ovat harvinaisia, mutta voivat tuottaa hyvän pitkäaikaistuloksen. Prospektiivisia tutkimuksia tarvitaan arvioimaan, ketkä potilaat hyötyisivät kirurgiasta tai endoskooppisesta hoidosta ja ketkä pelkästä konservatiivisesta hoidosta.

CONTENTS

ABBREVIATIONS

AP	Acute Pancreatitis
AUDIT	Alcohol Use Disorders Identification Test
BMI	Body Mass Index
CD	Clavien-Dindo Classification
CP	Chronic Pancreatitis
CT	Computed Tomography
DM	Diabetes Mellitus
DPPHR	Duodenum Preserving Pancreatic Head Resection
EORTC	European Organization for Research and Treatment of Cancer
EP	Endoscopic Procedure
ERCP	Endoscopic Retrograde Cholangiopancreatography
ERP	Endoscopic Retrograde Pancreatography
ESWL	Extracorporeal Shock Wave Lithotripsy
EUS	Endoscopic Ultrasonography
FE1	Faecal Elastase-1
HbA1c	Glycated Haemoglobin
MRI	Magnetic Resonance Imaging
MRCP	Magnetic Resonance Cholangiopancreatography
NSAID	Non-Steroidal Anti-Inflammatory Drug

NBD	Normal Bone Density
OR	Odds Ratio
PC	Pancreatic Cancer
PD	Pancreaticoduodenectomy
PEI	Pancreatic Exocrine Insufficiency
PES	Pancreatic Enzyme Supplement
PMA	Psoas Muscle Area
QoL	Quality of Life
SBPC	The Scandinavian Baltic Pancreatic Club
SPINK1	Serine Peptidase Inhibitor Kazal type 1
TAUH	Tampere University Hospital
TP	Total Pancreatectomy
TPIAT	Total Pancreatectomy with Islet Autotransplantation

LIST OF ORIGINAL PUBLICATIONS

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1 INTRODUCTION

Chronic pancreatitis (CP) leads to morphological changes in the pancreas such as pancreatic fibrosis, calcification and pancreatic ductal dilatation (Engjom et al., 2021). Persistent inflammation often leads to pancreatic insufficiency. CP can be seen as a continuum of acute pancreatitis. (Agarwal et al., 2020; Singh et al., 2019) The main cause of CP in Finnish population is alcohol consumption with smoking also contributing to the disease. Other causes include efferent duct obstruction, nutritional factors such as hypertriglyceridaemia and autoimmune, hereditary and idiopathic pancreatitis. (Engjom et al., 2021; Fernandez et al., 2017; Lévy et al., 2014) CP causes a burden on patients by causing intermittent or persistent abdominal pain and may lead to complications such as pseudocysts, pseudoaneurysms and bile ductal obstruction (Chiang et al., 2014; Lu et al., 2006). Often conservative treatment is not enough and invasive treatments such as endoscopic stenting and surgery are needed (Dirweesh et al., 2022; Dominguez-Munoz et al., 2018)Endoscopic treatment is less invasive but, according to a recent meta-analysis, surgery may have a better long-term effect on pain relief. (Mendieta et al., 2021)

Surgery for CP is planned individually based on the morphological changes in the pancreas. Surgery involves pancreatic drainage, resection or both (Gardner et al., 2020).

The recent epidemiological data on CP patients with details regarding interventions, pain and QoL are limited.

CP with pancreatic insufficiency may cause malnutrition, sarcopenia and osteoporosis. The rates of osteoporosis and sarcopenia in the CP population are not well characterized. CP patients often need interventions but the frequency and outcome of these are unknown.

The purpose of this thesis is to investigate the treatment of CP not only in Finland but in the Scandinavian and Baltic countries. We are interested in the relationship of CP and osteoporosis and sarcopenia in CP patients. We focus on QoL in the CP population and look into the outcomes of surgical and endoscopic interventions in the CP population, including QoL and pain.

2 REVIEW OF THE LITERATURE

2.1 Anatomy and Physiology of the Pancreas

The pancreas lies in the retroperitoneum surrounded by most of the upper gastrointestinal organs and major abdominal blood vessels (Superior mesenteric artery, celiac artery, portal vein). It has a rich blood supply with many branches from the celiac and superior mesenteric arteries. The pancreatic gland is supplied with a nerve supply that regulates the blood flow and endo- and exocrine function of the pancreas. The pancreas is supplied by the celiac plexus which consists partly of the vagus nerve and spinal superior mesenteric ganglion. (Chien et al., 2019; Kimura, 2000; Vasiliadis, 2021)

The pancreas is divided into the head, neck (caput), body (corpus), tail (cauda) and the uncinate process. The pancreatic gland consists of smaller ducts, all of which drain into the main pancreatic duct (duct of Wirsung), in some cases there is an accessory pancreatic duct (duct of Santorini). The pancreatic duct joins the common bile duct to the papilla of Vater, which drains into the duodenum. (Hagai, 2003)

The pancreas functions as a digestive endocrine and exocrine gland that regulates blood sugar levels and supplies digestive enzymes to the gastrointestinal tract. The endocrine pancreatic tissue consists mainly of (Langerhans) islet cells, which produce insulin, glucagon and somatostatin, insulin production being the most crucial hormone function in glucose balance. Most of the pancreas consists of the exocrine gland formed from acinar cells producing exocrine enzymes that help digest mainly fat (lipase) but also carbohydrates (amylase) and proteins (trypsin) and normally only activate once inside the bowel. (Khan et al., 2022; Kiela & Ghishan, 2016; Shahid & Singh, 2022). The pancreatic ductal cells secrete an alkaline fluid which is vital for

the homeostasis of the pancreatic tissue due to the acidosis caused by exocytosis of the acinar cells (Hegyi & Rakonczay, 2015). Transportation and keeping the pancreatic enzymes inactive until the duodenum is another key role of the ductal cells in the pancreatic exocrine system (Angyal et al., 2021).
Trypsinogen is an inactive precursor protein to trypsin produced by acinar cells, which is normally inhibited in the pancreatic duct and only activated in the duodenum by an enteropeptidase. The trypsinogen theory behind pancreatitis is based on the premature activation of trypsinogen leading to self-digestion of the pancreatic tissue (Saluja et al., 2019).

Pancreatic stellate cells regulate the production of the extracellular matrix of the pancreas and are thought to be behind the fibrosis of the pancreatic tissue in both CP and pancreatic cancer (PC). Pancreatic tissue injury such as oxidative stress, cytokines can trigger stellate cells to produce fibrosis in the pancreatic tissue (Pothula et al., 2020).

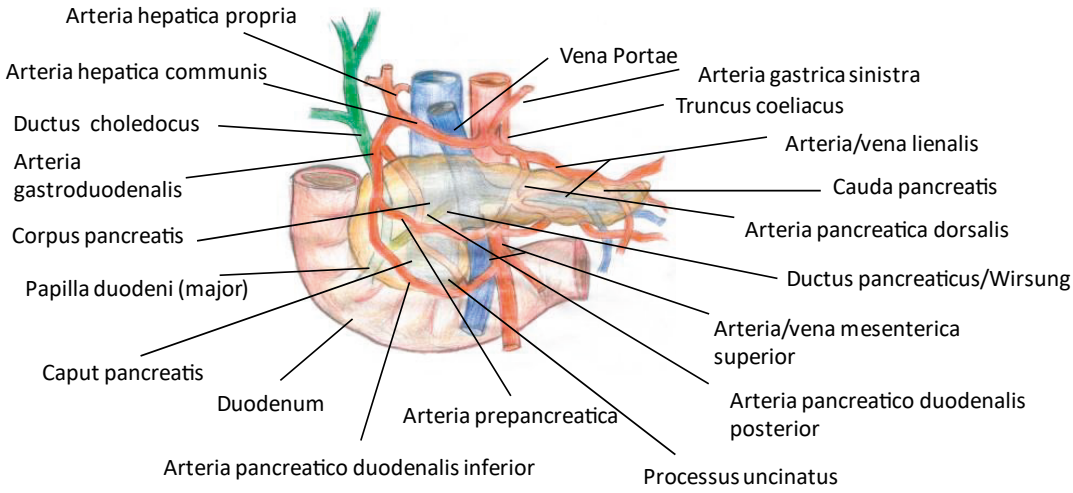


Figure 1. Anatomy of the pancreas

2.2 Chronic Pancreatitis

2.2.1 Incidence and Aetiology

Chronic pancreatitis (CP) is a sustained inflammatory disorder of the pancreas leading to morphological changes such as fibrosis, calcification, ductal structures and dilation of the pancreas, eventually leading in many cases to pancreatic exocrine and endocrine insufficiency and abdominal pain.

In Finland the incidence of AP is 70/100,000 and CP 13/100,000 (Jaakkola & Nordback, 1993). In Europe the prevalence of CP is 43-143/100,000 and incidence 7.8/100,000 (Lévy et al., 2014) and in the USA the prevalence is 41–91/100,000 and incidence is 4/100,000 (Machicado et al., 2019; Sellers et al., 2018; Yadav et al., 2011). No recent epidemiological data on CP in Finland have been presented.

Acute pancreatitis can lead to chronic pancreatitis (Machicado & Yadav, 2017), the most common risk factor being alcohol. Other aetiological causes are autoimmune pancreatitis, nutritional causes such as hyperlipidaemia, hypercalcaemia and hereditary and idiopathic pancreatitis. Smoking is also an independent risk factor for pancreatitis. Some genetic mutations such as Serine Peptidase Inhibitor Kazal type 1), (*SPINK1),* serine protease 1 *(PRSS1)* or cystic fibrosis transmembrane conductance regulator (*CTRC)* are known to be risk factors for CP (Schneider et al., 2007). Although bile duct stones are a common cause of AP, there is no consensus that it can cause CP (van Geenen et al., 2010; Yan, 2006). There is also a plethora of drugs suspected of causing AP and thus CP such as statins or metformin but causality is often hard to prove (Weissman et al., 2020). Pancreatitis may also be associated with inflammatory bowel disease and the medications used to treat the disease (Fousekis et al., 2018). Patients with celiac disease may be at higher risk for AP and CP (Alkhayyat et al., 2021).

Approximately 10% of patients with AP develop CP (Ahmed Ali et al., 2016). CP causes pancreatic morphological changes and parenchymal fibrosis. It may lead to pancreatic duct dilation and pancreatic pseudocysts. Pseudocysts can cause complications such as infection, pain, gastrointestinal tract or bile duct obstruction and haemorrhage. Pseudocysts are defined as cavities of pancreatic fluid; despite being walled-off, they lack an epithelial lining. Pancreatic calcifications and sometimes ductal stones are pathognomonic for CP. (Singh et al., 2019) The main symptom of CP is abdominal pain, even so, 10% of patients are primarily painless (Bhullar et al., 2022).

It is hypothesised in sentinel acute pancreatitis event (SAPE) theory that a first episode of AP can sensitize the pancreas to recurrent AP, thereby constituting as a risk for CP. This means that in order to develop CP a primary (sentinel) acute

pancreatitis episode is needed (Whitcomb, 2022). For instance, alcohol and its metabolites, such as acetaldehyde, cause damage to the pancreas by promoting autodigestion, damaging the endothelium and causing microcirculatory disturbances to the pancreas. This in turn can lead to fibrosis through activation of stellate cells, leading to possible duct strictures and high ductal pressure, in which case the flow of pancreatic juices is not optimal, promoting auto-digestion and the formation of calculi. (Grauvogel et al., 2012; J. C. & Parks, 2021)

It must be mentioned that only a small fraction (3-4%) of heavy drinkers ever develop AP, leading to the belief that there are other factors contributing to pancreatitis such as unknown genetic factors or environmental factors. (Lankisch et al., 2002) Also, not all patients, for instance, with *SPINK1* mutations develop pancreatitis (Nikkola et al., 2022).

2.2.2 Clinical Picture and Pain Mechanism

The clinical presentation of CP involves consistent or episodes of abdominal pain. Sometimes patients have acute pancreatic inflammations. In some cases, CP may emerge without prior AP.

Chronic pancreatic inflammation may lead to abdominal neuropathy, ischaemia and hyperalgesia, leading to abdominal pain regardless of cessation of the inflammatory process of the pancreas. One theory states that a lifestyle of heavy alcohol consumption and smoking leads to oxidative stress and ischaemia and further that exocrine insufficiency leads to low vitamin and antioxidant levels which may promote pain. (Drewes et al., 2020; Olesen et al., 2014, 2021; Sureshkumar et al., 2021; Tjora et al., 2020)

Other causes of pain and symptoms may be due to pancreatic complications such as pseudocysts, portal/splenic vein obstruction and pancreatic or bile duct strictures (Poulsen, 2013). (Figure 2)
Chronic inflammation of the pancreas can lead to neuropathic pain leading to both peripheral and central changes in the nervous system causing a sensitization of pain or stimulus-independent pain (Drewes et al., 2008; Olesen, Krauss, et al., 2017). Another issue is opioid usage related hyperalgesia and tolerance, which are common in CP patients (Saloman et al., 2022).
Pain patterns in CP range from intermittent pain to continuous severe pain. Pain patterns change during the disease but are not dependent on disease duration or pancreatic function (Kempeneers, Issa, Verdonk, et al., 2021).

Pancreatic exocrine insufficiency (PEI) can cause weight loss, bloating, steatorrhea and diarrhoea, risk factors for PEI being smoking and disease duration. These can lead to osteoporosis or vitamin deficiency (Duggan, Smyth, Murphy, et al., 2014; Jøker-Jensen et al., 2020) and affect patients' survival and quality of life (de la Iglesia-Garcia et al., 2018; Erchinger, Engjom, et al., 2022; Roberts et al., 2019). Endocrine insufficiency or diabetes is present in about 40-80% of CP patients (Malka et al., 2000; Olesen, Poulsen, et al., 2017). Endocrine insufficiency/diabetes must also be screened for in CP patients. (Meier & Giese, 2015).

2.2.3 Treatment

Treatment consists of abstaining from alcohol and smoking. Pain medication usually consists of opiates, antioxidants and neurogenic pain medication such as pregabalin. Pancreatic enzyme replacement therapy is used for malabsorption, abdominal pain and steatorrhea (Drewes et al., 2017; Shah et al., 2021; Sureshkumar et al., 2021).

Often conservative pain treatment is not enough and invasive treatments such as endoscopic stenting and surgery are needed. Endoscopic treatment is less invasive

but its long-term results may not be as good as those of surgery. Endoscopic procedures include pancreatic and bile duct stenting and celiac plexus interventions. Many CP related complications, such as pancreatic fistulas and pseudocysts, can be treated endoscopically. (Ma et al., 2021; Udd et al., 2020)

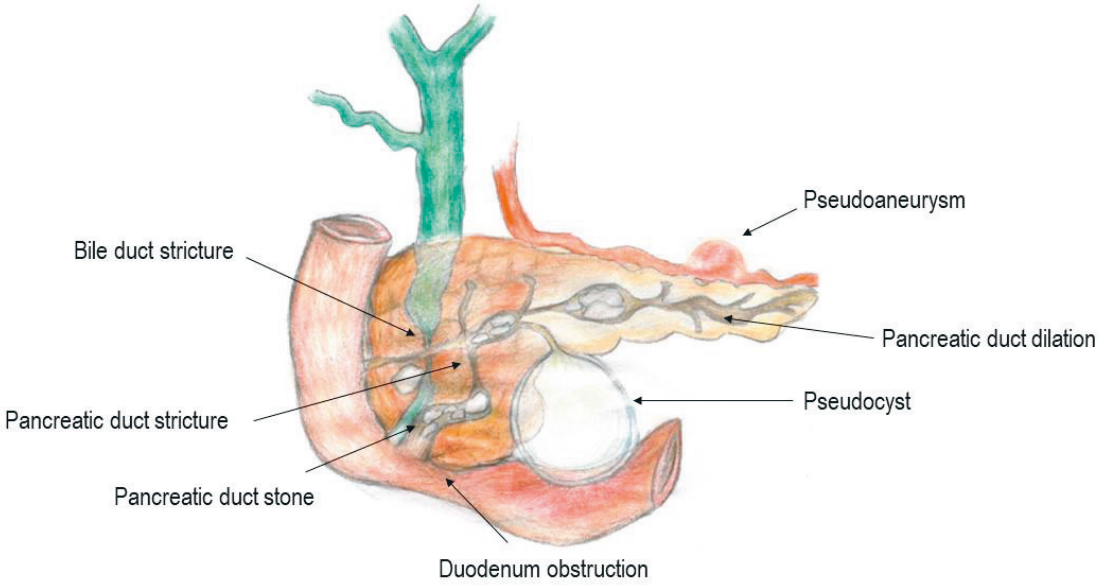


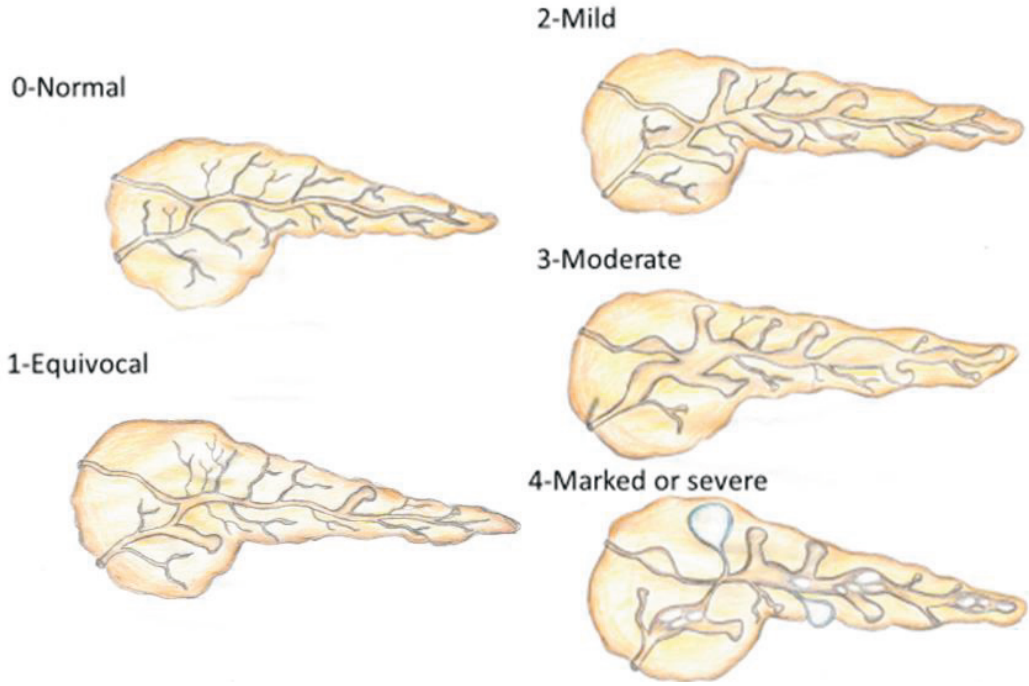
Figure 2. Most common complications related to chronic pancreatitis

2.3 Diagnosis and Classification of Chronic Pancreatitis

2.3.1 Diagnostic Criteria for Chronic Pancreatitis

The diagnosis of CP is based on typical clinical findings such as persistent abdominal pain (except in painless CP) and recurrent pancreatitis, imaging findings and pancreatic exocrine insufficiency. CP can also be diagnosed from a histological specimen. Probable diagnostic features include recurrent pseudocysts and endocrine insufficiency. Typical imaging findings include expanded or irregular pancreatic ducts, pancreatic calcifications and pseudocysts (Poulsen, 2013). Diagnosis of CP is not always simple especially in its early stages or if there is a tumour-like mass in the head of the pancreas and a dilated pancreatic and bile duct (double duct sign).(Kanchustambam et al., 2020) PC and CP symptoms can in some cases be the same (abdominal pain, pancreatic insufficiency and weight loss). (Lee et al., 2021)

Etemad and Whitcomb developed the TIGAR-O classification system, where risk factors involve T (toxic) e. g. alcohol, medication, smoking, chronic renal failure, I (idiopathic), G (genetic) e. g. hereditary CP and *SPINK1* mutation, A (autoimmune) autoimmune CP may be isolated or related to inflammatory bowel diseases, primary biliary cirrhosis or Sjögren´s syndrome, R (severe and recurring pancreatitis), O (obstructive) e. g. duct obstruction. The TIGAR-O classification emphasizes a pancreatic tissue biopsy which may be difficult to obtain. (Etemad & Whitcomb, 2001)



Cambridge Classification of severity of CP	Main duct	Abnormal side branches
0-Normal	Normal	None
1-Equivocal	Normal	Under three
2-Mild	Normal	Three or more
3-Moderate	Abnormal	Three or more
4-Marker or Severe	Abnormal and with cysts over 10mm, intraductal fillings, stricture, irregularity or organ invasion	Three or more

Figure 3. Different stages of ductal changes in chronic pancreatitis according to the Cambridge Classification

In 2006 A Schneider et al. created the M-ANHHEIM classification for CP with probable and definitive diagnostic criteria for CP (Schneider et al., 2007) (Table 1). Diagnosis requires a typical presentation of abdominal pain or prior pancreatitis, except for primary painless CP. Definitive criteria for CP are pancreatic calcifications, moderate or marked ductal lesions (according to the Cambridge classification (Sarner & Cotton, 1984) Figure 3), pancreatic exocrine insufficiency and steatorrhea reduced by Pancreatic Enzyme Supplement (PES) and/or histological specimen of the pancreas which consists of typical CP findings. Probable diagnostic criteria include mild pancreatic ductal changes, recurrent or persistent pseudocysts, pathological or pancreatic exocrine insufficiency, for example a low faecal elastase-1 (FE1) count and finally endocrine insufficiency, for example high fasting blood sugar.

Table 1. The M-ANHHEIM classification for chronic pancreatitis (CP) with probable and definitive diagnostic criteria for CP

	The M-ANNHEIM multiple risk factor classification [Schneider et al. 2006]
M	Multiple risk factors
A	Alcohol
N	Nicotine (Smoking)
N	Nutritional factors (e. g. hyperlipidaemia)
H	Hereditary factors (e. g. familial pancreatitis or mutations such as *SPINK1*)
E	Efferent duct factors (duct obstruction, pancreas divisum or pancreas annular)
I	Immunological factors (autoimmune pancreatitis or inflammatory bowel disease or primary sclerosing cholangitis associated CP)
M	Miscellaneous (hypercalcaemia or drugs such as valproate or azathioprine)

2.3.2 Imaging

There are several imaging modalities that can be used to image the pancreas, abdominal ultrasound being often the first-line in imaging because of its cost effectiveness, no radiation and ease of access. Ultrasound is good for detecting gallstones and complications such as portal vein thrombosis/portal hypertension and pancreatic lesions or pseudocysts. However, for diagnosis of CP and differentiation of tumours ultrasound is not sensitive enough (sensitivity 57-63%). CT scan is more standardized than an ultrasound and can be used for CP diagnosis and gives a good morphological view of the pancreas and possible complications. It also is better for detecting pancreatic duct stones and calcification. (Issa et al., 2017)

Endoscopic Retrograde Cholangiopancreatography (ERCP) used to be the gold standard for imaging in CP but because the Magnetic Resonance Imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) techniques developed and the complication rates of ERCP (1-5%) it is used only therapeutically (Cirocchi et al., 2017; Dahale et al., 2022; De'Ath et al., 2022; Ru et al., 2021). ERCP is an invasive technique usually done under sedation, where the papilla of Vater or papilla minor is cannulated retrogradely into the main pancreatic duct via a duodenoscope. The Cambridge classification of CP is graded according to the number of abnormal side branches or abnormal pancreatic main duct (Sarner & Cotton, 1984). MRCP is more sensitive for CP and is better than CT for viewing the changes in the pancreatic duct and is more sensitive than CT in early CP. A secreting stimulated MRCP can be used in cases to have better view of the pancreatic duct, for example in anatomical variations such as pancreas divisum. (Hill & Tirkes, 2020; Schima et al., 2020; Swensson et al., 2021)

EUS (Endoscopic Ultrasound) is a modern method for viewing the pancreas and a good method for diagnosing CP and differentiating from tumours via biopsies/fine needle aspirations. EUS provides a close and high-resolution image of the pancreas and can be accompanied by elastography to further evaluate the firmness of the pancreatic tissue. The Rosemont classification for CP assesses the following EUS findings: hyperechoic foci, lobularity, honeycombing, cysts and stranding (Catalano et al., 2009). The main problem with EUS is intra-observer variability in early stage CP, possibly leading to low specificity of CP (Mel Wilcox et al., 2020). Parenchymal findings of CP are based on assessment of fibrosis which may also be present in aging (J.-M. Löhr et al., 2018).

EUS can be used for endoscopic interventions such as pseudocyst drainage and pancreatic or bile duct drainage. (Costache et al., 2017; Sekine et al., 2021; Takasaki et al., 2020)

Differentiating between CP and PC can be difficult (Srisajjakul et al., 2020). CP patients are at a slightly higher risk for PC than the average population (relative risk 3-20) but in hereditary pancreatitis the risk is substantially higher with a relative risk of 10-70. The matter is quite complex since these diseases have an overlap of risk factors (e. g. smoking, alcohol consumption and diabetes) and PC can cause pancreatitis. Recent studies have found that most cases of PC were diagnosed quite soon after diagnosis of CP (under 2 years) indicating a probable misdiagnosis. (Greenhalf et al., 2020; Kirkegård et al., 2017; Korpela et al., 2020)

2.3.3 Pancreatic Function

PEI is often underdiagnosed and undertreated in CP patients (de Rijk et al., 2022). PEI can be tested in a number of ways: FE1, 13C mixed triglyceride breath test, faecal fat excretion measurement or by invasive methods such as pancreatic endoscopic or MRI function tests that are not clinically used (Ketwaroo et al., 2013;

Loser et al., 1996; Lust et al., 2006; Monachese et al., 2021; Nakamura et al., 2009; Stevens et al., 2008). In Finland a two-time FE1 measurement is most often used. The sensitivity of FE1 improves with the severity of PEI, thus it is not sensitive in mild PEI (25-65%). A cut-off value of under 200ug/g is used for a low FE1 count with values under 100ug/g indicating clinically severe PEI (Lüth et al., 2001; Vanga et al., 2018).

Diabetes in CP patients is diagnosed the usual way with fasting glucose, HbA1c or an oral glucose tolerance test, the latter being the most sensitive (American Diabetes Association, 2019; Meier & Giese, 2015).

2.4 Prevention

It is most important to focus on the cessation of alcohol consumption and smoking since both are common independent risk factors for CP (Tjora et al., 2020). Metabolic factors should also be considered in the prevention of CP. There is also evidence that a fatty pancreas could be a risk factor for developing CP (Fujii et al., 2019). In a recent retrospective study metabolic disorder was a risk factor for CP after AP (Bojková et al., 2020).

CP patients probably have a poor understanding of their disease and its prevention (Haritha & Wilcox, 2015) and there is evidence that patient guidance by a pancreas specialist is more effective than guidance from gastroenterologists and primary care physicians, leading to higher rates of cessation of alcohol consumption and smoking (Srivoleti et al., 2021a).

There is no medication for the prevention of CP, hence it is important to focus on guidance in lifestyles factors. However, there are a number of novel experiments ongoing to prevent the development of CP, such as vitamin D and tyrosine kinase

inhibitor which focus on prevention of fibrosis through the pancreatic stellate cells (Bansod et al., 2021; Zheng & Gao, 2022).

2.5 Management of Chronic Pancreatitis

Chronic pancreatitis is primally treated conservatively. The most important element in the management of CP is to avoid tobacco and alcohol.
Other treatments include treating pancreatic exocrine and endocrine insufficiency and pain. Invasive treatments consist of endoscopic procedures and pancreatic surgery. (Drewes et al., 2017)

2.5.1 Medical Management

Conservative management of CP involves the treatment of pain with analgesics and the diagnosis and treatment of pancreatic exocrine and endocrine insufficiency. The first-line analgesics for CP pain are NSAIDS and paracetamol. NSAIDS are not optimal for long-term use, with side effects such as gastrointestinal ulcers (Thiagarajan & Jankowski, 2012). Usually these are not enough as stronger pain medications such as tramadol and even opiates are needed for pain relief.

About half of CP patients are prescribed opioids at some point and this can be problematic in long-term use, since they can paradoxically cause hypersensitization to pain, causing more severe pain and eventually necessitating bigger doses (Keefer et al., 2016; Nusrat et al., 2012). There is evidence that pregabalin can be used for

CP-induced pain, thereby supporting the idea that there is an important neuropathic component to CP pain (Olesen et al., 2011; Sureshkumar et al., 2021).

Regarding the oxidative stress theory behind CP pain, in some clinical trials antioxidants have been shown to ease pain but novel data provide no evidence of antioxidants having an effect on CP pain. Nor have antioxidants been proven to help delay disease progression. More trials are needed on the subject if certain subgroups of patients may derive benefit from antioxidant therapy (Bhardwaj et al., 2009; Mohta et al., 2021; Shalimar et al., 2017; Wiese et al., 2021).

Exocrine insufficiency is treated by an enteric-coated PES consisting mainly of lipase and also protease and amylase. A recommended dose of 25-50 000 IU of lipase is usually needed at meals or snacks and can be individually adjusted according to symptoms. Because stomach acids dissolve pancreatic enzymes, a proton pump inhibitor can be used if the desired clinical effect is not achieved (Vecht et al., 2006). PES is effective for abdominal symptoms such as diarrhoea, bloating, flatulence and abdominal pain. However, there is no consensus on whether PES can relieve pancreatic pain. (de la Iglesia-García et al., 2017; Shimizu et al., 2022; Yaghoobi et al., 2016)

Endocrine insufficiency or diabetes is present in about 40-80% of CP patients (Malka et al., 2000; Olesen, Poulsen, et al., 2017). CP-related prolonged inflammation of the pancreas destroys the pancreatic islet cells leading to low secretion not only of insulin but also of glucagon, that counter regulates the effects of insulin. The first-line treatment is metformin but eventually insulin may be required. CP patients with diabetes and insulin have a higher tendency for hypoglycaemia and hypoglycaemia-related mortality, probably due to the low secretion of glucagon. (Ewald & Hardt, 2013; Lin et al., 2020)

Vitamin deficiency in CP patients should be screened as absorption of fat-soluble vitamins can be problematic in CP, especially if exocrine insufficiency is present (Martínez-Moneo et al., 2016; Sikkens et al., 2013).

2.5.2 Endoscopic Management

2.5.2.1 Pseudocyst Drainage

Endoscopic interventions are often needed in CP to treat pancreatic complications and pain. One of most common complications related to CP is pancreatic pseudocysts, which can cause pain, obstruction of the bile or gastrointestinal tract, infection, bleeding or even fistulas (Chauhan & Forsmark, 2013; Sikkens et al., 2013; Singhal et al., 2013). Pancreatic pseudocysts consist of generally homogenic fluid lined with fibrotic tissue without any epithelial lining and connected to the pancreatic tissue or branches and related to both AP and CP. Pseudocysts are most common in alcohol-related CP with a prevalence of 30-40% (Agarwal et al., 2020; Machicado et al., 2018). It is known that pseudocysts can have a tendency for spontaneous resolution although there are no recent data on the subject. However, it seems that CP-related pseudocysts have a smaller resolution rate. (Aghdassi et al., 2008; Gouyon et al., 1997). The preferred approach to a small (5-6cm) pseudocyst that communicates with the pancreatic duct is transpapillar pseudocystal drainage with a pancreatic stent. A transmural drainage approach can be used to drain symptomatic pseudocysts usually through the gastric wall, rarely can a transduodenal approach be used (Kitano et al., 2020; J. M. Löhr et al., 2017). Transmural drainage should be done under the guidance of an endoscopic ultrasound and the fluid can be drained either by a plastic or metal stent. Generally plastic stents are used for drainage as they are cheaper but several stents are sometimes needed compared to the new self-opening metal stents with a bigger lumen. The data on the superiority of the newer metal stents compared to the cheaper plastic stents remain inconsistent (Chen et al., 2018; Saunders et al., 2019; Shekhar et al., 2018). The 2017 United European Gastroenterology evidence-based guidelines and 2018 European Society of Gastrointestinal Endoscopy guidelines

recommend a primary plastic stent for pseudocysts. (Dumonceau et al., 2019; J. M. Löhr et al., 2017).

2.5.2.2 Biliary Duct Stenosis

Biliary duct stenosis is present in about 10-35% of CP patients causing jaundice and elevated bilirubin levels (Huizinga et al., 1992; Hyun et al., 2021; Sand & Nordback, 1995). CP-related benign biliary tract stenosis can be caused by pancreatic fibrosis, pseudocysts or an acute inflammation. Only approximately 30% of all biliary strictures are benign so brush cytology and proper pre-interventional imaging should be also done because brush cytology alone has a low sensitivity (45-60%) for malignant strictures (Navaneethan et al., 2015; Tummala et al., 2013).

Persistent and symptomatic biliary duct stenosis related to CP should be treated with a biliary tract plastic stent by ERCP. Usually, multiple procedures and stents are needed for an optimal clinical result. Usually, 1-3 biliary stents are placed simultaneously and changed 1-4 times a year. Seventy-five per cent of CP patients need multiple stents for biliary stenosis (Craig, 2012; Hyun et al., 2021). Fully covered self-expanding metal stents have been emerging in recent years for the endoscopic treatment of biliary strictures. They may necessitate fewer interventions and be kept for longer. (Hu et al., 2017) Both plastic and metal stents have been shown to achieve equally high (90%) stricture-free rates after two years(Haapamäki, Kylänpää, et al., 2015).

In a multicentre randomized trial comparing metal and plastic stents for CP-related strictures both stents seem to have similar efficiency with the metal stent group needing fewer re-interventions (Ramchandani et al., 2021). Although metal stents are more expensive, they seem to be cost-effective compared to plastic stents (Ramchandani et al., 2021). Inserting a metal stent for 10-12 months for biliary strictures in CP patients can results in 60% of patients not needing any additional interventions and being symptom-free in long-term 5-year follow-up (Lakhtakia et

al., 2020). It could be suggested that for CP-related benign biliary tract stenosis a covered self-expanding metal stent should be used as the first choice of treatment.

2.5.2.3 Pancreatic Duct Stones

Non-surgical ways to deal with pancreatic duct stones are endoscopic therapy, ESWL (Extracorporeal shock wave lithotripsy) or a combination of these. ESWL can be used if the duct stones are over 5mm, and, if there is a pancreatic main duct stricture it should be dilated to prevent it from inhibiting the clearance of the broken down stones (Dumonceau et al., 2019). ESWL has reportedly achieved a clinical success rate of 80% in pain reduction in 12-month follow-up (Korpela et al., 2016). ESWL can be useful for pain relief in calcific CP where the stones are in the head or body of the pancreas (Guda et al., 2005; van Huijgevoort et al., 2020).

2.5.2.4 Pancreatic Duct Strictures

Endoscopic retrograde pancreatography (ERP) and pancreatic duct stenting are usually performed for pancreas-specific conditions to facilitate diagnosis and for the treatment of pancreatic strictures, duct stones and leaks (ASGE Standards of Practice Committee et al., 2015). It must be stated that ERP is not usually used for diagnostic procedures alone due to the risk of complications and advances in modern imaging modalities (Obeidat et al., 2022).

While nearly 20% of patients undergoing ERP suffer adverse effects and even though CP patients have previously been thought to have decreased risk of complications (Cotton et al., 2009) a single retrospective study of n=1,288 patients

found CP patients to have an almost two-fold risk for complications (Han et al., 2021).

Pancreatic duct stenting, however, has been shown to provide short-term pain relief in up to 88-89% of patients with a proximal duct stricture (B. B. Shah et al., 2022; Tringali et al., 2019). Usually, a straight pancreatic stent is inserted into the pancreatic duct and needs to be changed every 3-18 months. Recently a physiological S-shaped stent has been to shown to yield better results and fewer adverse effects (Hori et al., 2021). Fully covered metal stents can also be used for pancreatic duct strictures with up to 71% of patients achieving pain relief but these may have a higher complication rate than plastic stents (Korpela et al., 2019; Sofi et al., 2021).

CP-related duct strictures are usually resolved with an endoscopic duct stent but when the stent is removed strictures may well recur and thus the pain may return. However, surgery may achieve a better outcome in long-term pain relief than endoscopic stenting (Cahen et al., 2011). Early surgery for CP pain in particular may give better pain relief and be more cost-effective (Issa et al., 2020; Kempeneers, Issa, Bruno, et al., 2021).

2.5.2.5 Celiac Blockade

The celiac plexus blockade is typically used for pancreatic cancer patients but has also been shown to be effective for CP (Urits et al., 2020). It can be produced CT-guided by a radiologist or EUS-guided (Fusaroli & Caletti, 2015; Matsumoto et al., 2022). It produces acceptable results and is safe (O'Toole & Schmulewitz, 2009). However, it seems that the long term (over 24 weeks) results are poor but more long-term studies are needed (Goodman & Gress, 2012).

2.5.3 Surgical Management

Even though endoscopic procedures provide good short-term results with less invasive treatments, there is evidence that surgery provides better long-term outcomes in early painful CP, with the same complication and mortality rates (Ahmed Ali et al., 2015; Jawad et al., 2017). Although there is no consensus on which is better (Jiang et al., 2018; Ma et al., 2021).

A Dutch study group released the ESCAPE randomized trial, where early (under 6 weeks) pancreatic surgery provided better pain relief (Issa et al., 2020).

A type of pancreaticoduodenectomy (PD) also known as the Whipple procedure was the original surgery used on CP patients. PD involves resecting the duodenum along with the head of the pancreas (Bachmann et al., 2013). A CP-specific duodenum preserving surgical technique has been developed, for example with the Frey, Puestow, Berger and Berne modifications (Frey & Smith, 1987; Puestow & Gillesby, 1958; Roch et al., 2014). The pancreatic tissue is either resected, drained or both, and a pancreatojejunostomy is performed with a Roux-Y loop, where, unlike in PD hepaticojejunostomy is not needed. Puestow's and Gillesby's operation involves a lateral pancreatic jejunostomy which drains the dilated pancreatic duct. Beger's modification involves a pancreatic head resection with pancreatic and bile duct anastomosis. (Mihaljevic et al., 2010; Ni et al., 2015)

In 1958 Puestow et al. introduced a modified lateral pancreatic jejunostomy involving cutting the dilated pancreatic duct open and resecting the spleen. A few years later the Partington and Rochelle modification was adapted, where the spleen was preserved and no caudal resection was performed (Partington & Rochelle, 1960).

Later the Beger procedure was introduced, where the pancreatic head is resected and the pancreas is divided above the portal vein. This is believed to reduce symptoms by resecting the inflammatory mass from the head of the pancreas and thus reducing the drainage blockage from the pancreatic ducts and portal vein and adjacent arteries (Beger et al., 1980).

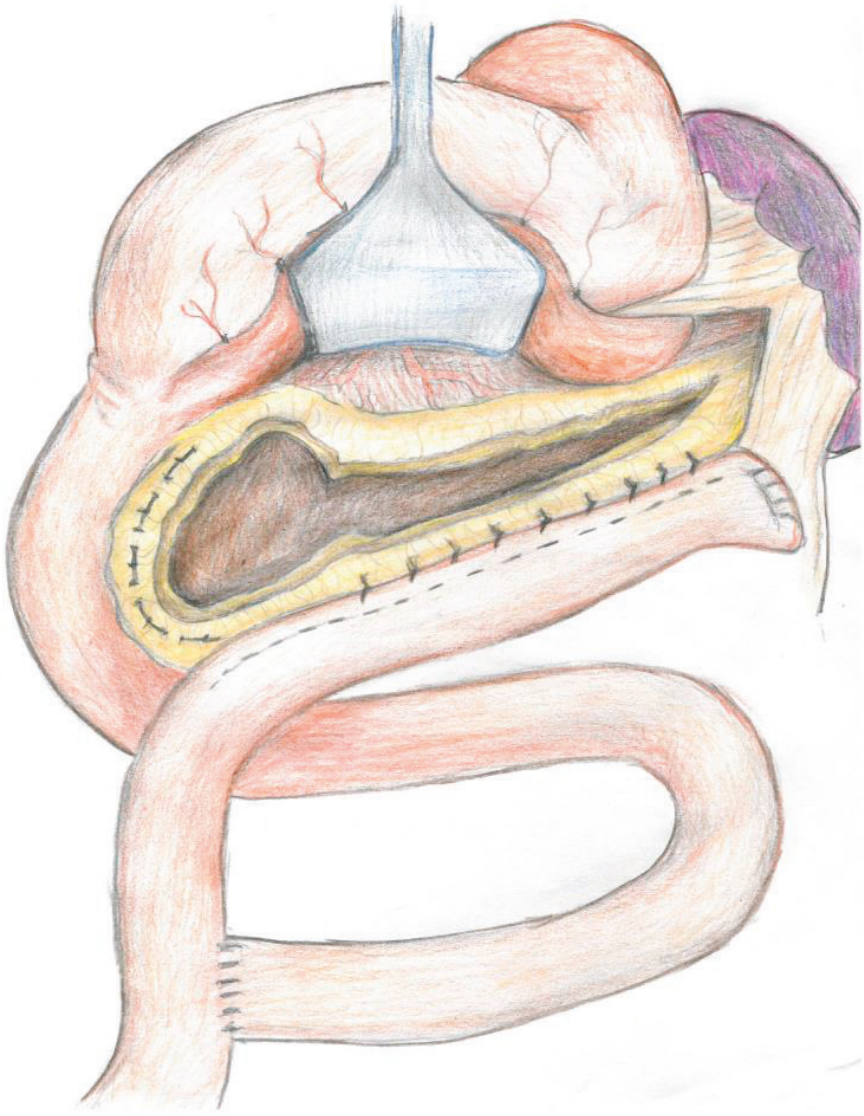


Figure 4. Frey´s duodenum-preserving pancreatic head resection for chronic pancreatitis with a side-to-side pancreaticojejunostomy

In 1987 the Frey procedure was introduced, where the pancreatic head is opened and resected following a lateral jejunostomy (Figure 4). From the Beger procedure a Berne modification has been developed. The Berne modification involves carving out the inflamed pancreas mass from the head of the pancreas and does not involve cutting the pancreas in half, thus it is less traumatic and involves only one pancreatojejunostomy (Frey & Smith, 1987; Gloor et al., 2001).

In 1998 Izbicki et al. presented the Hamburg modification of DPPHR, where the pancreas is opened in a V-shape pattern beyond the pancreatic head to the second and third pancreatic side branches. This is thought to give better drainage to the side branches and thus greater pain relief, especially in a small main duct CP(Bellon et al., 2019; Izbicki et al., 1998).

In rare cases total pancreatectomy (TP) is needed for CP complications or pain unresponsive to endoscopic or surgical interventions. Another indication for favouring TP is early onset hereditary pancreatitis or genetic pancreatitis with a higher cancer risk or small duct CP affecting the whole pancreas (Jabłońska & Mrowiec, 2021; Scholten et al., 2020). TP is often reserved for difficult-to-manage end-stage CP. TP can be combined with an islet cell autotransplantation (TPIAT), first done in the 70s in Minnesota (Najarian et al., 1977). The pancreatic islet cell grafts are isolated and reinjected usually into the liver through the portal vein. The long-term results are promising with up to 30% being insulin independent but on the other hand 30% lose the graft (Najarian et al., 1980; Sutherland et al., 2012). If CP patients have presurgical diabetes or even pre-diabetes the results are much poorer, with 16% being insulin independent after one year (Bachul et al., 2020). There are a limited group of centres that perform TPIAT and progress has been made in the selection, isolation and management of islet cell grafts in the past few years (Baldwin et al., 2021; Desai et al., 2022).

In Liverpool a near-total pancreatectomy (the LIVOCADO procedure) has been developed where the pancreas head is carved as in the Berne modification but extends the entire length of the pancreas reaching the tail. This procedure may be

appropriate for a selected group of patients where TP is not technically convenient due intra-abdominal scar tissue (Baron et al., 2021).

Thoracoscopic splanchnicectomy involves the dissection of the splanchnic nerve and is believed to ease pain from the upper abdomen. This technique is rarely used for the treatment of CP-related pain with pain reduction in the range 40-90% (Issa et al., 2014).

The choice of surgical technique for CP should be assessed according to the morphological changes in the pancreatic gland. There is no universal surgery for CP that is suited to all patients. A PPHD variation should be the treatment of choice, unless a pancreatic head tumour cannot be ruled out in which case a PD should be performed. (Mou et al., 2022). Disease duration seems to affect the surgical outcome in CP patients: CP patients benefit from early surgery before the pain has become centralized and narcotic use becomes a habit (Ratnayake et al., 2020). The 2020 international guidelines recommend early surgery for CP rather than in the advanced stage (Kempeneers, Issa, et al., 2020). Even though pancreatic surgery for CP can prevent PC it is not recommended as a prophylaxis except in hereditary pancreatitis (Kalayarasan et al., 2021; Willner et al., 2020).

2.6 Treatment Strategies

All in all, CP patients are a challenging group with multiple complications, chronic pain, alcohol consumption, smoking and opiate usage that not only impair their quality of life but markedly reduce life expectancy up to five-fold (Bilal et al., 2019; C. E. Keller et al., 2018). There is evidence that CP patients undergoing pancreatic surgery have a better prognosis (Murruste et al., 2021).

Good patient education and doctor-patient relationship are crucial, especially with some selected CP patients inclined to poor compliance with treatment and the social stigma the disease may carry (Bang eopioit al., 2014; Conwell et al., 2014).

CP is a heterogenic disease with multiple aetiologies and treatment strategies. There is no novel data on the epidemiology, treatment and QoL of CP patients in Finland. The long-lasting inflammation and malnutrition may lead to vitamin deficiency, osteoporosis and even sarcopenia in CP patients but the prevalence and clinical presentation are unknown and require more studies (Bundred et al., 2022; Hart et al., 2022).

There are numerous surgical and endoscopic interventions for CP-related pain and complications. The frequency and outcomes of these procedures are not well documented. Since CP patients are burdened with complications that impair their QoL it is necessary to determine the outcome after treating these complications.

3 AIMS OF THE STUDY

This thesis focused on treatment and quality of life in chronic pancreatitis in Finland and in the Baltic and Scandinavian countries. The specific aims of the studies were:

I. To investigate the current epidemiologic data and QoL of CP patients in Finland

II. To investigate the outcome and QoL in patients operated on for CP in Finland

III. To determine outcome and QoL after CP surgery in the Scandinavian and Baltic countries

IV. To determine the outcomes and QoL among CP patients undergoing endoscopic procedures in the Scandinavian and Baltic countries

4 METHODS

4.1 Methods

Demographic details of all of patients from the studies are presented in Table 2 and Figure 5. We included all CP patients according to the M-ANNHEIM diagnostic criteria who were treated in Tampere University Hospital (TAUH) during the period 2014-2015. Information was gathered on aetiology, disease duration, pancreatic function, treatment, complications, smoking, alcohol consumption (AUDIT) and quality of life (QoL) (QLQ-C30, PAN26).

We identified altogether 235 patients. After excluding those patients who were deceased or whose addresses were not available, 188 patients were asked to complete the QoL questionnaires EORTC (European Organisation for Research and Treatment of Cancer) QLQ-C30 and pancreatic specific EORTC QLQ-PAN26. The EORTC QLQ-C30 is a 30-question questionnaire originally developed for cancer patients. The EORTC QLQ-PAN26 is a questionnaire with 26 questions intended specifically for pancreatic cancer patients undergoing pancreatic interventions. However, both the QLQ-C30 and PAN26 have been used and validated for CP patients (Fitzsimmons et al., 1999, 2005). The United European Gastroenterology evidence-based guidelines recommend using the EORTC QLQ-C30 and PAN26 for the assessment QoL of CP patients (J. M. Löhr et al., 2017). The questionnaires were presented to the participants in their own respective native languages.

The EORTC scoring manual was used for the QLQ-C30 questionnaires and responses were scored from 0 to 100. A higher score on QOL/functioning indicates better quality of life as also does lower score on symptoms (e.g., pain or insomnia).

Mortality was recorded on 4 November 2018. The median follow-up time from disease onset was five years (2–43 years). For the QLQ-C30 control population a Swedish control population was used (n=2,998). A healthy control from the UK (n=102, median age 40, range 20-94) was used for the PAN26 questionnaire responses. We used the Finnish Institute for Health and Welfare 2017 Finnish Drinking Survey study (Mäkelä Pia) as a normative population for the AUDIT responses (n = 1,368, 44% males 28–79 years). We used the Finnish Current Care Guidelines to define hazardous alcohol consumption as over 6 AUDIT points for women and over eight points for men.

For the unpublished data we recruited patients from Study I with a definitive diagnostic criterion for CP. We excluded patients who had moved away from the catchment area of Tampere University Hospital, were dead, had advanced dementia or did not participate in the first study. We recruited 77 patients and 33 (42%) of those agreed to participate. Data about vitamin supplements, medication, possible fractures and menopause were recorded. We measured the patients' vitamin A, E and D levels, blood sugar, haemoglobin, albumin, FE1, weight and height. We also measured the bone density of all patients from the femur neck and lumbar spine. The WHO definitions for osteopenia and osteoporosis were used. Osteopenia was defined as a T score between -1 and -2.5. Osteoporosis was defined as a T-score of -2.5 or less. For patients under 50 years old, we used a Z-score instead of a T-score according to the ISCD guidelines. A Z-score of -2.0 or under was considered below the expected age range. We defined a 25 000-50 000 IU of pancreatic lipase per meal as an adequate amount. The patients who had a recent (under one year) CT or MRI scan had the mean area of both psoas muscles calculated from the middle of the 3rd lumbar vertebra. PMA under 8.0 cm^2 for males and under 5.5 cm^2 for females was used as a cut-off for sarcopenia.

Study II included all pancreatic resections from the Finnish National Institute for Health and Welfare HILMO register from the years 2000-2008. From these we selected patients having an ICD-10 code for CP (K86.01, K86.1, K86.08, K86.8 and K86.9) and procedural code (Nordic Classification of Surgical Procedures) of JLC* or JLW96. The number of patients was 97. We reviewed the medical records of all patients from 13 different hospitals and 30 patients who had CP-related pain as an indication for surgery were included in the final database. Dates of death were recorded on 22nd of September 2017.

Studies III and IV were multicentre studies and included data from the Scandinavian Baltic Pancreatic Club (SBPC) database. We chose patients from eight centres and four countries (Finland, Norway, Denmark and Lithuania) across northern Europe. The baseline population included 1,327 patients who met the M-ANNHEIM diagnostic criteria for chronic pancreatitis. Data collection was done during the period 2016-2019. In Study IV the reference population (n=870) consisted of CP patients on whom no interventions were performed.

We analysed patients who underwent pancreatic surgery. For the final surgery group, we included patients who had undergone pancreatic surgery for CP pain for Study III and patients undergoing endoscopic procedures and not surgery for Study IV. Patients undergoing emergency surgery or surgery for suspected malignancy were excluded from the final surgery group in Study III. We gathered data on disease duration, interventions, pancreatic function, QOL, pain and aetiology.

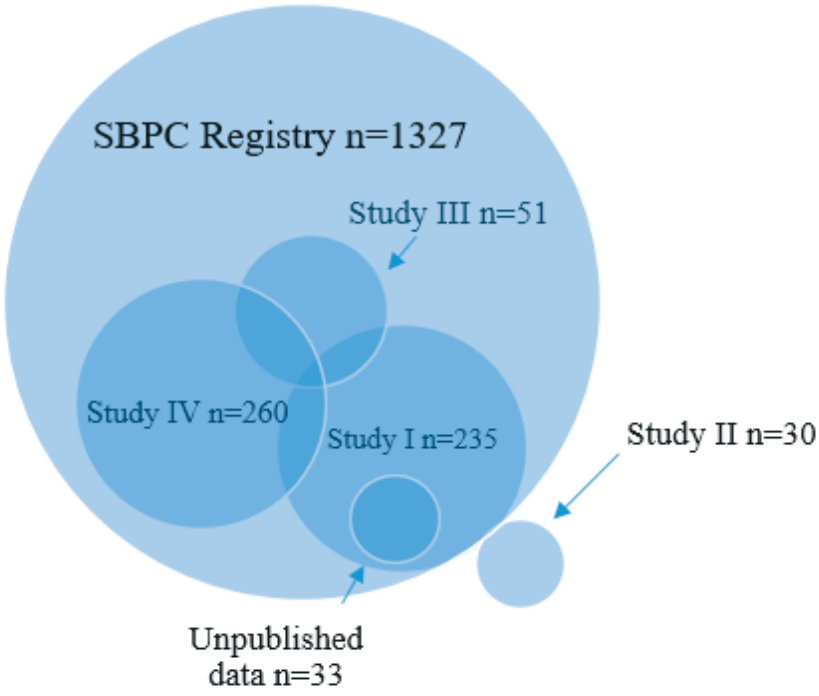


Figure 5. Diagram of all patients included in studies I-IV and the unpublished data. Studies I-II were from Finland. The SBPC registry consisted of patients from Denmark, Lithuania, Finland and Norway

Table 2. Demographic findings of the chronic pancreatitis patients in each study

Demographic table of CP patients	Females/Males	Age (years)	BMI	Disease duration (years)
Study I: Quality of Life in Chronic Pancreatitis n=235	34%/67%	58 (26-95)	23 (16-48)	4 (1-42)
Unpublished data n=33	39%/61%	62 (39-81)	28 (19-38)	6 (4-27)
Study II: Surgery for Chronic Pancreatitis in Finland n=30	23%/77%	45 (21-62)	Unknown	2 (0-10)
Study III: Pancreatic surgery and Quality of Life in Chronic Pancreatitis Patients n=51	33%/67%	48 (18-71)	23 (16-31)	6 (0-39)
Study IV: Endoscopic Procedures and Quality of Life in Chronic Pancreatitis Patients n=260	32% / 68%	59 (20-90)	23 (15-48)	4 (0-41)
SBPC database n=1,327	33%/67%	59 (15-109)	23 (13-48)	3 (0-61)
Reference group (no interventions) n=870	33% / 67%	60 (18-89)	23 (13-46)	2 (0-39)
Data is presented as median (range) or percentage (%). BMI= Body Mass Index				

4.2 Statistics

Data are presented as medians (range) unless otherwise stated. We used Pearson's Chi-Square or Fisher's exact test for categorical variables and the Mann-Whitney U test for ordinal or continuous variables. The EORTC scoring manual was used for the QLQ-C30 and PAN26 questionnaires, the responses were scored 0–100. A higher score on QOL/functioning represents better functioning/QoL and a lower score on symptoms (e.g., pain or insomnia) represents less symptoms. We considered a P-value of under 0.05 statistically significant. A multivariable analysis was conducted for Study IV using a hierarchical regression analysis model. The analysis was conducted separately for all quality of life variables using the following independent variables: aetiology (alcohol, smoking, efferent duct and hereditary pancreatitis), age, disease duration, gender and pain. We then measured the interaction effect of the variables using the R2-changes value. We considered a R2-value of 0.01 to affect the outcome by 1%. The IBM SPSS v24, v26 or v28 was used

for all statistical calculations. We had assistance from statistician Mika Helminen of Tampere University, Finland.

4.3 Ethical Aspects

The studies were approved by the Ethics Committee of Tampere University Hospital, Finland in Studies I, III and IV (ETL code R15187), in the unpublished data (ETL code R18107) and in Study II (ETL R16153). Each centre in the SBPC registry also had its own local ethical permit. All the patients recruited for the study provided informed written consent. We also had a licence for the HILMO register from the Finnish National Institute for Health and Welfare (THL/1854/5.05.00/2012).

5 RESULTS

According to the studies in this thesis the most common aetiologies were alcohol (49-68%) and smoking (36-71%). Most patients had pancreatic calcifications (58-91%) and pancreatic main duct lesions (40-87%). Pancreatic exocrine insufficiency (41-75%) and diabetes (39-75%) were common findings in CP patients. (Table 3)

Table 3. Findings of chronic pancreatitis patients in the respective studies

Demographic table of CP patients	Study I: Quality of Life in Chronic Pancreatitis n=235	Unpublished data n=33	Study II: Surgery for Chronic Pancreatitis in Finland n=30	Study III: Pancreatic surgery and Quality of Life in Chronic Pancreatitis Patients n=51	Study IV: Endoscopic Procedures and Quality of Life in Chronic Pancreatitis Patients n=260	SBPC database n=1,327	Reference group (no interventions) n=870
Aetiology							
Alcohol	68%	49%	60%	60%	65%	61%	60%
Smoking	54%	36%	50%	60%	71%	69%	68%
Nutritional	2%	0%	3%	0%	2%	3%	4%
Hereditary	3%	0%	0%	7%	4%	10%	10%
Efferent duct	10%	0%	17%	0%	14%	10%	7%
Immunological	3%	0%	0%	0%	2%	2%	3%
Unknown	21%	15%	33%	30%	6%	7%	7%
Pancreatic calcification	66%	58%	70%	91%	77%	69%	67%
Pancreatic main duct lesions	50%	40%	87%	74%	73%	57%	48%
Pseudocysts	58%	42%	57%	41%	54%	43%	35%
PEI	55%	75%	67%	41%	62%	60%	53%
DM	54%	75%	56%	39%	45%	44%	40%

Data is presented as median (range) or percentage (%). PEI= Pancreatic exocrine insufficiency and DM= Diabetes mellitus

5.1 Study I: Quality of Life in Chronic Pancreatitis

5.1.1 Clinical Characteristics of the Chronic Pancreatitis population

The total number CP patients included in the final database was 235. Median age was 58 years (range 26-95). Demographic findings can be found in Table 2. Definitive diagnostic criteria for CP were met in 91% (n=216) of the patients. Sixty-four percent had recurrent AP. Radiological imaging was done for 93% (n=219) of the patients during the follow-up period, 37% had marked changes, 20% had moderate changes, 12% had mild changes, 19% had equivocal changes and 12% had normal pancreas during imaging. Multiple aetiologies were common, with alcohol consumption the most common combined with smoking; half of the CP patients reported alcohol and smoking as risk factors. (Table 3) Over half of the patients had smoking as a risk factor and 78% continued smoking after diagnosis. One in five had idiopathic pancreatitis.

Alcohol related CP patients had more pseudocysts and pancreatic calcification than non-alcohol related CP patients (74% vs. 50%; $p<0.001$, 60% vs. 38%; $p<0.001$ respectively). In patients who smoked calcifications and pseudocysts were also more common than in non-smokers but did not reach statistical significance (65% vs. 53%; $p=0.071$, 61% vs. 54%; $p=0.262$ respectively)

CP related complications were the main reason for treating most patients in TAUH. There were numerous complications and up to 65% had some kind of complication, the

most common being pseudocysts (58%) followed by bile duct stenosis (10%). The most common complications are listed in Table 4. Alcohol-related CP patients had more pseudocysts than those with other aetiologies (60% vs. 38%, $p<0.001$).

Twenty-six percent of the patients (n=60) died during follow-up at a median age of 62 (range 26-85). Females died at a median age of 63 years and males at 62 years. Causes of death were recorded for 35% of the patients (Table 4). In 2017 the median age of death in Finland was 75 years for men and 81 years for women.

Table 4. Frequency of complications and causes of death in chronic pancreatitis patients from Study I

Chronic pancreatitis complications	**n=235**
Any complication	**65 %**
Pseudocysts	58 %
Bile duct stenosis	10 %
Pleural effusion	7 %
Ascites	7 %
Gastrointestinal tract bleeding	6 %
Porta/splenic vein thrombosis	6 %
Pancreatic fistulas	5 %
Pseudoaneurysms	5 %
Gastrointestinal tract stenosis	4 %
Death	**n= 60 (26%)**
Median age at death: 62 (range 26-85)	
Cause of death in CP	**n=21 (35%)**
Cardiovascular disease	19 %
Other malignancy	19 %
Liver cirrhosis	14 %
Chronic Obstructive Pulmonary Disease	10 %
Hypoglycaemia	10 %
Pancreatitis	10 %
Pancreatic adenocarcinoma	5 %
Polycystic kidney disease	5 %
Sepsis	5 %
Post-surgical sepsis	5 %

5.1.2 Quality of Life

We sent out questionnaires to 188 patients and 41% (n=77) completed the EORTC QLQ C-30 and PAN26 questionnaires and 40% (n=76) completed the AUDIT questionnaire. The median age of the responders was 57 years (range 28-88) and their disease duration was four years (range 2-42 years). They had the same distribution of alcohol aetiologies, pseudocysts and PEI as the rest of the CP patient population. Six CP patients who responded to the questionnaires died during two-year follow-up. The deceased respondents had more pancreatic pain ($p=0.042$), financial difficulties and poorer physical and cognitive functioning. In the C-30 responses all functioning and symptoms were worse in CP patients than in the Swedish normative control population (n=2,998). In the pancreas-specific PAN26 CP patients had more symptoms than the healthy control group (n=102). (Figure 6)

CP patients who were smokers reported more pain ($p=0.035$) and pancreatic pain ($p=0.007$). CP patients reported more abstinence from alcohol but on AUDIT they scored more +16 points (16% vs. 3%; $p<0.001$) than the Finnish control population.

Figures 7 and 8 show that poor QoL, functioning and more symptoms were present in CP patients who continued to smoke and use alcohol after being diagnosed.

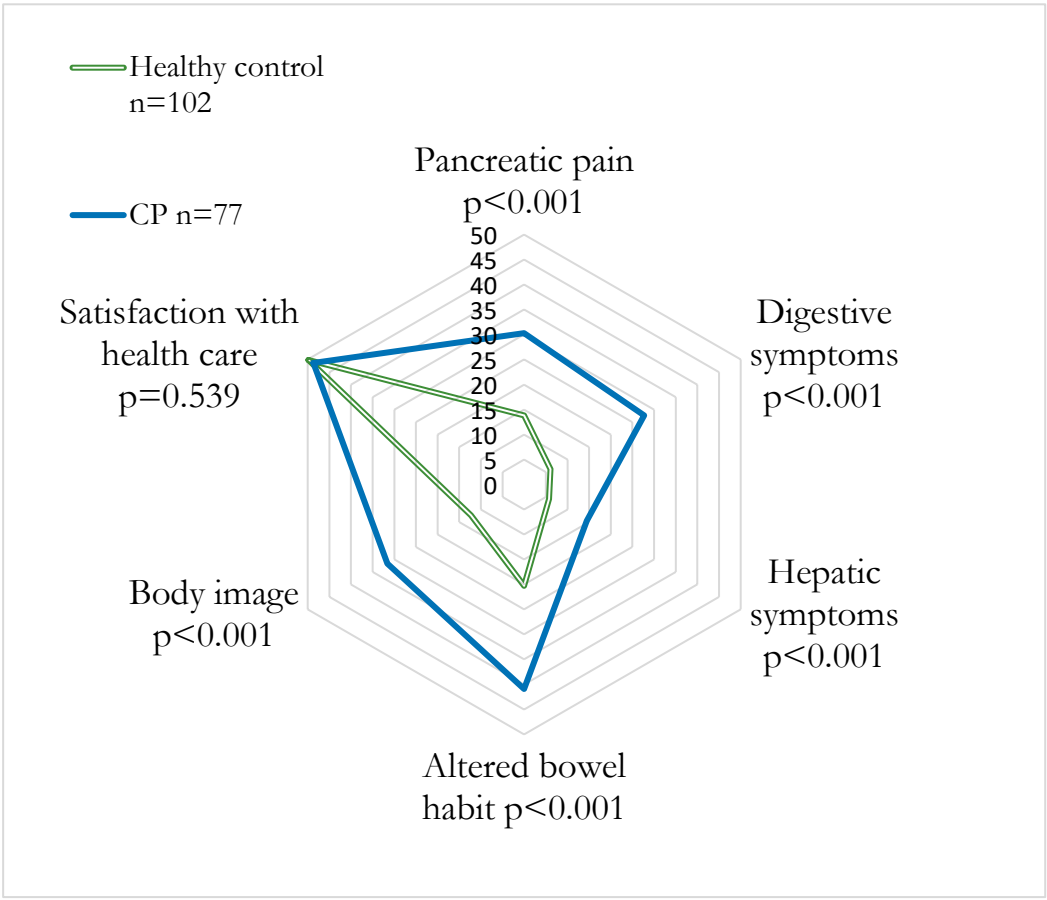
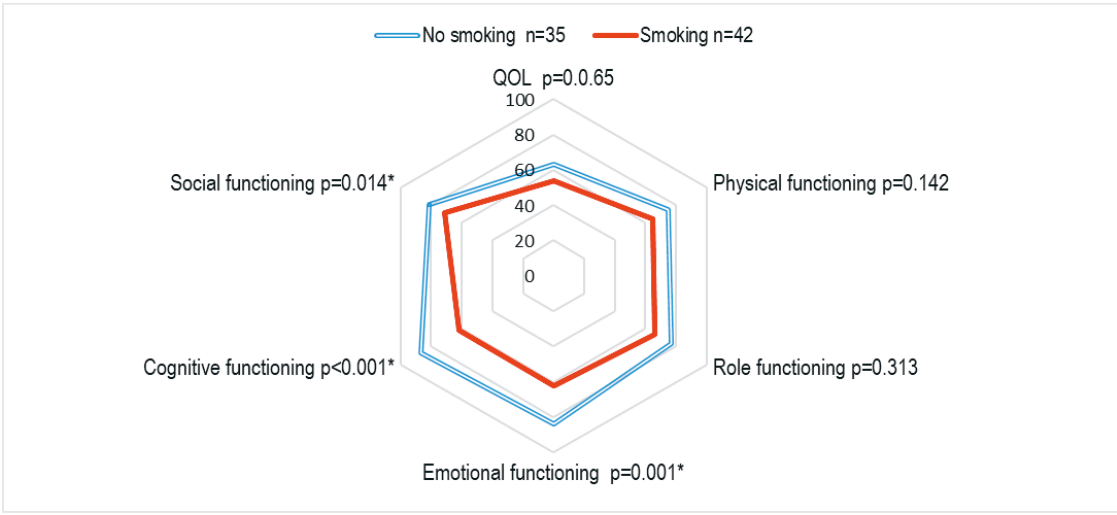


Figure 6. EORTC QLQ-PAN26 symptom score in chronic pancreatitis (CP) patients compared to a healthy control. The CP patients had more symptoms on all parameters



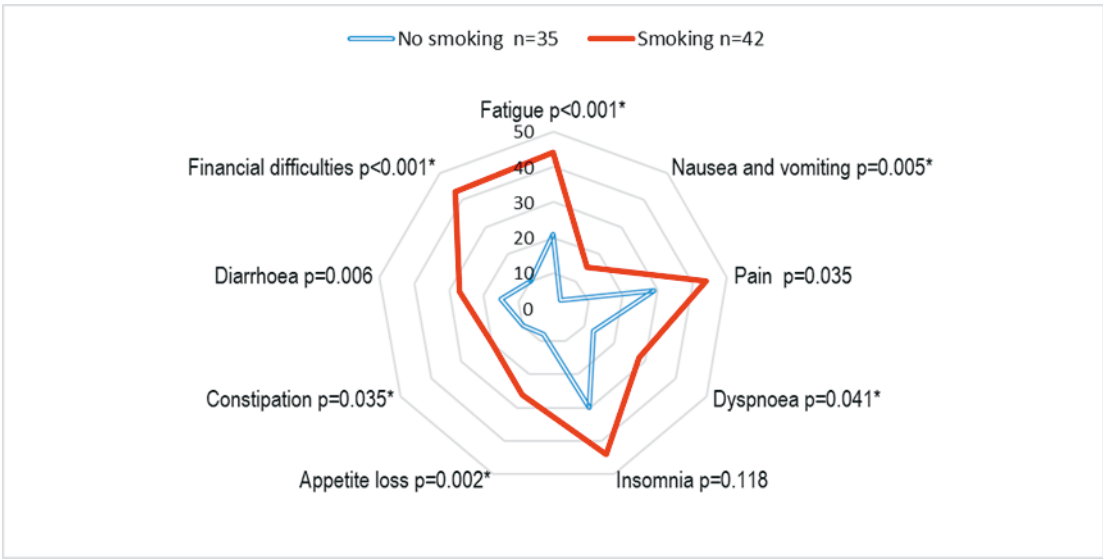
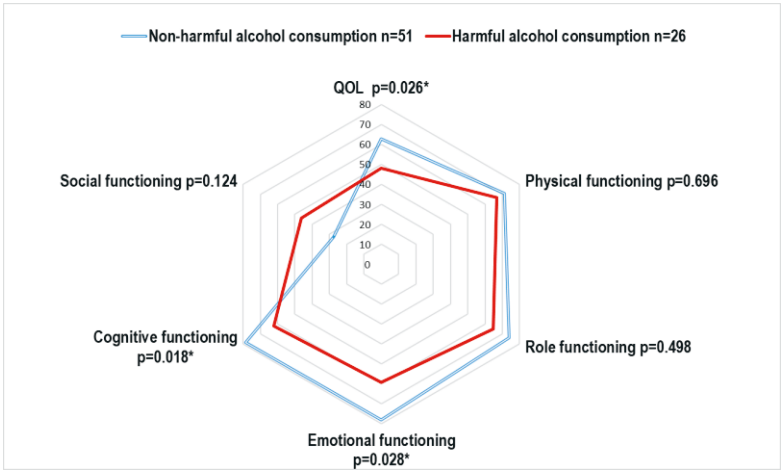


Figure 7. EORTC QLQ-C30 scores of CP patients continuing to smoke after diagnosis. Patients who continued smoking had poorer social, cognitive and emotional functioning. *=statistically significant



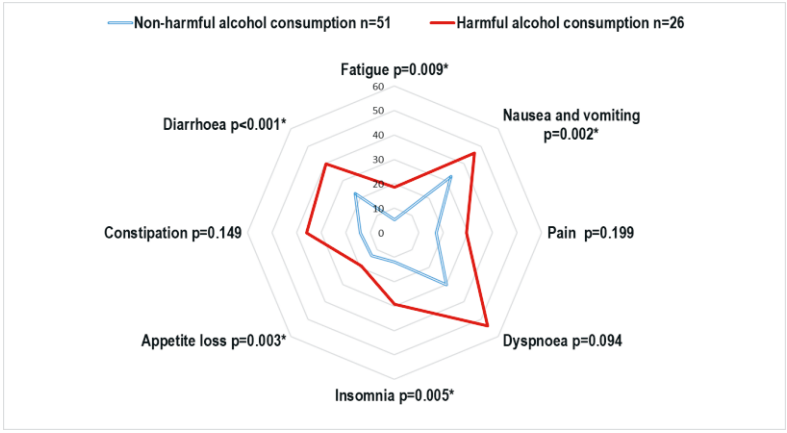


Figure 8. EORTC QLQ-C30 scores of CP patients with harmful alcohol consumption according to their AUDIT scores. Patients with harmful alcohol consumption had poorer QoL and cognitive and emotional functioning and also more fatigue, nausea, insomnia, appetite loss and diarrhoea than those with non-harmful alcohol consumption. *=statistically significant

5.2 Unpublished data

5.2.1 Osteoporosis

Patient characteristics are presented in Table 3. Out of the 33 CP patients seven (21%) had previously undiagnosed osteoporosis (Table 5).

42% had PEI and inadequate PES treatment, which was linked to osteoporosis 43% vs. 5.6% (OR 2.3 CI 95%: 0.8-6.9; p=0.013)

Alcohol consumption differed in the abnormal bone density group compared to the normal bone density group (NBD) 67% vs. 29%, p=0.035 but there was no difference between the osteoporosis and the NBD group (p=0.141) in alcohol consumption. Also, there was no difference between smoking (p=0.171), age (p=0.268), gender (p=0.833), BMI (p=0.620) or low testosterone level (p=0.456) between the osteoporosis and the NBD group. Of the patients in the unpublished data, 64% had supplementary vitamin-D and there was no difference between the osteoporosis and non-osteoporosis groups (p=0.629). Low vitamin D (25-hydroxyvitamin D under 50 nmol/l) levels were found in 15% of patients and two of them had osteoporosis.

Table 5. Findings from unpublished data. Undiagnosed osteoporosis was found in 21% of CP patients. The abnormal bone density group consisted of osteoporosis and osteopenia patients

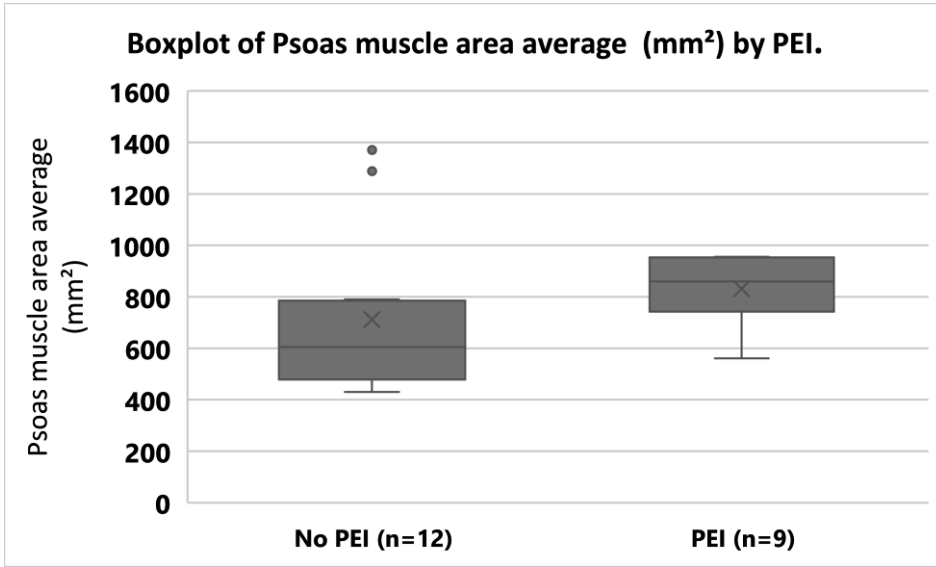
	Osteoporosis n=7	Osteopenia n=8	Abnormal bone density n=15	Normal bone density n=18
Age (years)	64 (44-79)	62 (51-70)	63 (44-79)	59 (39-81)
Female/Male % (n)	43% (3) / 57% (4)	38% (3) /63% (5)	40% (6) /60% (9)	39% (7) /61% (11)
Time after diagnosis (years)	7 (5-15)	6 (4-16)	6 (4-16)	6 (4-27)
Faecal Elastase-1 (ug)	20 (15-387)	51 (15-375)	45 (15-375)	66 (15-500)
PEI (Elastase-1<100ug)	57% (4)	75% (6)	67% (10)	78% (14)
Alcohol aetiology	71% (5)	63% (5)	67% (10)	33 %(6)
Alcohol abstinence	29% (2)	38% (3)	33% (5)	50% (9)
Current smoking	57% (4)	25% (2)	40% (6)	28% (5)
Smoking	86% (6)	75% (6)	80% (12)	50% (9)
Idiopathic pancreatitis	0 %	25% (2)	13% (2)	17% (3)
BMI	28.3 (20-29)	26.7 (22-36)	28 (20-28)	28 (19-38)
Overweight	57% (4)	63% (5)	60% (9)	72% (13)
Obese	0 %	25% (2)	13% (2)	33% (6)
Low testosterone in males	0 %	25% (1)	11% (1)	2 (18%)
Menopause in females	100% (3)	100% (3)	100% (6)	0
Vitamin D supplementation	71% (5)	63% (5)	67% (10)	61% (11)
Cortisone medication	14% (1)	0	0	0

Data is presented as median (range) or percentage (%) and amount (n). BMI= Body Mass Index, PEI= Pancreatic exocrine insufficiency

5.2.2 Sarcopenia

PMA (Psoas Muscle Area) measurement was done on 21 patients and 48% of these had sarcopenia. The median PMA in females was 561 (430-959 mm2) and 809 (467-1371) mm2 for males. The median age of patients with sarcopenia was 59 years (39-64) and 61 (53-73) for those without sarcopenia $p>0.05$.

The sarcopenia patients had more PEI in non-sarcopenic patients (80% vs. 36%) OR 7.0 (95% CI:0.97-50.6); $p=0.044$). We found that longer disease duration correlated with lower PMA ($r= -0.434$, $p=0.049$), but age did not correlate with lower PMA ($r=0.263$, $p=0.249$). Figure 9 shows the association of sarcopenia with disease duration and PEI.



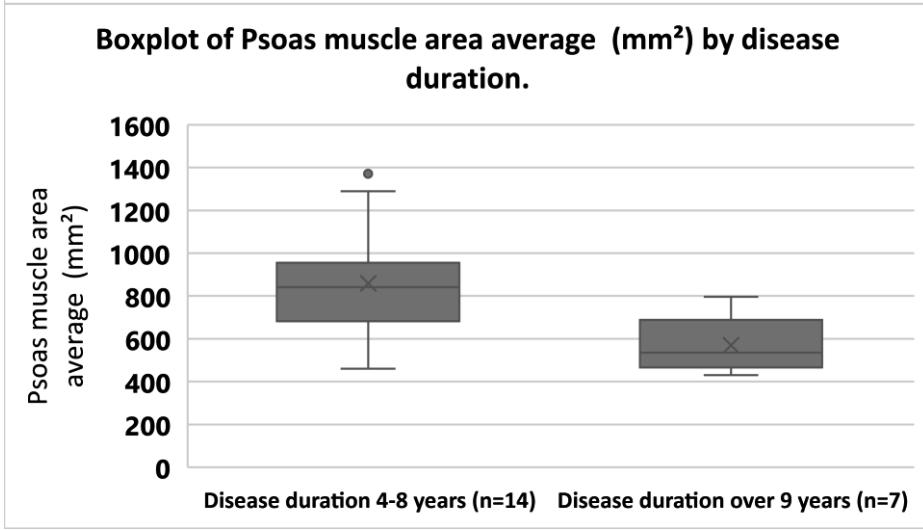


Figure 9. Boxplot demonstrating the trend towards sarcopenia in patients with PEI (p=0.041) and longer disease duration (p=0.021). The box indicates the upper and lower interquartile ranges with the median line. The whiskers indicate the minimum and maximum datasets except for the possible outlier (dot). The X marks the average

5.2.3 Pancreatic Exocrine Insufficiency and Vitamin Deficiency

In unpublished data we found PEI in 57% and patients with alcohol consumption after their diagnosis had a higher rate of PEI (80% vs. 35%, p=0.011) but there was no difference between patients who smoked and those who did not (p=0.947). Low vitamin E levels were found in the PEI group (21%) and we found that inadequately treated PEI was associated with low vitamin E levels OR 14.4 (95% CI:1.2-169); p=0.01). We measured low vitamin D levels in four patients (21%) of the PEI group and in one patient (7%) of the non-PEI group. All the patients had normal vitamin A levels.

5.3 Study II: Surgery for Chronic Pancreatitis in Finland

5.3.1 Patient Characteristics

The final study cohort included 30 patients who underwent pancreatic surgery for pain due to CP in Finland during the period 2000-2008. Surgery was performed a median of two times (1-7) per hospital and was spread over 13 different hospitals. The patients had surgery a median of two (0-10) years after being diagnosed. Follow-up time was 16 (10-26) years and eight (24%) patients died a median of five (0-16) years after their surgery. Nine out of ten patients had recurrent episodes and 60% were alcohol induced CP, 50% of the patients smoked and 33% had idiopathic pancreatitis (Table 3). All of the smoking

CP patients had opioid usage before surgery compared to 42% of the non-smokers; $p<0.001$.

During the nine years, 30 operations were performed and of these one was a drainage procedure (Puestow), nine were DPPHRs, and there were 20 pancreatic resections (16 distal pancreatectomy and 4 PDs). Fifteen patients had splenectomies. Out of the DPPHR patients, four were Frey´s procedures, two were Beger´s procedures and three were Puestow´s drainages combined with caudal resection.

Post-operative complications were found in 17% (n=5) of the patients: two had Clavien-Dindo (CD) grade 1 complications, two had CD grade 2 complications and one CD grade 3b complication. One patient died within three weeks of surgery; this patient had undergone four prior laparotomies and had intraoperative haemorrhage during the surgery for CP.

We found PEI in 34% patients pre-operatively and 67% post-operatively. Diabetes was found in 32% pre-operatively and in 56% post-operatively. The frequency of PEI and diabetes was the same, compared to the CP patients in Study I who did not have pancreatic surgery (n=195). Opiate usage dropped significantly after surgery (73% vs. 37%, $p=0.004$).

Endoscopic procedures were performed on 83% of the patients before surgery, which was more than on the CP patients in Study I (83% vs. 27%, $p<0.001$). Recurrent AP was more common in the surgery group (87% vs. 67%, $p=0.007$).

5.3.2 Pain and Quality of Life

Primary pain relief was reported in 70% of the patients after surgery. All those patients who had not undergone endoscopic procedures prior to surgery had primary pain relief compared to 64% of those who had undergone prior endoscopic procedures; the non-endoscopic group was so small that the difference was not statistically significant (p=0.010). (Figure 10). Eight patients from 21 completed the symptom questionnaire, QLQ-C30, Pan26 and AUDIT questionnaire. There was no difference between the responders and the non-responders in gender, pancreatic calcifications, PEI, recurrent AP or alcohol aetiology. All the patients who responded to the questionnaires had a history of smoking and 63% continued smoking compared to 35% among non-responding patients p=0.003. Because all the responding CP patients undergoing surgery were smokers, the control group (Study 1) consisted solely of CP patients who smoked. There was no statistically significant difference in the QLQ-C30 and PAN26 responses compared to those of the control population. Most patients (88%) reported that the surgery helped their pain and 63% were almost or entirely pain-free 14 (10-18) years after surgery (Figure 11). The AUDIT point median was the same in the control population from Study I (4 vs. 3, p=0.764). There was no statistically significant difference in the QLQ-C30 and PAN26 responses compared to those of the control population.

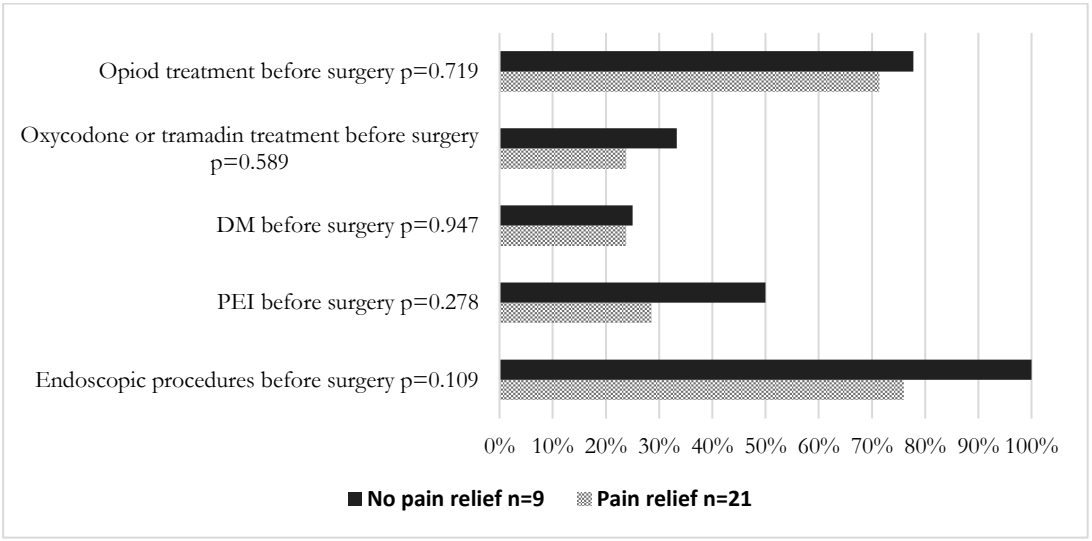


Figure 10. Findings in chronic pancreatitis patients who had primary pain relief and no pain relief after pancreatic surgery for pain. Most patients had opioid treatment before surgery. Patients who had pain relief after surgery had less PEI and fewer endoscopic procedures but the difference was not statistically significant because of the small study size

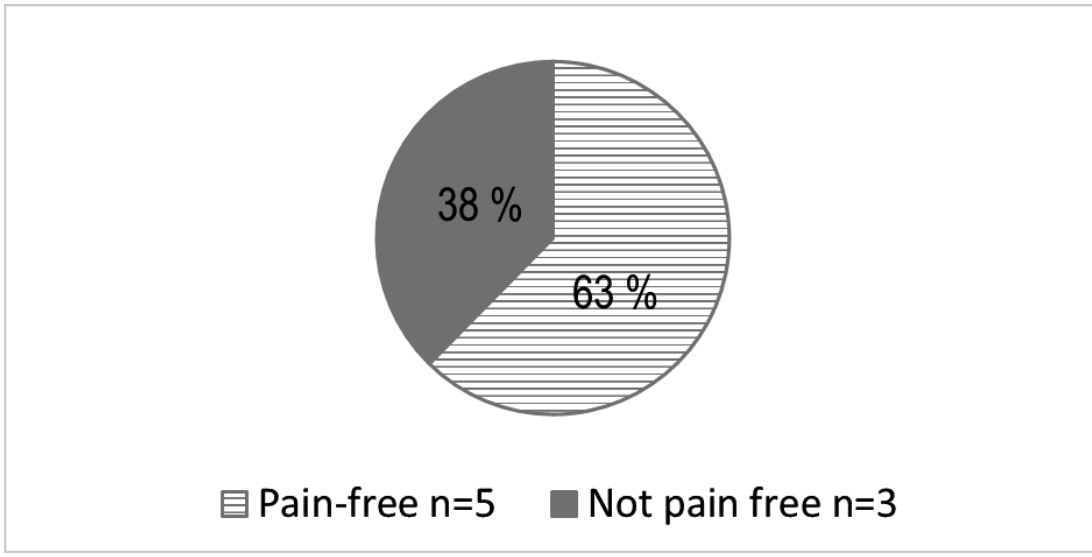


Figure 11. Share of pain-free chronic pancreatitis patients 14 years after surgery for CP pain

5.4 Study III: Pancreatic Surgery and Quality of Life in Chronic Pancreatitis Patients

5.4.1 Patient Characteristics

The SBPC database included 1,327 patients of whom 95 (7%) had pancreatic surgery. The indications for surgery were pain in 54% (n=51), complication caused by CP in 28% (n=27) and suspected malignancy in 16% (n=15). Data on indications were missing for two patients. Two (14%) of the patients with suspected malignancies had cancer according to the pathologist's assessment.

The final study group was formed from the 51 patients who underwent pancreatic surgery for chronic pain (PSCP group). The follow-up was two years (range 18-71) after surgery. The female/male ratio was 33%/67% and median age at the time of surgery was 48 (range 18-71) years. Disease duration at the time of data collection was six (0-39) years. (Table 2). Surgery was performed a median of three years (range 0-28) after their diagnoses. Most (91%) patients had pancreatic calcifications and 74% had an abnormal pancreatic duct (Table 3).

Prior endoscopic procedures had been performed on 75% of the patients. DPPHR (Frey, Berne or Beger procedures) was the most common procedure with 54% (n=28), followed by pancreatic resections (33%, n=17; pancreaticoduodenectomy, distal resections and total pancreatomies) and drainage procedures (13%, n=7; Puestow/ Partington-Rochelle and pseudocyst drainage) (Figure 12). Post-operatively PEI was found in 41% and 39% had diabetes.

The patients in the SBPC database were older than those in the PSCP group median 59 vs. 51 years ($p<0.001$). Idiopathic pancreatitis, calcifications and ductal dilation were more common in the PSCP group. Endoscopic procedures were more often performed in the PSCP group (75% vs. 26% $p<0.001$). Both groups had the same amount of diabetes, but PEI was more common in the PSCP group.

Deaths were registered separately from all eight centres a median of 12 years after surgery (range 1-31) for 88% (45/51) of the patients. During this follow-up time, only one patient (2%) died of unknown causes one year after surgery.

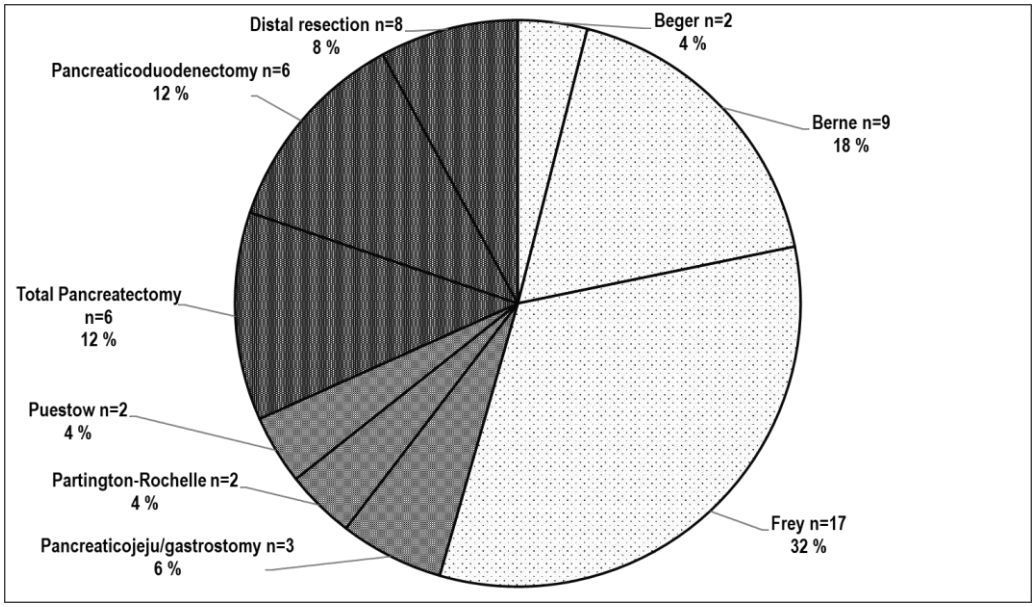


Figure 12. Distribution of different surgical procedures for CP

5.4.2 Pain

Both the PSCP and the rest of the SBPC database patients had the same amount of pain medication and pain distribution (Table 6). The PSCP patients with constant pain had longer disease duration before surgery than the CP patients without constant pain 11 (1-28) vs. 3 (1-23) years, p=0.034.

5.4.3 Quality of Life

The majority (n=31 (61%)) of the PSCP group completed the EORTC QLQ C30 questionnaire. The PSCP group had worse social functioning (p=0.028) but QoL and other functioning responses did not differ from those of the SBPC database (n=514). In symptom responses, the PSCP group reported more constipation, nausea and insomnia (p=0.009, p=0.002 and p=0.001 respectively). CP patients with ERCP prior to surgery (n=25) had worse outcomes for physical, role and social functioning (p=0.017, p=0.040 and p=0.040) and more severe fatigue and pain symptom scores (p=0.041 and p=0.006) than patients without prior ERCP (n=6). When comparing different surgical approaches, pancreatic drainage resulted in most patients with constant pain (p=0.015) while DPPHR resulted in the least amount of constant pain (drainage 50%, resection 23% and combined 4%) p=0.013.

5.5 Study IV: Endoscopic Procedures and Quality of Life in Chronic Pancreatitis Patients

5.5.1 Patient Characteristics

The study included 260 patients who underwent endoscopic procedures (EP) from the SBPC baseline cohort 1,327 patients (Table 2). Median age was 59 years (range 20-90). We compared the EP group to a reference population on whom no interventions were performed (n=870).

Median disease duration was higher than in the reference population - four years (0-41) years compared to two years (0-39) years, $p<0.001$. The EP group also had more pancreatic calcification 77% vs. 67%, ($p=0.003$), ductal stones 49% vs. 34%, ($p=0.003$), ductal lesions 73% vs. 48% ($p<0.001$), 54% vs. 35% pseudocysts ($p<0.001$) and PEI 62% vs. 53% ($p=0.020$) than the reference population. Both groups had the same frequency of diabetes 45% vs. 40% ($p=0.152$). (Table 3)

The EP group also had more efferent duct obstruction 14% vs. 7% ($p=0.004$) and less hereditary pancreatitis 4% vs. 10% ($p=0.003$) than did the reference population.

5.5.2 Endoscopic Procedures

Just under half (44%) of the patients had more than one EPs performed n=115. Pancreatic stenting was done in 146 patients (56%) and a majority (72%) had multiple pancreatic stents (median 2 stents). Biliary stenting was performed on 97 patients (37%). Both pancreatic and biliary stenting were done on 33 (13%) patients.

Metal biliary stents were used on 14%, plastic stents on 57% and 29% had both stents. Over half (55%) of the patients needed multiple biliary stents (median 2 stents)

Percutaneous pseudocyst drainage was performed on 8% of the patients and endoscopic drainage on 32%. Of the EP group 21% (n=54) also had ESWL performed.
Delayed pancreatic surgery was performed on 23% (n=60) of the EP group a median of one year (0-11) year after their first EP. The surgeries included 49% DPPHR, 34% pancreatic resections and 17% were drainage procedures.
Patients undergoing ESWL (n=186) had less pancreatic surgery than patients who did not have ESWL performed (n=74); 7% (n=13) vs. 27% (n=20), p=0.02. Patients undergoing surgery had fewer biliary metal stents (p=0.004), pseudocysts (p=0.012) and fewer of them reported smoking (p=0.018) and had more idiopathic pancreatitis (p<0.001) than the EP patients who did not need pancreatic surgery.

5.5.3 Pain

In the EP group, post-procedural pain was presented as: 42% being pain-free, 42% with intermittent pain and 17% with constant pain. The reference group had more pain-free (p=0.008) and fewer intermittent pain patients (p=0.035).
Data on pain medication were lacking in up to 61% of the EP group and 56% of the reference population. The EP group had more opioid usage than the reference group (31% vs. 13%, p<0.001) but both patient groups had the same number of patients without pain medication (p=0.354).
Patients undergoing pancreatic duct stenting also had more opioid usage than the reference group (26% vs. 13%, p=0.004) but the amount of constant pain, intermittent pain and the numbers of pain-free patients were the same. Both groups

also had the same numbers of patients without pain medication (65% vs. 63%, p=0.668). The pain graph shows pain patterns from the study in Table 6.

5.5.4 Quality of Life

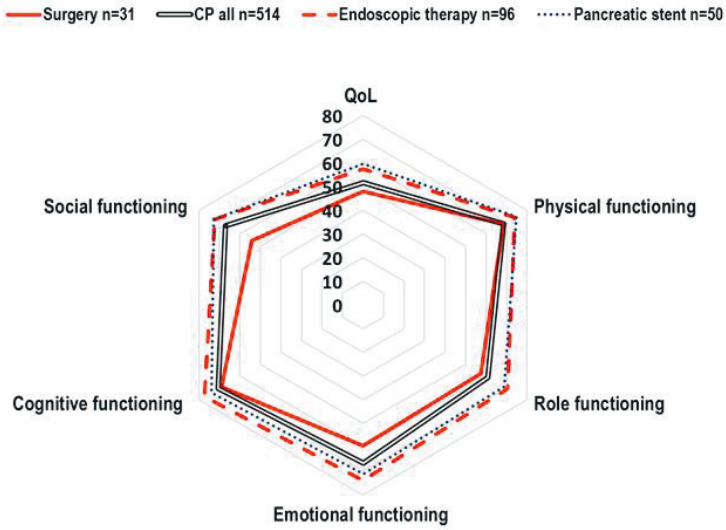
The EORTC QLQ-C30 was completed by 96 (37%) patients from the EP group four years after their first intervention and by 382 patients (44%) in the reference group (no interventions) two years after their diagnoses.

The EP group had better QoL (p=0.047) and scored higher on role (p=0.035), emotional (p=0.043) and cognitive functioning (p=0.046) than did the reference group. The EP group also performed better in the symptoms score with less fatigue and appetite loss. Of the EP patients subsequently undergoing pancreatic surgery 32 (53%) had the QoL questionnaires recorded, the surgical patients had statistically significantly more pain (p=0.043), fatigue (p=0.021) and financial difficulties (p=0.041). QoL results from Study III and IV are shown in Figure 13. We also included a separate group from the EP group on whom only pancreatic stenting was performed n=50.

We also performed a multivariable analysis of the EP patients and reference group QoL questionnaire scores with the following variables: disease duration, alcohol aetiology, smoking, hereditary pancreatitis, efferent duct pancreatitis, age, sex and disease duration but found none of the variables to have a significant interaction effect on the responses.

Table 6. Comparison of post-procedural pain findings in chronic pancreatitis (CP) patients who underwent surgery for pain, endoscopic pancreatic stenting, the reference group and the SPBC population

	Pancreatic surgery for pain (Study III)	Patients who had pancreatic stenting (Study IV)	CP Reference group (no intervention)	SBPC population
	n=51	n=128	n=714	n=1327
Constant pain	16 %	13 %	14 %	16 %
Intermittent pain	37 %	40 %	34 %	37 %
Painless	47 %	47 %	52 %	47 %
Opioids	21 %	26 %	13 %	19 %
No pain medication	64 %	65 %	63 %	57 %



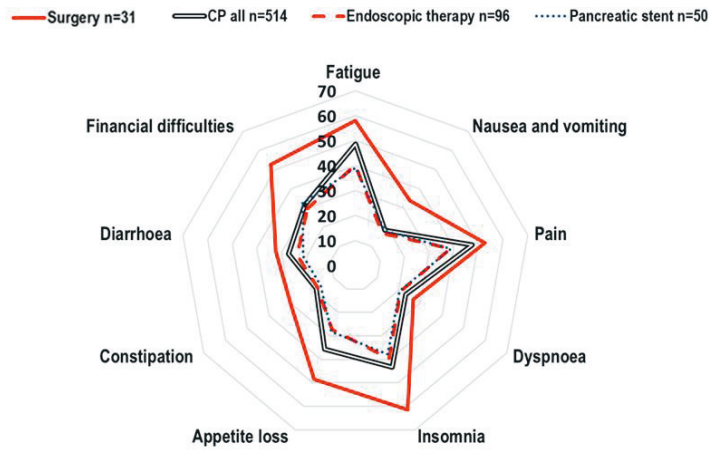


Figure 13. EORTC findings from surgical and endoscopic patients with Studies III and IV combined, showing that patients with endoscopic procedures had better quality of life and fewer symptoms

6 DISCUSSION

6.1 Aetiology and Complications

In Finland we have one of the highest incidences of CP in Europe but there are no recent epidemiological data on CP (Jaakkola & Nordback, 1993). The aim of Study I was to investigate the current status and treatment of CP patients. Study I revealed the burden CP patients cause to the healthcare system, especially patients with alcohol consumption and smoking, who are at higher risk of developing complications. Alcohol and smoking contributed to the majority of the aetiologies of CP and half of the patients continued smoking and drinking after their diagnoses.

A significant number (7-33%) of aetiologies in our studies are idiopathic. Possibly some of these could be due to biliary microlithiasis not always shown in routine imaging (Räty et al., 2015; Umans et al., 2020). The rise in the use of EUS in the diagnosis of pancreatic diseases may change this in the future (Mazza et al., 2022). EUS has also proven to be a safe and precise method in pancreatic biopsies (Thomsen et al., 2022). Other risk factors for CP include genetic mutations that could even predispose to the disease in the case of patients with alcohol-related CP, since not everyone with the same lifestyle develops AP or CP(Xu et al., 2022).

CP patients are at risk of dying younger. In our population the median age of death was 62 for males and 63 for females while in Finland as a whole it was 75 years for men and 81 years for women(*Official Statistics of Finland (OSF): Deaths*, 2018). Lower

survival is multifactorial and not solely attributable to lifestyle factors but also to malnutrition and complications (Kalas et al., 2022; Rivelsrud et al., 2021). In Study I 30-35% of the deaths were possibly CP related (post-surgical sepsis, hypoglycaemia, pancreatitis and PC).

Pancreatitis-related endocrine insufficiency has been shown to have more adverse outcomes, such as hypoglycaemia, than type 2 diabetes (Olesen et al., 2022). Untreated PEI also reduces survival (de la Iglesia-Garcia et al., 2018). CP has been linked to a higher risk of myocardial infarction (Khan et al., 2021). In our population (Study I) 20% of the patients died of cardiovascular disease, which is actually lower than in the Finnish population as a whole (36%) (*Official Statistics of Finland (OSF): Causes of Death [e-Publication]*).

Smoking is a major independent risk factor for CP development and pain (Hao et al., 2022). Most of the CP patients in Study I continued smoking after their diagnoses and only 22% stopped smoking. More patient and medical professional education is needed on the risk of smoking on CP. In Study I patients who smoked had a higher rate of calcification and pseudocysts, but this did not reach statistical significance. In a previous SBPC study smoking has been associated with pancreatic duct and bile duct strictures and pancreatic insufficiency.(Olesen, Nøjgaard, et al., 2019)

We found that according to our questionnaire a significant number of CP patients abstained from alcohol (42%) while only 13% of the Finnish population practise abstinence from alcohol (Härkönen et al., 2017). A similar finding was reported in a prospective cohort study from the United States (Machicado et al.), where 80% of CP patients abstained from alcohol (Machicado et al., 2017). Nevertheless, there was a substantial number of patients with AUDIT scores over 16 compared to the Finnish population 16% vs. 3%. Patients would benefit from an early intervention on alcohol usage(Ocskay et al., 2022).

In our study we found more complications with alcohol-related CP than with non-alcohol related CP. Alcohol-induced CP had higher rates of pseudocysts,

calcifications and miscellaneous complications. Similar findings have been reported in earlier research, where pseudocysts have been associated with alcohol-related CP (Engjom et al., 2021) .

6.2 Pancreatic Exocrine Insufficiency

In our studies about 55-60% of the CP patients had PEI and patients undergoing surgery for pain (Study III) had significantly less PEI than the CP patients who did not need surgery at 41% vs. 60%, p=0.019, even though they had longer disease duration. There is evidence to suggest that pancreatic surgery could prevent PEI, in a recent review (Pathanki et al., 2020), who found that there was less PEI postoperatively after PD. On the other hand in a Dutch multicentre study pancreatic surgery was associated with PEI (Kempeneers, Ahmed Ali, et al., 2020). In a retrospective study consisting of patients without interventions, large-duct CP was associated with an increased risk of PEI and diabetes compared to small-duct pancreatitis (Mahdi et al., 2022). This demands prospective trials to compare if pancreatic surgery can decrease the inflammation and maybe pancreatic insufficiency in CP patients. In the unpublished data a concerning share of 40% of the patients with PEI had no PES. Which could be due to a lack of follow-up and poor compliance in CP patients (Akanbi et al., 2021).

More patient education on CP and PEI should be provided and information should also be directed to the treating physicians (Haritha & Wilcox, 2015). Websites and videos have been proven to reach a large audience and may be used to help with patient education and adherence to treatment (Munigala et al., 2018).

Treatment of PEI is straightforward with modern capsulated PES and the recommended dose is 25 000-50 000 IU of lipase per meal or snack (J. M. Löhr et al., 2017). The dose can be adjusted if steatorrhea or bloating is present. There are no dietary fat restrictions for CP patients(Arvanitakis et al., 2020).

We found that patients with PEI, especially if untreated, had low vitamin E levels. Similar findings have been reported in an earlier study where 10% of the CP patients

with PEI had low vitamin E levels and it was even more common if PEI was left untreated. Vitamin E is a fat soluble antioxidant and low levels are exceptionally rare in the general population (Atkinson et al., 2021; Kemnic & Coleman, 2022). Deficiency of vitamin E may lead to neurological and cognitive disorders (Traber, 2021). It might be advisable to measure vitamin E levels in patients with PEI and administer supplementary vitamins.

Patients who continued to consume alcohol after their diagnosis had more PEI than the rest of the CP population. This contrast with a multicentre study where alcohol consumption was not associated with PEI (Erchinger, Engjom, et al., 2022). In an earlier study heavy drinking and smoking were both associated with poor treatment of PEI in CP patients, with only 42% of the patients being adequately treated (Erchinger, Tjora, et al., 2022). In a retrospective study less than half of the patients followed the lifestyle recommendations but were more likely to abstain from alcohol if treated by pancreatologists (Srivoleti et al., 2021).

An international survey was conducted where only 20% of the clinicians routinely checked for PEI and conducted nutritional tests for CP patients and only 75% of pancreatologists prescribed PES if steatorrhea was present (de Rijk et al., 2022). This calls for a change of mindset in treating PEI and in the follow-up of patients with CP. In the unpublished data we found that 40% of CP patients with PEI did not receive adequate treatment.

6.3 Osteoporosis

CP patients are at a risk of osteoporosis and hence osteoporotic fractures (Vujasinovic et al., 2021). We did not know how this was addressed in daily clinical practice. We found that nearly half of the CP patients in the unpublished data had

osteopathy and 21% had osteoporosis, all of which was previously unknown. Patients with PEI and no PES had more osteoporosis.

Bone density measurement for CP patients is recommended by the United European Gastroenterology guidelines (Dominguez-Munoz et al., 2018). The fact that osteoporosis is so common in our study population supports these findings. The Finnish guidelines for screening for osteoporosis also recommend focussing on high-risk patients, which includes CP patients (working group appointed by the Finnish Medical Society Duodecim et al., 2018). It should be noted that there are multiple risk factors for osteoporosis such as age, sustained glucorticosteroid usage, gender, menopause, immobilization and many risk factors which intersect with CP patients such as alcohol consumption, diabetes and smoking (Abrahamsen et al., 2014; Cheraghi et al., 2019; DeShields & Cunningham, 2018). CP patients often need CT scans and there are preliminary studies suggesting that these could be used to diagnose osteoporosis in CP patients (McNabb-Baltar et al., 2022).

In a recent retrospective study CP patients treated by pancreatologists were more likely to have their bone density and vitamin D levels tested than were patients treated by primary care physicians or gastroenterologists (Srivoleti et al., 2021b). This emphasizes the importance of education on the treatment guidelines for CP patients.

We found that 15% of the CP patients had low vitamin D levels and only 67% had received supplementary vitamin D. The prevalence of vitamin D deficiency in Finnish adults is 21-26%, which is actually higher than in our study population and probably due to selection bias and to the fact that the CP patients used more often vitamin D supplements than do general Finnish population 67% vs. 57% (Raulio et al., 2016). In earlier studies where up to 63% of CP patients had vitamin D deficiency (Duggan, Smyth, O'Sullivan, et al., 2014; Greer et al., 2019) but vitamin D deficiency was not unique to the CP population.

More care should be taken that all CP patients have basic prevention of osteoporosis, which includes vitamin D supplements and adequate calcium intake, exercise and avoidance of alcohol and smoking. The ESPEN guidelines recommend 20ug daily

of vitamin D and 500mg-1000mg of calcium for CP patients (Arvanitakis et al., 2020).

6.4 Sarcopenia

Sarcopenia is a muscle disease initially causing loss of muscle mass but now the focus has turned towards decreased muscle function (Sayer & Cruz-Jentoft, 2022). Muscle mass and strength are known to decline with age (K. Keller & Engelhardt, 2013).

In the unpublished data we focussed on imaging-based sarcopenia diagnosis. Nearly half the patients who had their PMA assessed had sarcopenic levels (n=10). Risk factors for sarcopenia were disease duration and PEI. We found no association between age and sarcopenia, which could be due to the limited study size.

Sarcopenia can be assessed with CT or MRI imaging, both of which are often performed on CP patients (Bieliuniene et al., 2019). Sarcopenia is associated with a number of chronic diseases besides chronic pancreatitis, such as chronic renal and heart insufficiency, rheumatoid arthritis and diabetes. Chronic pancreatitis has been more strongly associated with sarcopenia than PC indicating an association of sarcopenia with chronic diseases (Bieliuniene et al., 2019).

Possible sarcopenia should be ascertained before surgery since it may be a risk factor for pancreatic fistulas and failure to rescue from complications (Pecorelli et al., 2018; Vitali et al., 2016). Sarcopenic CP patients have significantly higher one-year mortality (16% vs. 3%) and sarcopenia is also associated with increased hospitalization rates (Bundred et al., 2022; Olesen, Büyükuslu, et al., 2019).

More prospective studies on how to prevent and find risk factors for sarcopenia in CP patients are needed.

6.5 Endoscopic Procedures

CP patients often require EP for CP-related complications and pain. We showed that patients needing EP have a morphologically different pancreas, which is logical, as these changes can contribute to pain and complications (Drewes et al., 2017).

In Study IV one in five CP patients needed EP and 40% multiple procedures. Pancreatic duct stenting was performed in 60% of the patients and 72% of these had multiple stents. We did not find any difference in pain patterns or medication in patients needing multiple or one pancreatic stent. Biliary duct stenting was performed in 40%. Pseudocyst drainage was also common as 30% underwent endoscopic drainage. The EP group took more opioids after their procedures than did the reference population.

Obstructive pancreatic duct stones can be treated with ESWL and combined with ERCP. In Study IV one in five of patients who underwent ESWL also had ERCP. Patients who underwent ESWL probably needed less surgery, which could be due to availability and clinics' ways of treating pancreatic calcifications. ESWL combined with ERCP is a viable alternative to surgery if malignancy can be ruled out (Geusens & van Malenstein, 2021).

Benign biliary strictures often need EP and can be treated with duct dilation combined with plastic or self-expanding metal stents (Haapamäki, Udd, et al., 2015; Nabi & Lakhtakia, 2021). Often multiple procedures are needed. Half of the patients in Study IV needed multiple procedures and 84% had plastic stents and 42% had metal stents. Patients with metal stents needed less pancreatic surgery.

Endoscopic transpapillar or transmural drainage is the preferred method to manage symptomatic pseudocysts (Kitano et al., 2020). In Study IV one third of the EP patients underwent endoscopic drainage and 8% had percutaneous drainage. In a prospective study percutaneous drainage was associated with worse outcomes compared to endoscopic drainage(Hao et al., 2022). However, no prospective randomized studies have been reported comparing the endoscopic, percutaneous or surgical drainage of pancreatic pseudocysts.

It can be presumed that the treatment of pseudocysts depends on the treatment options available at the various hospitals and the anatomical location and size of the pseudocysts. We found that pseudocysts were more common in patients needing EP than in the non-interventional reference group and the surgical group. This could be due to a general trend and development in endoscopic techniques in the treatment of pseudocysts leading to a decrease in surgical drainage (Quinn et al., 2022).

6.6 Surgical Procedures

Based on findings of Studies III and IV we can conclude that surgery for CP pain is rare in Finland and northern Europe. Most surgical procedures performed on CP patients are due to pancreatic complications, such has pseudocyst infections or haemorrhage or suspicion of malignancy.

According to our findings in Study II, CP surgery achieved long-term pain relief and there was a reduction in the use of opiates after surgery. It seems that in the whole of Finland only three operations per year were performed during the inclusion period of Study II and that under one percent of CP patients undergo surgery for pain. Surgery was also spread out over many hospitals with a median of two surgeries performed per hospital during the eight-year study period. Since Study II pancreatic surgery has been centralized in Finland.

In Study III 7% of CP patients had pancreatic surgery and half of these procedures were performed due to CP-related pain. According to earlier studies surgery has been much more common in North America or Hungary, with 20% of patients undergoing surgery, while in Studies IV and V most CP patients underwent EP before surgery (Machicado et al., 2017; Szücs et al., 2017). Recent decades have

witnessed an increase in endoscopic techniques, which may explain the low surgery rates for CP patients, which raises the threshold for embarking on demanding surgery due to a benign disease (Dirweesh et al., 2022). Moreover, CP patients tend to show low compliance with treatment, which may also effect the decision to opt for less invasive endoscopic procedures(Akanbi et al., 2021).

In Study III patients suffering constant pain after surgery had longer disease duration. The patient population was too small to ascertain a difference in disease duration and outcomes. It is agreed that if pancreatic surgery for CP is chosen it should be done in early rather than in late-stage CP although there is no consensus on how to clinically define late-stage CP in individual patients (Kitano et al., 2020).

We found that most patients in Study II were on opioids before surgery and opioid consumption was lower after surgery. However, 36% of the patients in Study II and 21% of those in Study III still took opioids after surgery. Persistent pain over three months and opioid usage have both been associated with post-operative pain in abdominal surgery (Strik et al., 2019). It is known that chronic opioid usage can paradoxically induce hyperalgesia (Sampaio-Cunha & Martins, 2022). One possibility would be to consider surgery before opiates are needed daily.

Numerous different surgical techniques were used in the studies. We can only presume that the clinics´ and surgeons' own customs affect the surgical methods chosen. Pancreatic surgery for CP should be based on morphological findings of the pancreas. Guidelines recommend a more parenchyma preserving Berne or Frey-type surgery over PD (Kempeneers, Issa et al., 2020). A lateral jejunostomy (Puestow) can be considered only if there is no inflamed pancreatic head, bile duct stenosis or portal vein stenosis (Dua & Visser, 2017). In Study III patients with pancreatic drainage had the most symptoms and pain post-operatively compared to those undergoing resection or drainage and resection.

In Study II the patients undergoing surgery had the same amount of post-operative PEI and in Study III they had less PEI than the control population in spite of a longer disease duration. We also found less DM in surgical patients. Earlier studies have also reported similar findings, where patients who undergo surgery instead of EP have less pancreatic insufficiency, leading to the idea that pancreatic surgery could delay inflammation and preserve pancreatic function (Issa et al., 2020; Ma et al., 2021). So far no recent trials have been reported investigating if early surgery could prevent inflammation and pancreatic insufficiency (Nealon & Thompson, 1993).

We found that half of the patients who underwent surgery in Study II were smokers and they also took significantly more opioids before surgery. It is now known that smoking is an independent risk factor for CP and has a negative impact on QoL (Machicado et al., 2017). Smoking cessation has been associated with a better quality of life after pancreatic surgery (Bordaçahar et al., 2018). It could be advisable to underline the importance of cessation of smoking to CP patients before surgery.

6.7 Quality of Life and Pain

In Study I we found that CP patients reported poorer QoL in the EORTC QLQ-C30 and Pan26 responses than the normative control. We found that patients with higher AUDIT-scores scored worse in the C30 questionnaires but not in the pancreatic specific PAN26 questionnaire. Patients who continued to drink alcohol after their diagnoses had more complications but did not have more pancreatic pain. Patients who smoked had more pancreatic pain. Whether this is because of the need to relieve symptoms of chronic pain or that smoking causes pancreatic pain through ischaemia remains unknown (Edderkaoui & Thrower, 2013). Our result contradicts an earlier study where idiopathic CP patients who smoked had less pain than in alcohol-related CP without smoking (Hao et al., 2022). We found more deaths in our

follow-up among patients suffering from severe pancreatic pain and financial difficulties than patients who did not have pancreatic pain or financial difficulties.

We found in Studies II and III that CP patients who undergo surgery for pain have better QoL and functioning after surgery than the rest of the CP population. In Study III the surgical group did have more symptoms (nausea, constipation and insomnia) but they had the same pain scores in the QLQ-C30 as the rest of population a median of two years after surgery. This could be considered a good result given that surgery is probably reserved for difficult-to-manage patients.
We found in both in Studies III and IV that if endoscopic procedures were performed before surgery, it produced a worse outcome in the QoL parameters and patients had more post-operative pain medication. Furthermore, patients who underwent surgery without prior EP needed no opiates. This could be due to early surgery after onset of symptoms rather than to the endoscopic procedures themselves. Similar findings were reported in the ESCAPE trial, where a surgery-first approach resulted in less pain (Issa et al., 2020). Other randomized trials that have also reported results where surgery seems to be superior to endoscopy (Cahen et al., 2007, 2003). However, we cannot conclude that either surgery or endoscopy is superior. Since we do not have detailed information on the technical success of the prior endoscopic procedures of our patients in Studies III and IV.

Yet it is not so simple. Endoscopy does indeed produce good results and in Study IV patients who underwent EP had better QoL and fewer symptoms than the reference group and the surgically treated group. There is a subgroup of patients who benefit from EP but a way to identify such patients has yet to be discovered. Probably early timing of the intervention is important before the sensitization to pain (Olesen, Krauss, et al., 2017). However, disease duration has not been found to be associated with CP pain (Vipperla et al., 2021).

It should also be noted that EP and surgery focus on the treatment of radiological findings (stricture, calcification and duct dilation), which do not have any correlation

with clinical symptoms (Wilcox et al., 2015). There are multiple studies where endoscopic treatment of ductal obstructions with metal or plastic stents relieves pain but pain may remerge later after stent removal (Sofi et al., 2021; Tringali et al., 2019, 2022).

Constant pain is present in 14-16% of CP patients and 42-50% of CP patients were painless after treatment or medication. There are believed to be several mechanisms behind CP pain. Traditionally pancreatic duct hypertension has been thought to be the main cause (White & Bourde, 1970). Now there is no consensus on the duct hypertension theory and it is known that the accompanying CP is much more complex, involving factors such as inflammation, oxidative stress and neural sensitization, hyperalgesia and depression (Kuhlmann et al., 2019; Poulsen, 2013; Sarkar et al., 2022).

Most studies on the treatment of CP pain involve comparing two interventions while leaving out the non-interventional control group (Drewes et al., 2019). There is ongoing a sham-controlled trial to ascertain if ductal decompression with ESWL and EP can truly relieve pain (Olesen et al., 2020).

6.8 Strengths and Limitations

The studies have several weaknesses since most of the medical data was gathered retrospectively, except for the unpublished data and the AUDIT, QLQ-C30, PAN26 questionnaires. Smoking was not always recorded accurately or at all and due to this smoking may be more common than reported. Another factor that needs to be noted is the lack of a reliable alcohol consumption history before the CP diagnosis or what criteria were used for alcohol-related CP. Also, alcohol consumption history was based on the patients' own reports leading to a possible bias. A suggested amount of five drinks (60g) per day has been proposed as a risk factor for CP but smaller quantities of alcohol can lead to CP in susceptible individuals (Hegyi et al., 2020).

All the patients in Studies I, III and IV were from tertiary care hospitals, which may have affected the types of CP patients found in the study.

An obvious limitation is that we had a low response rate in Studies I and II (38%-42%) due to the challenging patient group, leading to a small number of patients, especially in Study II and a probable bias in patient selection. Another limitation is that we lack pre-interventional QoL from Studies II, III and IV and opioid usage in Studies III and IV. The effect of surgery on pancreatic pain was elicited 14 years after surgery, which may have caused a bias. Also, follow-ups times differed in not being consecutive, thereby causing limitations in analysing the causality between interventions and outcomes.

Multivariable analysis could only be performed in Study IV due to the small population. The reference (Study IV) and control (Study III) groups are debatable as conservatively managed patients most likely differ from patients needing endoscopy or surgery. Regarding the endoscopic procedures we do not have information on why some patients had multiple procedures; for instance, they may have had another procedure because of technical failure, lack of pain relief or even a new complication.

More standardized reporting of pancreatic surgery for CP is needed. The International Study Group of Pancreatic Surgery (Siriwardena et al., 2020) proposed a standard in reporting surgery for CP including pre and post-operational medications, pancreatic function, morphology, pain and quality of life to better evaluate the outcomes. Compliance with these standards will improve the evaluation of surgical outcomes for CP patients.

We used the EORTC QLQ-C30 and PAN26 quality of life questionnaires for all studies. These questionnaires were originally intended for cancer patients, with PAN26 being pancreatic cancer specific but there is no questionnaire available intended solely for CP patients. The QLQ-C30 has been shown to evaluate the well-being of CP patients independent of age, likewise the 12-Item Short-Form Health Survey used to assess global quality of life in patients with chronic conditions(Pezzilli et al., 2007). Another point worth noting is that the QLQ-C30 measures patients' general pain, but not specifically abdominal pain. We had good sized control population for the QLQ-C30 (n=2,998) but the PAN26 control population was

rather small (n=102). It must be conceded that no specific validation has been done for the Finnish translation of either QLQ-C30 or PAN26.

The strengths of Studies I and II were that they included all patients in their cohorts, giving a good view of this hard-to-reach population. Thus, we provided novel data on the CP population in Finland. Studies III and IV were multicentre studies from four countries from the SBPC database, which is the largest CP registry to date.

6.9 Improving the Treatment of CP

One of most important factors in CP treatment is to get the patient to stop smoking and consuming alcohol. This seldom happens: in a prospective study where CP patients were put into a cessation programme for smoking none of the patients stopped smoking (Han et al., 2016). There is an ongoing trial to see if recurrent AP and thus CP can be prevented by a specialized cessation programme (Ocskay et al., 2022). More tools are needed with which to reach the patients and support them in stopping smoking. Preventing recurrent AP through cessation of smoking and drinking alcohol, is critical in the prevention of CP and leads to fewer symptomatic patients and less burden on the healthcare system (I. Shah et al., 2022). It is important for physicians to educate patients with pancreatitis.

Since CP patients are a heterogeneous population with many complications, opioid usage and chronic pain combined with possible malnutrition, they may need endoscopic or surgical interventions often involving multiple specialities. Multidisciplinary teams are needed to optimally plan the treatment for CP patients (Waage et al., 2022). In the future prospective trials will be needed to find the ideal treatment for CP pain. More effective ways are needed to reach CP patients who do not adhere to the lifestyle recommendations.

7 CONCLUSION

7.1 Study I: Quality of Life in Chronic Pancreatitis

CP patients had poor quality of life and poor functioning on all the parameters measured. Half of the patients continued smoking and drinking despite their diagnoses. Patients who continued to drink and smoke had more pancreatic pain.

7.2 Study II: Surgery for Chronic Pancreatitis in Finland

Surgery for CP is very uncommon but seemed to produce good long-term results and reduce opiate usage.

7.3 Study III: Pancreatic surgery and Quality of Life in Chronic Pancreatitis Patients

Half of the patients reported being pain-free after surgery. Patients who underwent a DPPHR or pancreatic resection seemed to achieve better symptom relief than patients undergoing surgical drainage.

7.4 Study IV: Endoscopic Procedures and Quality of Life in Chronic Pancreatitis Patients

CP patients who underwent endoscopic procedures had better QoL and fewer symptoms than the rest of the CP population.

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9 AUTHOR'S CONTRIBUTION

The author (*Mikael Parhiala*) contributed to the ethical permits, data collection, design and implementation of the research, to the analysis of the results and to the writing of all the manuscripts. The author was the first author in all studies.

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13 ORIGINAL PUBLICATIONS

PUBLICATION

I

A population-based study of chronic pancreatitis in Finland: Effects on quality of life

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Original Article

A population-based study of chronic pancreatitis in Finland: Effects on quality of life

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ABSTRACT

Background/Objectives: In Finland the incidence of chronic pancreatitis (CP) is high compared to that in most European countries. Recent epidemiological data is lacking. Our aim was to investigate the current epidemiologic and behavioural data on CP patients in Finland.
Methods: CP patients according to M-ANNHEIM criteria in Tampere University Hospital (TAUH) during 2014–2015 were included. Aetiology, time from diagnosis, pancreatic function, treatment, complications, smoking, alcohol consumption (AUDIT) and quality of life (QoL) (QLQ C30, PAN26) were gathered.
Results: 235 CP patients (57 (26–88) years, 65% men) were included. Time since diagnosis was 5.5 (1–41) years. Aetiology was alcohol in 67%, and smoking contributed in 54%. Of these patients 78% continued smoking and 58% continued to consume alcohol even after CP diagnosis. CP related complications were common. Pseudocysts were more common in alcohol related CP than in non-alcohol related CP (60% vs. 38%, $p < 0.05$). Reported QoL and pain were worse in the CP patients than in controls. Alcohol consumption differed from that of the Finnish population; the CP patients were either total abstainers or heavy alcohol consumers.
Conclusions: CP constitutes a great burden on the health care system and on the patients. The patients frequently develop complications and symptoms and their QoL is inferior to that of controls. The most important measure to halt the progression of CP would be to prevent acute phases and for patients to stop smoking, which does not happen in many CP patients. It would be beneficial to increase awareness among CP patients and medical professionals.

Introduction

Chronic pancreatitis (CP) causes permanent morphological changes to the pancreatic tissue. The persistent inflammation may lead to abdominal pain and pancreatic insufficiency, seen as secondary diabetes and malnutrition, as well as to various complications such as pseudocysts [1–4]. Furthermore, CP patients carry a slightly increased risk for pancreatic cancer, especially those suffering from pancreatitis at a young age due to prolonged inflammation, which constitutes a risk factor [5–7]. Out of the multiple CP aetiologies, the most recognized and common is alcohol, which causes about 70% of the CP in Western countries. Other risk factors for CP include duct obstruction, hyperlipidaemia, autoimmune, hereditary and anatomical factors [8,9]. The most prominent symptom of CP is persistent or recurring abdominal pain. Treatment of CP pain is not easy, and strong opioids may be needed. The progression of CP can be delayed by stopping smoking and preventing acute phases. Smoking exacerbates CP but is not the sole cause. Avoiding alcohol and smoking would thus be crucial in the prevention of disease progression [10].

In Western countries the prevalence of CP is between 43 and 143/100,000 in Europe and 41–91/100,000 in the USA [2,11–14]. In Finland the incidence of acute pancreatitis (AP) is 70/100,000 and the incidence of CP 13.4/100,000, which is one of the highest incidences of CP in Europe. However, no recent epidemiological data involving CP in Finland exists [15,16].

Objectives

The aim of this study was to investigate the current status and treatment of CP in Finland; findings, complications, pancreatic function, conservative and interventional treatment, lifestyle habits and quality of life (QoL).

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Methods

All adult patients who had been treated for CP (ICD-10 diagnosis code K86*) in Tampere University Hospital (TAUH) in the period 2014–2015 were selected and reviewed for inclusion in the database.

The diagnostic criteria according to M-ANNHEIM were used. This classification system for CP considers multiple risk factors: alcohol, nicotine, nutrition, hereditary factors, efferent duct factors, immunological factors and miscellaneous factors. In our study we grouped all the unknown aetiologies into miscellaneous factors. The M-ANNHEIM diagnostic criteria are grouped into definitive and probable. The definitive criteria involve one or more of the following: pancreatic calcifications, moderate or marked ductal lesions (according to the Cambridge classification), exocrine insufficiency requiring pancreatic enzyme supplementation or an adequate histological specimen. The probable criteria include mild duct lesions, persistent/recurrent pseudocysts, pathological test of exocrine or endocrine function of the pancreas i.e. low faecal elastase or abnormal glucose tolerance. The diagnosis also requires a typical clinical history of CP which includes recurrent abdominal pain or pancreatitis, except for painless pancreatitis [10].

Medical records of all patients were reviewed. Patients who did not meet the diagnostic criteria were excluded from the database. The patients who were verified as CP patients formed the final database. The following data was collected: date of birth, gender, pancreatic insufficiency, aetiologies, complications, year of diagnosis, mortality, alcohol consumption, smoking, interventions and imaging findings. Originally 235 patients were identified. After excluding the patients who were deceased or whose address information was not available, 188 patients were asked to complete the QoL questionnaires EORTC (European Organisation for Research and Treatment of Cancer) QLQ-C30 and pancreatic specific EORTC QLQ-PAN26 [18]. Mortality was recorded on November 4, 2018. The follow-up time median from the beginning of the disease was five years (2–43 years).

A Swedish control population (n = 3069; mean age 51 years, 53% female) was used as a control population for the QLQ-C30 [19]. Sweden and Finland have similar lifestyles and climate, both of them being Nordic countries. In the C30 normative population 5% of subjects had suffered from asthma, while in the Finnish population 4–7% had asthma, 5% of the C30 had diabetes while 5–6% of the Finnish population had diabetes [20].

A normative control from the UK was used for the PAN26 questionnaire responses [21], the normative population includes n = 101 responders, median age 39.5 (range 20–84) years. The Finnish AUDIT (Alcohol Use Disorders Identification Test) control population (n = 1,368, 44% male 28–79 years) was used as a control population for alcohol consumption; Mäkelä Pia 2017 Finnish Drinking Survey THL [22].

Data is presented as medians (range) unless otherwise stated. The statistical analysis was calculated by IBM SPSS statistic version 24 using Pearson's Chi-Square or Fisher's exact test, for the analysis of the QLQ-C30 and PAN26 questionnaires the Mann-Whitney U -test was used. The EORTEC scoring manual was used for the QLQ-C30 and PAN26 questionnaires, the responses were scored to 0–100. A higher score in QOL/functioning represents a better score and a lower score in symptoms (e.g. pain or insomnia) represents a better score. $P < 0.05$ was considered statistically significant.

Ethical aspects

The study was approved by the Ethics committee of Tampere University Hospital, Finland (ETL code R15187).

Results

In total 235 CP patients who met the CP diagnostic criteria were included in the final study database. Median age was 57 years (26–88 years), and 65% were male. The median time since diagnosis was 5.5 (1–41) years. Of the CP patients 91% (n = 216) met one or more of the definitive diagnostic criteria for CP. Recurrent AP was recorded in sixty-four percent. Out of the 235 patients, 219 underwent radiological imaging during the follow-up period: 37% had marked changes, 20% had moderate changes, 12% had mild changes, 19% had equivocal changes and 12% had normal pancreas during imaging.

The aetiology was diverse and multiple aetiologies were common (Table 1). Alcohol consumption combined with smoking was the leading factor for CP; 50% of the patients reported at least alcohol consumption and smoking as risk factors. We have information about smoking history on 234/235 patients (99.6%) and about alcohol consumption on 232/235 patients (98.7%), but without information on the amount of alcohol consumed. Smoking was a risk factor in 54% and 78% continued smoking after their diagnosis. Smoking pack-years (20 cigarettes per day for a year) median was 37 years (5–70 years) n = 66 (52% all smokers). A further 20% had unknown aetiologies for CP and 10% had efferent duct factors as a risk factor. Six patients underwent genetic testing and five patients were found to have a SPINK1 mutation.

Twenty-six percent of the patients (n = 60) died during follow-up at a median age of 62 (range 26–85). Females died at a median age of 63 years and males 62 years. Cause of death was available for 21 patients, and these are listed in Table 1. In the year 2017 the median age of death in Finland was 75 years for men and 81 years for women.

Complications are listed in Table 1. Pancreatic calcifications were found in 66% of patients and ductal lesions in 50%. Of the patients 55% had pancreatic exocrine insufficiency (PEI) and 54% had pancreatic endocrine insufficiency (High HbA1c count or fasting blood sugar levels diagnostic for diabetes mellitus). Pseudocysts were more common in alcohol related CP than in non-alcohol related CP (60% vs. 38%, p = 0.0005). In patients who smoked, pseudocysts (62% vs. 52% p = 0.262; ns) and pancreatic calcifications tended to be slightly more frequent (72% vs. 58% P = 0.071; ns) than among non-smokers. Bile duct stenosis requiring interventions was found in 10% and 7% of the patients had abdominal ascites and pleural effusion, and a further 5% of the patients with CP also had liver cirrhosis.

Interventions are listed in Table 1. Endoscopic procedures where performed on 27% of the patients. Out of these, 20% needed endoscopic interventions multiple times and one patient had an endoscopic celiac blockage.

Nine per cent of the patients underwent surgical procedures. Surgical interventions (n = 21) included treatments for complications, such as pseudocysts or stenosis, involving cystojejunostomies (n = 11), gastrojejunostomies (n = 2) and hepaticojejunostomies (n = 2). Whipple procedures (n = 4) were mostly performed to rule out malignancies. Two Beger-type operations were performed.

Out of the 188 patients requested to complete the questionnaires, 77 (41%) returned the QoL questionnaires (QLQ-C30 and Pan-26) and 76 (40%) the AUDIT questionnaire (Fig. 1). Among the responders who answered the questionnaires the median age was 57 years (range 28–88), the median since diagnosis was four years (range 2–42 years). The proportion of alcohol aetiologies, pseudocysts and PEI were similar compared to all patients alive in the total study population. Out of 77 patients who responded six died in 2-year follow-up. Patients who died had statistically higher pancreatic pain (49 vs. 29) p = 0.042, financial difficulties, difficulties in physical functioning and in cognitive functioning.

Table 1
a) Demographics, risk factors and complications of CP patients in a Finnish tertiary hospital in 2014–2015. b) Complications by risk factors c) Multiple risk factors are possible. Alcohol and smoking are the largest risk factors of CP in Finland. Efferent duct factors include mostly bile duct stones. Immunological factors include autoimmune pancreatitis and Sjögren's syndrome. All of the Hereditary CP was connected to SPINK1 mutation.

a

Chronic pancreatitis patients n = 235	
Age median	58 *(26–95) years*
BMI median (n = 109)	23 [16–48]
Gender	34% female 67% male
Time after diagnosis median (range) n = 107	4 [1–42] *years*
Risk factors n = 234	
Alcohol	68%
Nicotine	54%
Unknown	21%
Efferent duct factors	10%
Hereditary	3%
Immunological	3%
Nutrition	2%
More than one aetiology	57%
One aetiology	43%
Smoking pack years median (range) n = 66	37 (5–70) years
Complications n = 234	
Calcifications	66%
Pseudocysts	58%
Exocrine insufficiency	55%
Endocrine insufficiency	54%
Ductal lesions	50%
Bile duct stenosis	10%
Pleural effusion	7%
Ascites	7%
GI-tract bleeding	6%
Pancreatic fistulas	5%
Porta thrombosis	5%
Pseudoaneurysms	5%
GI-tract stenosis	4%
Death	(n = 60) 26%
Cause of death in CP n = 21 (35%)	
Cardiovascular disease	19%
Other malignancy	19%
Liver cirrhosis	14%
COPD (Chronic Obstructive Pulmonary Disease)	10%
Hypoglycemia	10%
Pancreatitis	10%
Pancreatic adeno ca	5%
Polycystic kidney disease	5%
Sepsis	5%
Post surgery sepsis	5%
Interventions n = 234	34%
Endoscopic	27%
Surgery	9%
Percutanous drainage	8%
Celiac block	0.40%

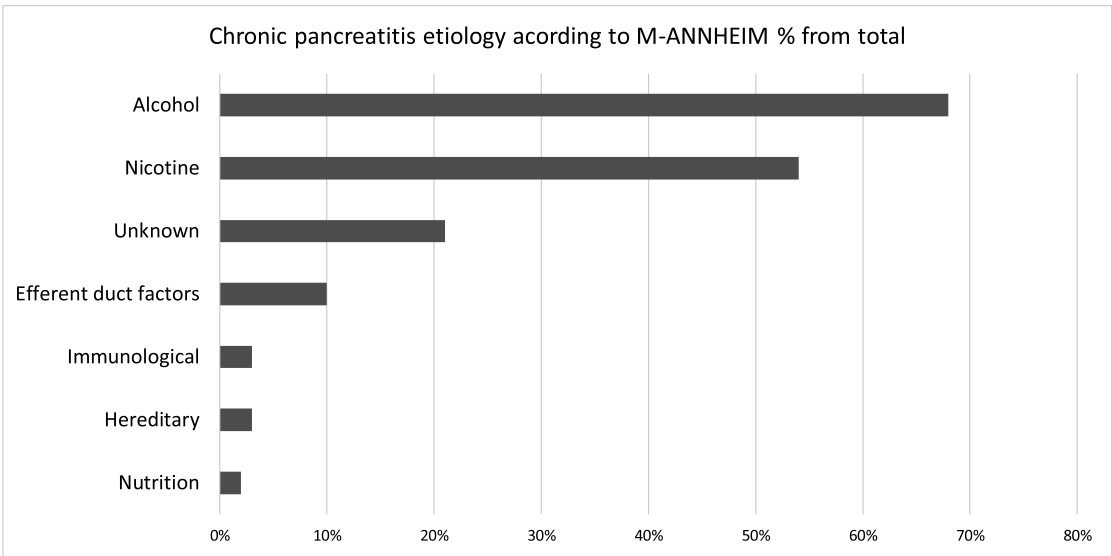
b

Risk factors and complications		Calcifications		Pseudocysts		Any complication	
Alcohol n = 232	**Yes**	74%	p«0.05	66%	p«0.05	72%	p«0.05
	No	50%		42%		46%	
Smoking n = 234	**Yes**	65%	p = 0.071	61%	P = 0,262	68%	p = 0.103
	No	53%		54%		58%	

c

Table 1 (*continued*)

c



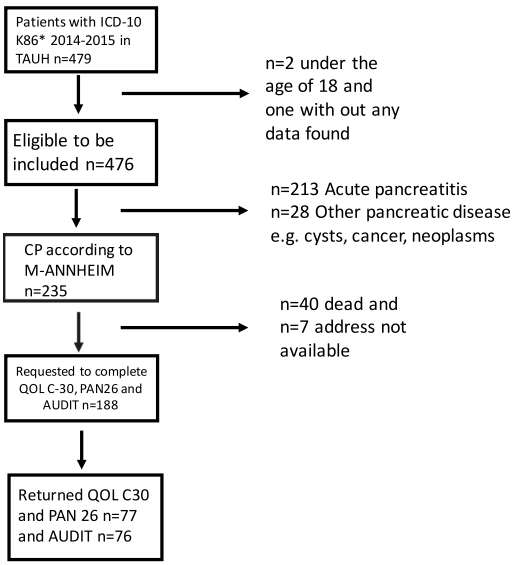
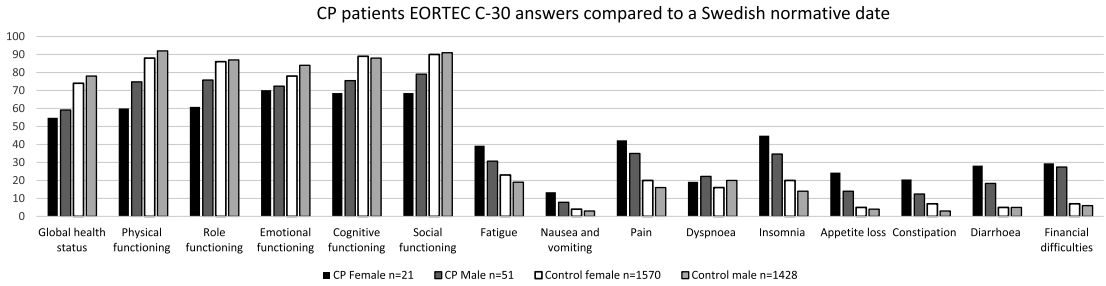


Fig. 1. Flowchart of CP patient recruitment in TAUH 2014–2015.

The QLQ-C30 and Pan26 data (n = 77) are shown in Figs. 2 and 3. There was no statistically significant difference in the C30 and PAN26 in men and female CP patients except for men having better physical functioning and fewer digestive symptoms. In the C30 responses all functioning, and symptoms were poorer in CP patients than in the controls. In the PAN26 all symptoms were statistically more severe than in the control group but for satisfaction with health care no difference was found.

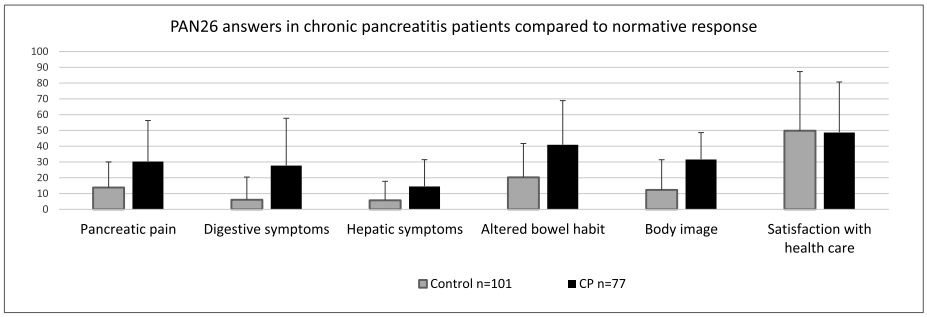
When comparing the EORTC QLQ C30 and PAN26 questionnaire responses between smoking and non-smoking patients, smokers had poorer functioning and more severe symptoms in all categories, although not all of the categories reached statistical difference. For example, there was a statistical difference in pain and pancreatic pain. (Fig. 4). This difference was not found when comparing AUDIT (0 points, 6 Female/8 male or 16 or over points) scores to responses on pain or pancreatic pain. (Fig. 5). There was no significant difference in pain or pancreatic pain in any of the groups. No significant differences in the pancreatic-specific responses (PAN26) were found when grouping the AUDIT questionnaires except for hepatic symptoms when comparing AUDIT<16p vs AUDIT $\geq$16p (12 vs 26 mean; $p = 0.018$). There were many statistical differences between the C30 responses to different AUDIT scores (Fig. 5).

Fig. 6a shows the distribution of AUDIT scores compared to those of 28 to 79-year-old Finnish men and women. The AUDIT scores were grouped into four groups, the first group being 0–6 points for women and 0–8 points for men based on the Finnish Current Care Guidelines screening limits for hazardous alcohol consumption. CP patients more often scored over 16 points on AUDIT than did the rest of the population (16% vs. 3%; $p < 0.005$). In addition, CP patients more often scored over six for females and over eight for males, compared to the controls (33% vs 23%; $p = 0.041$). Total abstinence among the CP patients was 42%, and women had a higher percentage of total abstinence (62% vs. 32%; $p = 0.013$). Since abstinence differed greatly by age and gender, we divided it into two age groups per gender (Fig. 6b). In males aged 28–59 years abstinence was 26% in CP patients vs. 10% in controls; $p = 0.006$. In women aged 28–59 years abstinence was 50% in CP patients vs. 13% in controls; $p = 0.0001$). CP men over 60 years (42% vs. 14%; $p = 0.001$) and women over 60 years (75% vs. 26%; $p = 0.0002$) were more often total abstainers from alcohol than were the controls.



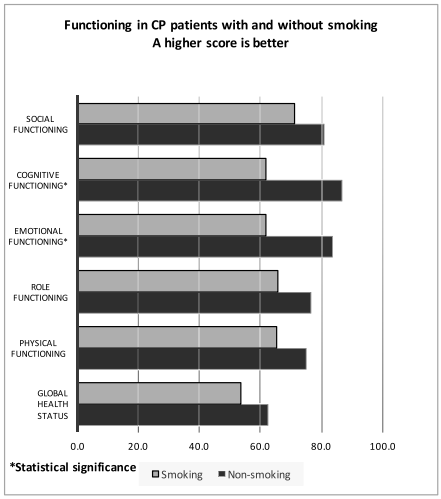
EORTEC QLQ-C30 data from chronic pancreatitis patients Functioning and quality of life	n=77	n=26	n=51	p-value	*n=1570*	*n=1428*	n=35	n=42	p-value
	CP (st dev)	CP female	CP male	Female vs male	*Control female***	*Control male***	Non-smoking (st dev)	Smoking (st dev)	Smoking vs non-smoking
Higher the value= better functioning									
QOL	58 (24)	55 (26)	59 (23)	0.54	*74 (22)*	*78 (21)*	63 (21)	54 (25)	0.065
Physical functioning	70 (26)	60 (26)	75 (24)	**0.017***	*88 (18)*	*92 (16)*	75 (22)	65 (28)	0.142
Role functioning	71 (31)	61 (35)	76 (28)	0.076	*86 (24)*	*87 (24)*	77 (26)	66 (34)	0.313
Emotional functioning	72 (28)	70 (28)	72 (27)	0.651	*78 (22)*	*84 (20)*	84 (20)	62 (29)	**0.001***
Cognitive functioning	73 (28)	69 (34)	75 (23)	0.746	*89 (18)*	*88 (17)*	87 (15)	62 (31)	**0.000***
Social functioning	76 (34)	69 (34)	79 (34)	0.097	*90 (20)*	*91 (19)*	81 (34)	71 (34)	**0.0138**
Symptoms: Higher the value= worse symptoms									
Fatigue	34 (27)	39 (29)	31 (26)	0.208	*23 (22)*	*19 (21)*	21 (19)	44 (29)	**0.000***
Nausea and vomiting	10 (18)	13 (24)	8 (15)	0.39	*4(11)*	*3 (10)*	3 (8)	15 (23)	**0.005***
Pain	37 (32)	42 (35)	35 (30)	0.469	*20(27)*	*16 (23)*	29 (29)	44 (33)	**0.035***
Dyspnoea	21 (29)	19 (34)	22 (25)	0.197	*16 (24)*	*20 (28)*	13 (22)	28 (32)	**0.041***
Insomnia	38 (35)	45 (37)	35 (33)	0.256	*20 (28)*	*14 (25)*	30 (29)	44 (38)	0.118
Apetita loss	18 (26)	24 (30)	14 (23)	0.112	*5 (15)*	*4 (14)*	8 (16)	26 (30)	**0.002***
Constipation	15 (24)	21 (29)	12 (20)	0.287	*7 (18)*	*3 (12)*	10 (20)	20 (25)	**0.035***
Diarrhoea	22 (27)	28 (37)	18 (20)	0.599	*5 (16)*	*5 (15)*	15 (23)	27 (29)	0.056
Financial difficulties	28 (36)	29 (38)	27 (35)	0.986	*7 (21)*	*6 (19)*	10 (26)	43 (37)	**0.000***

Fig. 2. Quality of life: overall. QLQ-C30 scores (mean, SD) in CP patients compared to the Swedish normative data (15). All functioning and symptom scores are worse in CP patients compared to the controls. The smoking CP group had worse functioning and symptoms scores. A higher score in QOL/functioning represents a better QoL. A lower score in symptoms represents a better QoL.



QLQ-PAN26 data from chronic pancreatitis patients	n=77 kpl	n=26	n=51	p-value	n=101	n=35	n=42	p-value
	CP (st dev)	CP female	CP male	Female vs male	Control population**	Non-smoking (st dev)	Smoking (st dev)	Smoking vs non-smoking
Pancreatic pain	30 (26)	38 (30)	26 (23)	0.088	14 (16)	22 (23)	37 (27)	**0.007***
Digestive symptoms	28 (30)	40 (31)	21 (27)	**0.005***	6 (14)	21 (24)	33 (33)	0.157
Altered bowel habit	41 (28)	47 (30)	38 (27)	0.281	20 (21)	32 (23)	48 (30)	**0.015***
Hepatic symptoms	15 (17)	16 (20)	14 (16)	0.811	6 (12)	9 (14)	19 (18)	**0.005***
Body image	32 (30)	40 (38)	27 (25)	0.316	13 (19)	20 (20)	41 (34)	**0.005***
Satisfaction with health care	49 (32)	40 (36)	53 (29)	0.086	50 (37)	52 (32)	46 (32)	0.411
***Swedish population (Michelson et al.2000)*				**Statistically significant***				

Fig. 3. Quality of life: overall. QLQ-PAN26 scores (mean, SD) in CP patients compared to a normative Chicago population (17). All symptoms are worse compared to the control. A lower score in symptoms represents a better score, except for satisfaction with health care. CP patients have worse scores in all parameters except satisfaction with health care. CP that smoke had worse pancreatic pain, altered bowel habits, hepatic symptoms and body image.



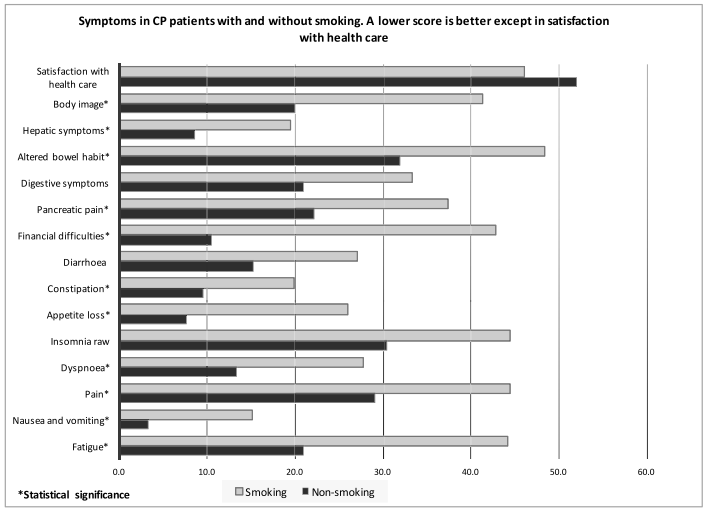


Fig. 4. Quality of life: smoking. QLQ C30 and PAN26 functioning and symptom scores in CP patients who smoke and do not smoke. CP patients who smoke have worse functioning QoL and more symptoms. * marks as a statistical significance ($p < 0.05$). A lower score in symptoms represents a better QoL, except for financial difficulties.

AUDIT scores compared to EORTEC QLQ-C30 and PAN26 data									
Functioning and quality of life	**n=46**	**n=31**		**n=51**	**n=26**		**n=64**	**n=13**	
Higher the value= better functioning	*AUDIT=0p*	*AUDIT ≥ 1p*	*p-value*	AUDIT≤ 6F/8M	AUDIT > 6F/8M	p-value	AUDIT < 16 points	AUDIT≥1 6 points	p-value
QOL	*61.2*	*55.2*	*0.286*	62.8	48.1	**0,026***	60.8	42.3	**0.018***
Physical functioning	*72.1*	*68.1*	*0.724*	71.1	66.9	0.696	70.5	66.2	0.666
Role functioning	*72.4*	*69.6*	*0.991*	74.0	64.7	0.498	72.1	64.1	0.628
Emotional functioning	*78.6*	*66.7*	*0.135*	78.2	59.3	**0.028***	76.3	48.7	**0.008***
Cognitive functioning	*80.7*	*67.8*	*0.052*	78.7	62.2	**0.018***	77.9	50.0	**0.001***
Social functioning	*26.7*	*38.5*	*0.291*	27.6	46.2	0.124	29.7	53.0	**0.046***
Symptoms: Higher the value= worse symptoms									
Fatigue	*4.2*	*13.7*	*0.152*	5.3	18.6	**0.009***	6.0	28.2	**0.008***
Nausea and vomiting	*31.8*	*41.5*	***0.007****	32.7	46.2	**0.002***	34.4	52.6	**0.000***
Pain	*14.6*	*26.5*	*0.195*	17.0	29.5	0.199	17.7	38.5	0.124
Dyspnoea	*30.2*	*43.7*	*0.062*	30.0	53.8	0.094	31.8	69.2	**0.014***
Insomnia	*12.5*	*21.2*	*0.126*	12.0	29.3	**0.005***	12.5	44.4	**0.001***
Apetita loss	*13.5*	*16.3*	*0.191*	13.3	19.2	**0.003***	13.5	23.1	**0.000***
Constipation	*14.6*	*26.7*	*0.547*	14.0	35.9	0.149		38.5	0.050
Diarrhoea	*21.9*	*32.6*	***0.038****	22.7	39.7	**0.000***	24.5	46.2	**0.005***
Financial difficulties	*26.8*	*33.0*	*0.199*	26.8	37.8	**0.037***	28.6	39.1	**0.045***
QLQ-PAN26 data from chronic pancreatitis patients									
Pancreatic pain	*26.8*	*33.0*	*0.463*	26.8	37.8	0.204	28.6	39.1	0.366
Digestive symptoms	*27.6*	*27.8*	*0.663*	25.7	32.7	0.530	27.6	28.2	0.656
Altered bowel habit	*34.9*	*45.2*	*0.180*	37.3	48.1	0.214	39.8	46.2	0.673
Hepatic symptoms	*10.9*	*17.0*	*0.192*	11.7	19.2	0.111	12.2	25.6	**0.018***
Body image	*25.5*	*35.9*	*0.214*	27.0	41.0	0.060	29.4	42.3	0.135
Satisfaction with health care	*55.7*	*43.6*	*0.129*	52.4	41.7	0.184	51.3	35.9	0.109
*Statistically significant									

Fig. 5. Quality of life: AUDIT scores. And CP patients with a higher AUDIT score had worse functioning and symptoms in the QLQ-C30 responses but there was no difference in the PAN26 responses except for hepatic symptoms when comparing AUDIT plus 16 points. A higher score in functioning represents a better score. A lower score in symptoms represents a better score, except for satisfaction with health care.

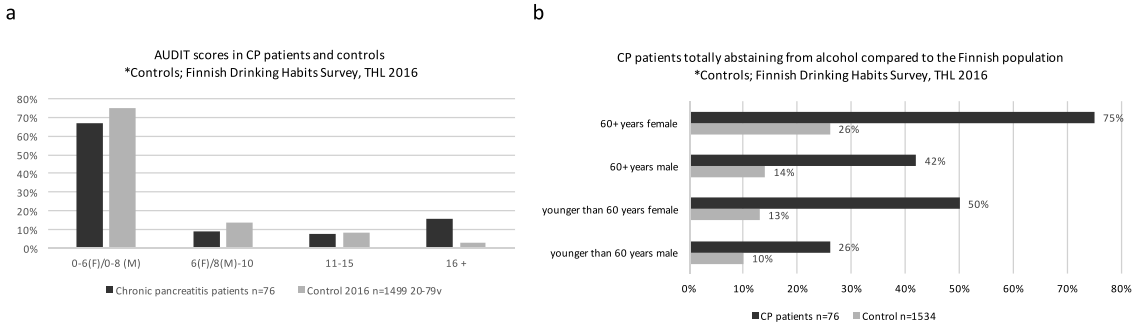


Fig. 6. Alcohol usage. a) AUDIT score distribution in CP patients n = 76 compared to the Finnish population (18) of the same age. Male and female scores were grouped differently due to different scores ratings. There was a statistical difference between 0 and 6 (Female)/0–8 (male) groups and 16+ groups ($p < 0.05$). b) The distribution of totally abstaining CP patients compared to the Finnish population. All the differences were statistically significant ($p < 0.05$).

Discussion

Finland has one of the highest incidences of CP in Europe. However, no recent epidemiological data involving CP in Finland exists. Our aim was to investigate the current status and treatment of CP patients. The study reveals the burden of CP on the healthcare system: the patients with the most common aetiologies - alcohol and smoking - also are at higher risk of developing complications. Half of the patients continue smoking and drinking despite their diagnoses. These patients have poorer QOL and more complications. Women were more likely to totally abstain from alcohol.

Alcohol and smoking contributed to the majority of aetiologies of CP but a significant number of aetiologies remained unknown (21%). It is possible that at least some of these could have been caused by biliary microlithiasis [23]. It is also possible that these patients with unknown aetiologies have a genetic mutation causing CP, possibly some of the CP patients identified as having CP of alcohol origin have a genetic factor predisposing to the disease. Not everyone with the same lifestyle develops AP or CP. Those with a genetic cause behind pancreatitis have many clinical similarities with alcohol induced pancreatitis [24,25]. Even though having the same aetiology (alcohol) a low percentage of CP patients had developed liver cirrhosis, and similar findings have also been presented in an earlier study [26], This reason why only some of those who consume hazardous amounts of alcohol and who smoke develop CP might be explained with a genetic predisposition towards developing pancreatitis. More research is needed on this subject.

In the year 2017 the median age of death in Finland was 75 years for men and 81 years for women compared to 62 for males and 63 for females in our CP population [27]. In our follow-up there were more deaths among CP patients with financial difficulties, pancreatic pain and worse physical and cognitive functioning this not been recorded in previous studies.

We found that most of the CP patients continued smoking after their diagnosis (42% of all CP patients continued smoking and only 22% had stopped smoking). Similar findings have been reported elsewhere, with 50–63% patients continuing smoking after diagnosis and 25% were former smokers [28,29]. CP patients and medical professionals need to be educated about the risks of smoking. This means that not only alcohol consumption history but also smoking history should be elicited.

Despite continuing smoking, a significant number of CP patients according to our questionnaire abstained from alcohol: 42% versus general Finnish population 13% [22]. In a prospective cohort study from the United States (Machicado et al.) a similar trend was seen where 80% of CP patients abstained from alcohol [29]. In our study alcohol related CP was more susceptible to complications than non-alcohol related CP. Alcohol related CP had statistically significant higher rates of pseudocysts, calcifications and combined complications. In earlier research pseudocysts have been associated with alcohol related CP [30–32]. No current data on alcohol consumption after diagnosis was available, nor on how it effects QOL.

In our study CP patients with a higher AUDIT score had a worse QOL, functioning and symptoms (C30) but pancreatic symptoms (PAN26) were not more common except for hepatic symptoms in the AUDIT 16p plus group. In our study CP patients with alcohol consumption after their diagnosis in addition to having more complications have more pancreatic pain, although this difference did not reach statistical significance. There was a major group of CP patients who were still drinking heavily ((AUDIT +16) 16% vs. 3% controls), these patients could benefit from an intervention preferably early on, before AP progresses to CP [33–35]. No earlier comparison of AUDIT scores in CP and general population has so far been presented.

In our study, women were more likely to follow advice on abstinence. Abstinence remains a challenge in this patient group. In our clinical practice, information on the importance of abstinence was given during hospitalization and at discharge by a doctor and a nurse. Information about further supportive programmes for abstinence in primary health care was offered to the patients during hospitalization, and given if the patient was willing to receive this information. However, contacting the support providers in the primary health care was the patients' own responsibility.

In our study smokers had a slightly higher rate of calcifications and pseudocysts although this did not reach statistical significance. Earlier research has reported a connection between the risk of calcifications and smoking [36,37].

Our pseudocyst percentage was higher than that reported in most studies ((12–40%) vs. 58%) [38–40]. A probable cause behind this is that our study was conducted in a tertiary care hospital with more severe cases of CP and modern imaging (CT, MRI, US) being more precise and more easily available than before.

The number of endoscopic procedures (27%) performed was approximately the same as reported in other studies (23–37.7%) but surgical interventions - surgery for CP pain in particular - was fairly rare (9%), compared to other reports (11–39%). In a Hungarian study 18.6% of patients had surgical pseudocyst drainage versus our 4.7% and 11.1% had pancreatic decompression surgery versus 0.9% in our study population. Pancreatic decompression surgery for pancreatic pain is very rare in Finland [28,29,41,42].

The CP patients' quality of life was poor, and they have more symptoms than in the control population. In a Polish demographic study A. Mokrowiecka et al., 2010 [42]. With QLQ C-30 and Pan26, CP patients had even more severe symptoms and poorer QOL scores in all sections than in our study. However, in the Polish study there was a higher percentage of current smokers than in our study (84% vs. 49% respectively), which may explain the difference. In a cross-sectional study by S Han et al. CP patients who smoked had higher rates of depression, anxiety and poorer quality of life [43].

CP patients had an inferior quality of life and poorer functioning in all the parameters measured (cognitive, social, emotional, financial and physical) especially those patients who continue to drink and smoke have more pancreatic pain. Similar studies also corroborate that CP patients have inferior QOL and also shorter lower life expectancy, most probably due to pain, pancreatic insufficiency and complications [2,29,42,44–47]. In our findings CP patients who continue to smoke have more pancreatic pain, which could be due to pancreatic ischaemia [48]. CP patients who had higher AUDIT score had poorer functioning and more severe symptoms in the QLQ-C30 response but there was no statistically significant difference in the PAN26 responses except for hepatic symptoms. This differs from the studies by Mokrowiecka et al. and Wehler et al. [42,49].

In general, CP patients are treated by gastroenterologists and surgeons. In Finland surgeons perform most ERCP procedures, and thus the endoscopic and surgical interventions are considered simultaneously. In our study population pancreatic surgery for CP pain was rare and was mainly performed to rule out malignancies or to treat complications. Over half of our study population had recurrent AP. It is speculated that AP and CP are part of the same disease spectrum but not all who have AP develop CP. In a 2015 meta-analysis Sankaran et al. involving 14 studies only 36% of patients with recurrent AP develop CP [50,51].

The strength of this study is the prospectively gathered AUDIT scores and QOL questionnaires. Since we gathered data from all CP patients treated in our hospital region catchment area this study gives a good view of the aetiology, treatment and lifestyle of CP patients in Finland.

The weaknesses of the study include that the first part of our study was conducted retrospectively relying on the medical archives. Because of this, smoking was not always recorded accurately or at all. Thus, smoking could be even more common than stated for CP patients. Because our data comes from a tertiary care hospital we do not have records from CP patients treated in general medicine. The percentage of these patients remains unknown, but presumably these are pain-free CP patients without complications, as they have not been in contact with specialized health care. Our questionnaire provides current data about the quality of life and alcohol consumption of CP patients. The response rate, only 41%, was lower than expected.

In conclusion, our study provides current data about the complications, lifestyles and quality of life of CP patients. CP causes a burden on the health care system and also on the patients. CP patients are a diverse population of different ages and with multiple aetiologies. Each person should be treated individually according to morphological changes, pancreatic function and pain. Half of the patients continue smoking and drinking despite their diagnoses and this affects their QOL. In the CP patient population there seems to be more who are totally abstinent and more heavy drinkers than in general population.

According to current knowledge, the most important measure to halt the progression of CP would be to prevent acute phases and for patients to stop smoking. Currently this does not happen in many of the CP patients, and it would thus be beneficial to increase awareness among CP patients and medical professionals.

Declaration of competing interest

The authors have no conflicts of interest.

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PUBLICATION

Unpublished Study

Osteoporosis and sarcopenia are common and insufficiently diagnosed among chronic pancreatitis patients

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Submitted

Osteoporosis and sarcopenia are common and insufficiently diagnosed among chronic pancreatitis patients

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Abstract

Purpose

Chronic pancreatitis (CP) leads to diabetes and pancreatic exocrine insufficiency (PEI). PEI may lead to maldigestion and malnutrition, which may cause fat-soluble vitamin deficiency, sarcopenia and abnormal bone density. We aim to study the prevalence of osteoporosis, sarcopenia and vitamin deficiency among CP patients.

Methods

Long-term (4-5 years) follow-up was implemented on CP patients. We recorded CP duration, BMI, smoking, alcohol consumption and medication. We determined the serum values for A, D and E vitamins, albumin, creatinine, haemoglobin, calcium and magnesium. Bone density measurement was taken from the proximal femur and lumbar spine. CT/MRI scans were used to measure for psoas muscle area.

Results

A total of 33 patients (median age 62 [39-81] years, 61% male) were included. None of these patients had earlier diagnosis of osteopathy, and none of them had known vitamin deficiency or were sarcopenic. Nineteen patients (57%) had pancreatic exocrine insufficiency and of these seven patients (37%) had no pancreatic enzyme replacement therapy (PERT) and one (5%) had inadequate enzyme therapy. During the study, osteoporosis was diagnosed in 20% and sarcopenia in 48% of patients. PEI and inadequate PERT was associated with low E vitamin levels (75% vs. 0%, p=0.012), higher risk of osteoporosis (43% vs. 5.6%, p=0.013) and sarcopenia (80% vs. 36%, p=0.044)

Conclusion

This study demonstrates that chronic pancreatitis is associated with osteoporosis, sarcopenia and vitamin deficiency. If untreated, pancreatic exocrine insufficiency is associated with increased risk of these outcomes. This highlights the importance of identifying and treating PEI in CP patients.

Keywords:

Vitamin Deficiency; Pancreatic Insufficiency; Exocrine Insufficiency; Alcohol; Pancreatic Enzyme Replacement Therapy; Bone Mineral Density; Psoas Muscle Area

Abbreviations

BMD	Bone Mineral Density
BMI	Body Mass Index
CP	Chronic Pancreatitis
DXA	Dual-energy X-ray Absorptiometry
FE-1	Faecal Elastase-1
PEI	Pancreatic Exocrine Insufficiency
PERT	Pancreatic Enzyme Replacement Therapy
PMA	Psoas Muscle Area
QoL	Quality of Life

Introduction

Chronic pancreatitis (CP) manifests as a persistent or intermittent inflammation of the pancreas, which may over time cause morphological changes to the pancreatic tissue. This can lead to permanent pancreatic exocrine (PEI) and endocrine insufficiency. The exocrine pancreas has an essential role in the digestive system secreting digestive enzymes (e.g., lipase, trypsin and amylase) in a bicarbonate solution which break down fats, proteins and carbohydrates. Exocrine insufficiency can lead to steatorrhoea, maldigestion and malnutrition. Overall exocrine insufficiency may impose patients to fat-soluble vitamin deficiency, sarcopenia and osteoporosis. (1-4)

Osteoporosis is defined as a skeletal disease with low bone strength leading to an increased risk of fractures, while sarcopenia is defined as loss of muscle mass and impaired physical performance (5-6). Diagnosis of osteoporosis is based on bone mineral density (BMD), typically measured from the femoral neck or the lumbar bone (7). Sarcopenia and osteoporosis have both been found to be associated with higher mortality, lower quality of life (QoL) and increased risk of hospitalizations. There is recent evidence that CP patients could have sarcopenia with an incidence of 17-62% with exocrine insufficiency and pancreatic fibrosis being a suspected risk factor (8-9). There is also evidence that almost 25% of CP patients have osteoporosis (10) and are at risk for vitamin deficiency (11). Since all these conditions are interlinked in that they are caused by probable malnutrition, maldigestion, possible alcohol consumption and chronic inflammation our aim was to determine how possible sarcopenia, osteoporosis and vitamin deficiency were diagnosed and treated in CP patients. The nutritional status and osteoporosis and possible sarcopenia of CP patients in Finland have not been studied.

Methods

Consecutive patients with CP at Tampere University Hospital, Finland between 1 January 2014 and 31 December 2015 were included. CP was defined according to the definitive diagnostic criteria of

CP according to the M-ANNHEIM criteria in a study illustrated in Figure 1 (12-13). The definitive diagnostic criteria include one or more of the following: Enlargement of the main pancreatic duct, (moderate or marked ductal pancreatic ductal lesions according to the Cambridge classification), pancreatic calcification, pancreatic exocrine insufficiency with pancreatic steatorrhoea clearly reduced by pancreatic enzyme replacement therapy (PERT) or a typical histological specimen of the pancreas.

Data regarding medication, vitamin supplements, menopause, testosterone, albumin and vitamin D, E and A levels were measured in 2019. We also elicited information on possible fractures. We measured the participants' weight and height and calculated the body mass index (BMI) kg/m^2. BMI $\geq$ 25 kg/m^2 was considered overweight and BMI $\geq$30 kg/m^2 was considered obese. (14) The patients provided blood and stool samples and a bone density measurement was taken. A faecal elastase-1(FE-1) level less than 100 μg was considered clinically relevant. An adequate amount of PERT was defined as 25-50 000IU of pancreatic lipase per meal according to the 2020 ESPEN guidelines. (15-16)

Bone density measurement

Bone density measurement or dual-energy x-ray absorptiometry (DXA) was done at both femur neck and lumbar spine in 2019. The Lunar iDXA (GE Medical Systems, Milwaukee, Wisconsin, USA) with enCORE v16 software was used for all bone density measurements. The measurements were based on the World Health Organization definition of a T score of -2.5 or less. Osteopenia defined as T score between -1 and -2.5. In patients under the age of 50 years we used a Z score instead of a T score according to the International Society for Clinical Densitometry guidelines. A Z score of -2.0 or under is "below the expected range of age" (17-18)

Sarcopenia measurement

Psoas muscle area (PMA) was identified by CT or MRI scans gathered retrospectively within one year from the time when the DXA measurement was taken between the years 2018 and 2020. (19) We calculated the mean area (mm^2) of both left and right psoas muscles from the middle of the third lumbar vertebra, so that both transverse processes were visible. The psoas muscle area was precisely drawn by the same clinician and area calculated (mm^2) using the Sectra Workstation version 23.1 (Sectra AB, Linköping, Sweden). This method had been previously tested and described to be applicable by a single clinician in a routine clinical setting. (20) To define possible sarcopenia we used a PMA of under 800 mm^2 for males and under 550 mm^2 for females as a cut-off based on an earlier Finnish study (21).

All the data except for aetiology and PMA from CT/MRI scans were gathered prospectively.

Data are presented as medians (with min-max) if variables were not normally distributed or as averages (standard deviation) if variables were normally distributed. The statistical analysis was calculated using Pearson's Chi-Square or in continuous values, the Mann–Whitney U test (not normal distribution) or Student's t-test (normal distribution) was used. For correlation calculation we used the Pearson's Correlation Coefficient test (r). The odds ratio (OR) was calculated using binary logistic regression and are presented with a 95% confidence interval (CI 95%) Statistical analyses were done with IBM SPSS v28 (IBM Corp, Armonk, New York, USA). A p-value of under 0.05 was considered statistically significant.

Results

A total of 33 patients (median age 62 years [range 39-81] years) were included, with a median disease duration of six (range 4-27) years. Aetiology for CP was alcohol related in 49% (n=16) of the cases. Thirty-six percent of patients (n=12) were active smokers and 64% (n=21) had a smoking history with a median of 30 (4-60) pack-years of smoking. Median BMI was 26.9 (18.8-38) kg/m^2, 66% of the patients were overweight and 24% obese. Forty-seven percent of patients with PEI were

overweight and 11% obese, compared to 93% and 43% of those without PEI. Sixty-four percent of patients (n=21) had a daily vitamin D substitute median 20 (10-75) µg and 15% (n=5) had low levels of vitamin D. Fifty-two percent of patients (n=17) had undergone interventions due to CP related complications. Surgery was performed on seven patients: including three pancreatic resections and four due to pseudocystal or pancreatic fistula complications. Pancreatic surgery was performed a median of four years (2-5) before the study. Endoscopic procedures were performed on eleven (33%) patients. Nineteen patients (57%) had PEI (FE-1 levels under 100) and out these seven patients (37%) had no PERT and one (5%) had inadequate PERT consumption. Patient characteristics are presented in Table 1.

Osteoporosis, osteopenia and osteoporotic fractures

None of the CP patients were known to have had osteoporosis, osteopenia or osteoporotic fractures prior to the study. Forty-five percent of males and 58% of females had abnormal bone density. Osteoporosis was diagnosed in 20% (n=7) and osteopenia in 23% (n=8) of patients. Twenty percent of the males (median age 62 [44-69] years) had osteoporosis and 23% of the females (median age 62 [39-79] years) had osteoporosis, while 45% of males and 58% of females had abnormal bone density. Patient characteristics are presented in Table2.

Alcohol consumption after diagnosis of CP was associated with abnormal bone density: 67% in patients with alcohol consumption vs. 29% in patients without alcohol consumption, p=0.035 but there was not statistical difference alcohol consumption and osteoporosis: 33% with alcohol consumption vs. 12% without alcohol consumption, p=0.141. Smoking (p=0.171), older age (p=0.268), female gender (p=0.833), BMI (p=0.620) and low testosterone (p=0.456) were not associated with higher risk of osteoporosis.

Median BMI of the patients with osteoporosis was 28.3 (19.9-29.1) and 27.3 (18.8-38) among non-osteoporotic patients (p=0.62). None of the obese patients (BMI>30) had osteoporosis (p=0.092; not

significant). Low testosterone levels in males were detected in two CP patients but neither had osteoporosis. The female osteoporotic patients were all post-menopausal and one was taking long lasting cortisone medication. None of the patients who had pancreatic surgery had osteoporosis, this did not reach a statistical difference (p=0.122).

The patients with PEI and no PERT had more osteoporosis than did CP patients with PERT and PEI 43% vs 5.6% (OR 2.3 CI 95%: 0.8-6.9; p=0.013).

Psoas muscle area

Psoas muscle area (PMA) was measured in 21 patients. The median PMA for females was 561 (430-956) mm^2 and for males 809 (467-1371) mm^2. Possible sarcopenic PMA levels were registered in 48% (n=10) of the patients. PEI was found in 80% of the sarcopenic group vs. 36% in non-sarcopenic patients (OR 7.0 (95% CI:0.97-50.6); p=0.044). The trend between PEI and low PMA is present in Figure 2A. There was no difference in patients with PEI and no PERT in the possibly sarcopenic and non-sarcopenic group (p=0.157). Longer disease duration was correlated with lower PMA (r -0.434, p=0.049), age did not correlate with lower PMA (r 0.263, p=0.249). Patients with possible sarcopenia had median nine (4-27) years' history of CP, compared to five (4-8) of those without sarcopenia, p=0.002. The association between disease duration and PMA is illustrated in Figure 2B.

PEI and vitamin deficiency

PEI was found in 57% (n=19) of the patients and was associated with alcohol consumption after diagnosis of CP 80% vs. 35%, p=0.011. Smoking was not associated with PEI (p=0.947). Of the PEI group 21% (n=4) had low levels of vitamins D and E.

In the non-PEI group all patients had normal levels of vitamin E and one1 had a low level of vitamin D. All low vitamin E levels were found in the PEI group (p=0.067). Three (75%) were found in CP

patients with inadequate PERT. CP patients with PERT had less vitamin E deficiency than CP patients without PERT (OR 14.4 (95% CI:1.2-169); p=0.01).

They also had lower levels of vitamins D and A, but the difference was not statistically significant. No low levels of vitamin A were measured. Of all participants15% (n=5) had low vitamin D levels. Most of patients with PEI 74% had supplementary vitamin-D (74%) and half of the non-PEI group had supplementary vitamin-D (p=0.162).

Discussion

CP patients carry a high risk for osteoporosis and for osteoporotic fractures (22-23). It was unknown how this is addressed in daily clinical practice. In our study, nearly half of the CP patients had abnormal bone density while none of them had been diagnosed with osteoporosis or osteopenia. CP patients with PEI and no enzyme substitute had more osteoporosis than CP patients with PEI and enzyme substitute. CP patients with PEI and long disease duration were found to have an increased risk for sarcopenia.

The United European Gastroenterology 2018 guidelines have previously recommended DXA and serum vitamin D (25-hydroxyvitamin D3) measurement in CP patients. (24) Our findings support these recommendations. As we demonstrated, osteoporosis is common among CP patients, and none of our study patients had known osteoporosis when they were enrolled for this trial. The Finnish guidelines for screening for osteoporosis focus on high fracture risk patients or patients who have already sustained fractures. (25). Osteoporosis has multiple risk factors, the most common being age, menopause, glucocorticosteroids, low peak bone mass and immobilisation with multiple risk factors related to CP such as diabetes, high alcohol intake, smoking and malabsorption. (26-28) The authors recommend screening high-risk patients, also those with CP.

More detailed follow-up might serve to reduce the risk not only of osteoporosis and osteoporotic fractures, but also of vitamin deficiency and sarcopenia. CP patients have a higher mortality rate than

to controls with known risk factors such as diabetes and smoking, but it should also be taken into account that PEI may be an independent risk factor for low survival and should be treated appropriately. (29-31)

The cause of sarcopenia and osteoporosis in CP is multifactorial and includes nutritional components: maldigestion of fats and fatty vitamins, chronic inflammation, alcohol and smoking (32). In our study half of the patients had low PMA indication of possible sarcopenia and this was associated with PEI and longer disease duration. Sarcopenia has been associated with lower survival and increased hospitalisation in CP patients (33). Even though no evidence has so far been presented that sarcopenia is related to a higher complication rate in CP patients, a connection to failure to overcome complications related to surgery has been reported (34-36). Sarcopenia in CP could be due to malnutrition and assessment and prevention of this needs to a focal point in treatment of CP (37).

Since low physical activity has been linked to both sarcopenia and osteoporosis there is no studies investigating the effect of physical activity on CP patients (38).

None of the patients who underwent pancreatic surgery for CP had osteoporosis. There is no literature that we know of looking into bone density in CP patients after surgery. This needs further exploration.

We found it concerning that nearly 40% of the patients with PEI had no pancreatic enzyme substitute. This could be due to lack of follow-up and poor compliance in CP patients (39). More patient education on PEI should be provided. Exocrine insufficiency can be diagnosed via FE-1, faecal fat collection or C13 mixed triglyceride and is treated with a pancreatic enzyme replacement therapy PERT taken at every meal. (4) An adequate number of PERT is needed to treat PEI. The United European Gastroenterology guidelines for the treatment of CP recommend 40-50 000 IU lipase for meals and 20-25 000 IU for smaller meals (40). In our study 12% of CP patients had low levels of Vitamin E, a risk factor being PEI with inadequate PERT consumption. Vitamin E is a fat-soluble antioxidant, low levels being extremely rare in normal population (41-42). Vitamin E deficiency may

cause neurological disorders (43). An earlier study found that low levels of Vitamin E were common (10%) in CP patients with PEI, especially if no PERT was used (42). Vitamin E levels should be measured and supplementary vitamin-E given with a low threshold, especially to patients with PEI. We did not measure any low levels of Vitamin A. Low levels of vitamin A have only been reported in CP patients with PEI and without PERT. (44)

In Finland the prevalence of vitamin D deficiency in adults is 21-26%, which is actually higher than in our selected population (15%). Moreover, in our study CP patients had a higher rate of vitamin D supplementation than the average Finnish population 74% vs. 57%. (45). This could be due to selection bias in our study population.

We found that patients who continued to consume alcohol after their diagnosis of CP had more abnormal bone density and PERT. Patient education concerning CP is insufficient and better tools for reaching these patients are needed (46). In a 2021 retrospective study Srivoleti et al. found that less than half of the patients followed recommendations regarding lifestyle changes for CP and that patients treated by pancreatologists were more likely to abstain from alcohol. (47)

In a recent international survey 75% of pancreatologists prescribed PERT in clinically evident steatorrhea while only 20% of clinicians routinely checked for PEI and conducted nutritional tests during follow-ups (48). This may suggest a need for guidelines and a change of mindset in the treatment of CP. In our study two out of five of CP patients with PEI did not receive sufficient treatment. In our study patients without proper PERT, with osteoporosis or vitamin deficiency were contacted and advised to contact their physician.

It must be stated that FE-1 is considered to be unspecific for excluding mild or moderate PEI and consensus is lacking regarding the ideal cut-off value (40). The most used cut-off value is 200 faecal μg per one gram of faeces. In this study we used a cut-off value of 100 μg FE-1 due to it being more specific and having the same sensitivity as the previously used 200 μg (15).

A strength of the study is its prospectively gathered data on bone density, medication and laboratory test in this somewhat hard-to-reach patient group. Among the limitations is that we were unable to measure vitamin K levels, which might have had an impact on bone metabolism. Sarcopenia is defined as loss of muscle mass and function. In this study we were able to assess only muscle mass. Furthermore, we only measured muscle mass of psoas muscle. Whether this represents overall sarcopenia remains beyond the scope of this study. We used imaging CT/MRI imaging to asses possible sarcopenia which still remains the primary modality for assessment of sarcopenia due to availability and ease of use (49) and it is still considered a practical method of assessing sarcopenia (50).

Next, we were able to assess psoas muscle in about two thirds of patients, which may have caused some patient selection bias. A low number of patients recruited in our study illustrates problems in performing studies in selected group of patients. While this study was conducted over several years in high volume centre, only a small number of patients took part in long-term follow-up. Chronic pancreatitis is relatively rare condition and attending patients have high drop-out rate. In our earlier study the drop-out rate was 60%, while it was 57% in this study. High drop-out rate may cause some patient selection bias, as those motivated for trials may be also more motivated to change their life habits, ea. alcohol and tobacco use. Nevertheless, we emphasize that all those with chronic pancreatitis may require more holistic approach in future. Similar problems with low patient count are likely to arise in multicentre trials. Among the strengths was that we were able to conduct this population-based trial including all those with chronic pancreatitis living within a hospital district of a high-volume centre with comprehensive data available on all attending patients.

In conclusion, osteoporosis, osteopenia, sarcopenia and vitamin deficiencies are common in CP patients. In our study, all the osteoporosis was previously undiagnosed. More care should be taken in the basic treatment of PEI in this patient group. We concede that there is a need for improvement in the treatment of pancreatic exocrine insufficiency in CP patients. This study opens opportunities for

interventional prospective studies with interventions for clinicians to gain a better understanding of how to treat CP and PEI and to prevent or delay the progression of osteoporosis and sarcopenia in CP patients.

Declaration

Ethics Approval and Consent to Participate

The study was approved by the ethics committee of Tampere University Hospital, Finland (Ethical committee code R18107). All subjects recruited for the study provided written informed consent. The study follows the ethical principles of the Declaration of Helsinki (51).

Consent for Publication

Not applicable

Availability of data and materials

The data regarding this study are available on request from the corresponding author. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Competing interests

The authors declare no conflicts of interest.

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Author's Contribution

All authors contributed to the writing of the manuscript. Mikael Parhiala contributed to the data collection and implementation of the research and to the analysis of the results. Mika Ukkonen contributed to the design and analysis of the results. Juhani Sand contributed to the design of the

manuscript and helped supervise the project. Johanna Laukkarinen conceived the original idea and supervised the project.

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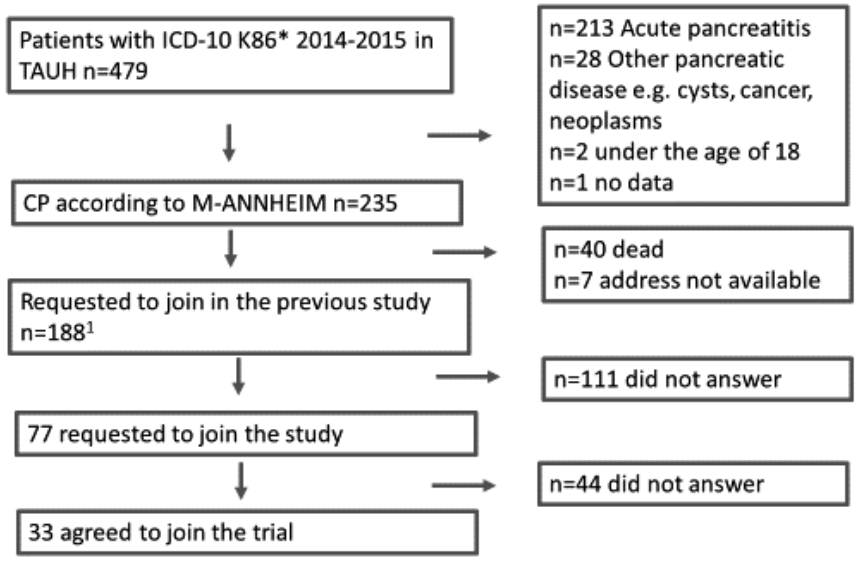
Figure 1. Flowchart of patient selection in the study. We selected all CP patients from 2014 and 2015 consecutively. All patients in the study had definitive diagnostic characteristics according to M-ANHHEIM



1)Parhiala et al. 2020 Pancreatology

Table 1. Demographic of chronic pancreatitis patients in the study

CP patient	Male (n=20)	Female (n=13)	Total (n=33)
Age median years (range)	61 (44-81) years	62 (39-79) years	62 (39-81) years
Time after diagnosis (range)	6.5 (4-16) years	6 (4-27) years	6 (4-27) years
Alcohol aetiology	55% (11)	38% (5)	49% (16)
Smoking	75% (15)	46% (6)	64% (21)
Elastase under 200	75% (15)	77% (10)	75% (25)
Elastase under 100	55% (11)	62% (8)	57% (19)
PERT	65% (13)	77% (10)	70% (23)
Inadequate PERT and PEI	55% (6)	25% (2)	42% (8)
Diabetes	95% (19)	69% (9)	75% (25)
BMI	27 (19-34)	28 (21-38)	28 (19-38)
Menopause	-	77% (10)	77% (females only)
Low Testosterone	10% (2)	-	10% (males only)
Osteoporosis	20% (4)	23% (3)	21% (7)
Osteopenia	25% (5)	31% (4)	24% (8)
Normal Bone Density	55% (11)	46% (6)	55% (18)
Possible sarcopenia	50% (7/14)	43% (3/7)	48% (10/21)
Endoscopic procedure	30% (6)	38% (5)	33% (11)
Pancreatic surgery	25% (5)	2 (15%)	21% (7)

BMI = Body Mass Index

PES = Pancreatic enzyme supplements

PEI = Pancreatic exocrine insufficiency

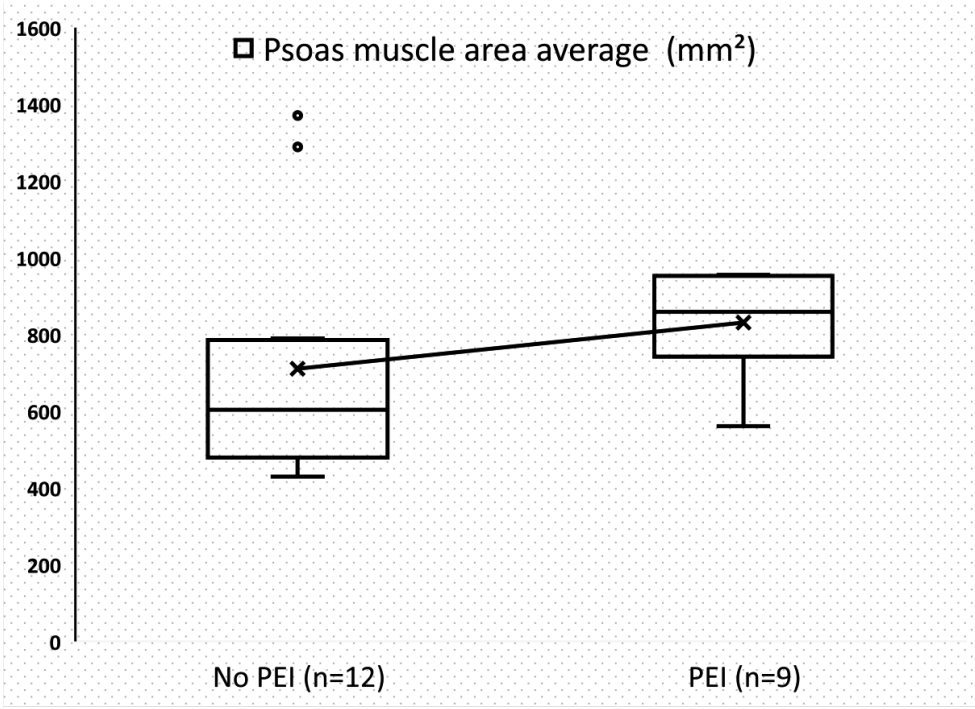
PERT= Pancreatic Enzyme Replacement Therapy

Table 2. Demographic chronic pancreatitis patients with osteoporosis. None of the CP patients had previously known osteoporosis, osteopenia or osteoporotic fractures before the study

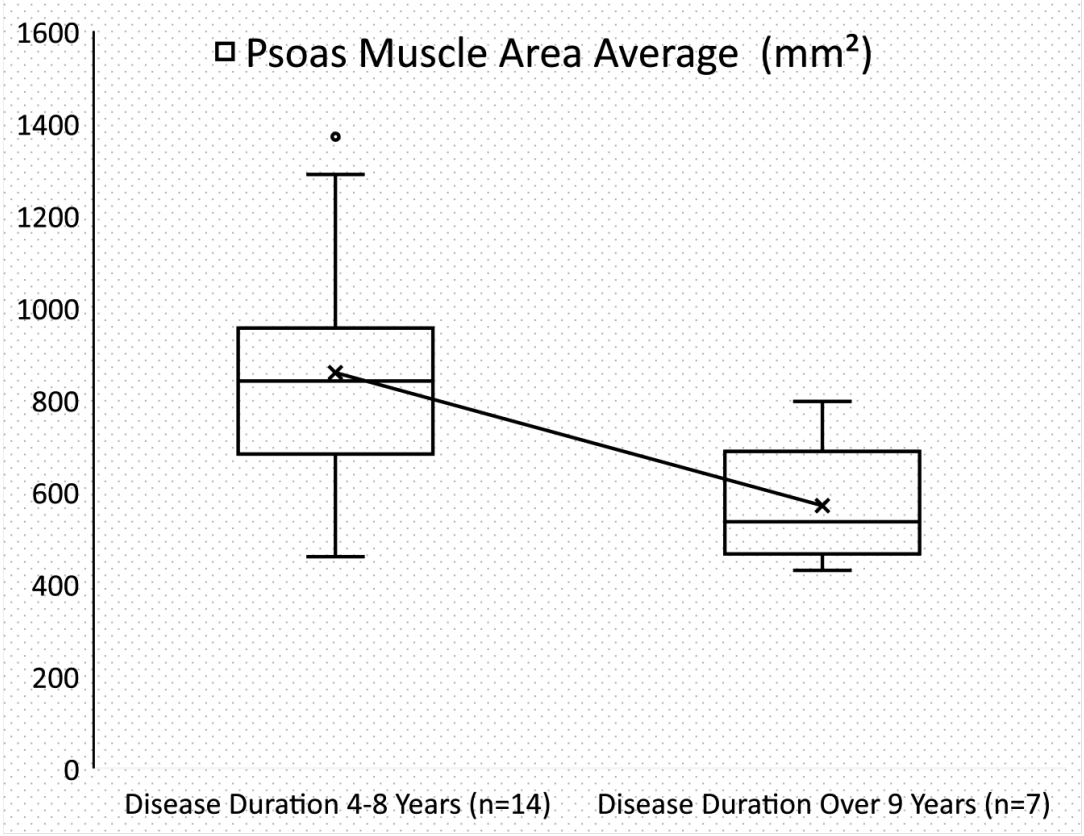
	Osteoporotic bone density <-2.5 Z-score (n=7)	*Bone density >-2.5 Z-score* (n=26)	*p value*
Age median (range)	**64 (44-79)**	**60 (39-81)**	*0.27*
Female/male ratio	**43%/57%**	**38%/62%**	*0.83*
Time after diagnosis (years)	**7 (5-15)**	**6 (4-27)**	*0.32*
Elastase-1 (µg/g) med (range)	**20 (15-387)**	**53 (15-500)**	*0.81*
Elastase under 200	**57% (4)**	**81% (25)**	*0.20*
Elastase under 100	**57% (4)**	**77% (20)**	*0.98*
PERT	**43% (3)**	**77% (20)**	*0.08*
Low elastase and no PES	**43% (3)**	**15% (4)**	*0.28*
Possible sarcopenia	**67% (2/3)**	**44% (8/18)**	*0.48*
Alcohol aetiology	**71% (5)**	**42% (11)**	*0.17*
Alcohol abstinence	**29% (2)**	**48% (12)**	*0.17*
Current smoking	**57% (4)**	**27% (7)**	*0.20*
Smoking	**86% (6)**	**58% (15)**	*0.32*
Idiopathic pancreatitis	**0%**	**19% (5)**	*0.21*
BMI	**28.3 (19.9-29.1)**	**27.3 (18.8-38)**	*0.62*
Overweight	**57% (4)**	**69% (18)**	0.55
Obese	**0%**	**31% (8)**	0.09
Haemoglobin (g/l)	**145 (118-167)**	**138 (88-162)**	*0.11*
Creatinine (µmol/l)	**75 (66-91)**	**75 (58-131)**	*0.61*
Glomerular filtration rate (GFR)	**89 (53-101)**	**89 (50-116)**	*0.11*
Albumin (36-45) (g/l)	**37 (32-42)**	**37 (24-41)**	*0.18*
Fasting blood sugar (4-6.1) (mmol/mol)	**6.4 (5.5.-13.9)**	**6.9 (5.8-16)**	*0.28*
HbA1c (20-42) (mmol/mol)	**41 (36-69)**	**46 (35-74)**	*0.13*
Triglycerides (<1,7) (mmol/l)	**0.89 (0.80-2.04)**	**1.33 (0.59-14.23)**	*0.29*
Vitamin D 1.25 levels (50-375) (nmol/l)	**54 (33-70)**	**65 (33-108)**	*0.14*
Calcium (2,15-2,51) (mmol/l)	**2.31 (2.20-2.37)**	**2.34 (2.27-2.62)**	*0.12*
Magnesium (0,71-0,94) (mmol/l)	**0.84 (0.81-0.95)**	**0.80 (0.57-0.97)**	*0.18*
Vitamin A levels (0,7-4,2) (µmol/l)	**1.6 (0.8-3.2)**	**1.9 (1-3.3)**	*0.29*
Vitamin E-levels (12-37) (µmol/l)	**19 (8-40)**	**24.5 (10-70)**	*0.14*
Low testosterone in males	**0%**	**12.% (2)**	
Menopause in females	**100%**	**0.0%**	
Vitamin D supplementation	**71% (5)**	**65% (16)**	*0.63*
Cortisone medication	**14% (1)**	**0%**	
Endoscopic procedures	**2 (29%)**	**9 (35%)**	0.76
Surgery	**0 (0%)**	**7 (27%)**	0.12

Figure 2. Boxplot of psoas muscle area (PMA). **A.** Demonstrating a trend towards lower PMA with pancreatic exocrine insufficiency (PEI). **B.** Demonstrates a lower PMA with disease duration of over 9 years despite there being no age difference

A.



B.


Psoas Muscle Area Average (mm²)
1600
1400
1200
1000
800
600
400
200
0
Disease Duration 4-8 Years (n=14)
Disease Duration Over 9 Years (n=7)

PUBLICATION

II

Surgery for chronic pancreatitis in Finland is rare but seems to produce good long-term results

Mikael Parhiala, Juhani Sand & Johanna Laukkarinen.

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ORIGINAL ARTICLE

Observational Study

Surgery for chronic pancreatitis in Finland is rare but seems to produce good long-term results

Mikael Parhiala, Juhani Sand, Johanna Laukkarinen

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Author contributions: Sand J and Laukkarinen J designed the study; Parhiala M contributed to the permits process, data collection and analysis; all authors contributed to the writing of the manuscript.

Institutional review board statement: The study was approved by the Ethics Committee of Tampere University Hospital, Finland (ETL code R16153). The data from the HILMO register was provided by the Finnish National Institute for Health and Welfare with a license/permission (THL/1854/5.05.00/2012).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work.

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Abstract

BACKGROUND

Abdominal pain in chronic pancreatitis (CP) may require invasive interventions. Surgical procedures are rare, and little is known about the long-term results.

AIM

To study the nationwide frequency of pancreatic surgery for CP in Finland, and postoperative symptoms and quality of life (QoL).

METHODS

All patients in Finland with a diagnosis of CP who had undergone pancreatic surgery during 2000-2008 were selected from a national register. Only patients with CP as an indication for pancreatic surgery were included. Medical records were studied and questionnaires QLQ-C30, PAN26 and AUDIT, and symptom questionnaires were sent out.

RESULTS

During the 9-year period, pancreatic surgery for CP was performed on 30 patients [77% men, median age 45 (21-62) years]. Eighty-three percent underwent endoscopic procedures before surgery. Surgery was performed a median 2 (0-10) years after the original CP diagnosis, and 17% developed postoperative complications. Primary pain relief after surgery was reported in 70% of cases. Need for strong pain medication was lower after surgery. Eight of 21 (38%) returned the questionnaires and 88% reported that surgery had reduced their pain and 63% were almost or entirely pain-free at a median 14 (10-18) years after surgery. QoL results did not differ from those in our control Finnish CP group.

CONCLUSION

Data sharing statement: We are not give permission to share data because the data is being used to future studies and patient data is not allowed to be shared because of the EU Regulation on the protection of personal data.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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Grade D (Fair): D
Grade E (Poor): E

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Surgery for CP is rare in Finland and most patients had prior endoscopic procedures. Patients who returned the questionnaires reported less pain and good QoL during the 14-year follow-up.

Key Words: Surgery; Pain; Chronic pancreatitis; Quality of life; Complication

Core Tip: Our study provides valuable insight on the current state of chronic pancreatitis (CP) surgery for chronic pain in Finland. We included all the CP patients who underwent surgery for CP symptoms during 2000-2008 in Finland. We found that surgery is rare. We estimate that 0.6%-0.8% of CP patients undergo surgery for CP pain, which produces good long-term effects. Opiate usage was reduced after surgery. Most of the patients had undergone endoscopic procedures before surgery. Complications after CP surgery were rare.

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INTRODUCTION

Chronic pancreatitis (CP) leads to permanent morphological changes in the pancreatic tissue such as ductal lesions and calcifications. Persistent inflammation may cause abdominal pain and also lead to pancreatic insufficiency, seen as secondary diabetes and malnutrition as well as various complications[1-4].

There are several mechanisms behind CP pain. High pressure in the pancreatic ducts due to pseudocysts or strictures may cause pain. High alcohol consumption and smoking may lead to oxidative stress, increasing pain. Exocrine insufficiency may result in low vitamin and antioxidant levels, causing pain. Even pancreatic ischemia may be behind the development and pain of CP[5-9].

Conservative pain treatment is often not enough and invasive treatments such as endoscopic stenting and surgery are needed. Endoscopic treatments, such as pancreatic stenting and celiac plexus interventions, are less invasive than surgery, but the long-term results may be of limited benefit[10-13].

Surgery for CP is planned individually depending on the pancreatic findings. Surgical methods can be classified as pancreatic drainage, pancreatic resection or a combination of these. The earliest surgery for CP was pancreaticoduodenectomy (PD) [14-17]. Duodenum-preserving surgery for CP includes the Frey, Puestow, Berger and Berne modifications, where pancreatic tissue is resected and/or drained and a pancreatojejunostomy is performed using a Roux-Y jejunal loop[18-23].

Surgery for CP is rare and no universal recommendations exist. Some evidence suggests that earlier surgery for CP may improve results. To the best of our knowledge, there are no nationwide data in Finland on the frequency of the various surgical procedures, or on the effect on pain and quality of life (QoL) during long-term follow-up after surgery.

The aim of this study was to investigate the variety of surgical procedures used and their impact during a long-term follow-up on symptoms and QoL in patients operated on for CP nationwide in Finland in 2000-2008.

MATERIALS AND METHODS

Study design and patients

All the pancreatic resections [Nordic Classification of Surgical Procedures codes JLC* (resection of the pancreas) or JLW96 (other operations on pancreas)] performed in Finland during 2000-2008 for a diagnosis of CP (ICD-10 code: K86.01, K86.1, K86.08,

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k86.8 and K86.9) were selected from the Finnish National Institute for Health and Welfare HILMO register. There were 97 patients. After reviewing their medical records, only 30 patients with CP as an indication for pancreatic surgery were included in the final database (Figure 1).

From the patient archives, information was gathered about medical history, time of CP diagnosis, etiology of CP, previous CP treatments, type of current surgical therapy, postoperative complications, possible reoperations, and exocrine and endocrine pancreatic insufficiency. The date of death was recorded on September 22, 2017.

QLQ-C30, PAN-26[24] and AUDIT questionnaires and a nonstandardized questionnaire about pain before and after surgery were sent to the patients.

A previously reported Finnish general CP cohort from 2014-2015 was used as a control for the AUDIT, QLQ-C30 and PAN26 questionnaires[25]. In the control cohort, the median age was 58 (26-95) years, 67% were male and median time after diagnosis was 4 (1-42) years. Around 68% and 58% of patients had alcohol and smoking, respectively, as a risk factor for CP. Calcifications were found in 66% of the patients and ductal lesions were present in half of the patients. Endoscopic procedures were performed on 27% of patients and 9% underwent surgery.

Ethical aspects

The study was approved by the Ethics Committee of Tampere University Hospital, Finland (ETL code R16153). The data from the HILMO register was provided by the Finnish National Institute for Health and Welfare with a license/permission (THL/1854/5.05.00/2012)

Statistical analysis

Data are presented as median (range). The statistical analyses were performed using Pearson's χ^2 or Fisher's exact test. For analysis of the QLQ-C30 and PAN26 questionnaires, the Mann-Whitney *U* test was used. The EORTEC scoring manual was used for the QLQ-C30 and PAN26 questionnaires, and the responses were scored as 0-100. A higher score on QoL/functioning indicated better QoL and a lower score on symptoms (*e.g.*, pain or insomnia) represented better QoL. $P < 0.05$ was considered statistically significant.

RESULTS

Thirty patients underwent pancreatic surgery for CP in Finland during the period 2000-2008 and formed the final study cohort.

Surgery was performed in 13 different hospitals; median two (range 1-7) per hospital. Of the patients 77% were men and the median age was 45 (21-62) years. Surgery was performed a median 2 (0-10) years after diagnosis of CP. During the 16 (10-26) years of follow-up, eight patients died, a median 4.5 (0-16) years after surgery. The etiology of CP was alcohol in 60%, while 47% had idiopathic disease. Eighty-seven percent had recurrent episodes of acute pancreatitis (AP).

Half of the patients smoked. All of the smoking patients were on opioids before surgery, compared to 42% in the non-smoking group ($P = 0.0004$).

Out of the 30 operations performed in the course of 9 years, one was a drainage procedure (Puestow), nine combined resection and drainage, and there were 20 pancreatic resections (16 distal and 4 pylorus-preserving PD/PDs). Fifteen included splenectomies (Figure 2). Out of the combined pancreatic resection and drainages, four were Frey´s procedure, two were Beger´s procedure and three were Puestow´s drainage combined with caudal resection (Figure 3).

Eighty-three percent ($n = 25$) of the patients had no postoperative complications, 17% ($n = 5$) developed complications: two had Clavien-Dindo (CD) grade 1 complications; two had CD grade 2 complications and one had CD grade 3b complications. One patient died within 3 wk of surgery; this patient had undergone four prior laparotomies and had intraoperative hemorrhage during surgery for CP.

Seventy percent of the patients had reported primary pain relief after the surgery and 64% of those who had undergone previous endoscopic procedures had experienced primary pain relief and all those with no previous endoscopic procedures had experienced primary pain relief, but the nonendoscopic group was so small that the difference was not significant ($P = 0.10$). No correlation was seen in time after diagnosis and primary pain relief ($P = 0.43$) (Figure 2).

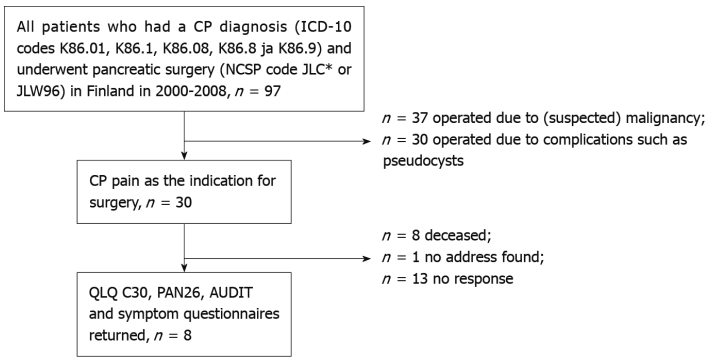


Figure 1 Flowchart of patients. The study included all patients who underwent pancreatic surgery for chronic pancreatitis in the whole of Finland in 2000-2008. CP: Chronic pancreatitis.

A

Total	*n* = 30
Male	77%
Female	23%
Time from diagnosis to surgery median (range)	2 (0-10) yr
Follow-up time median (range)	14 (0-18) yr
Age when surgery median (range)	45 (21-62) yr
Etiology	
Alcohol	60%
Nicotine	50%
Unknown	33%
Bile duct	17%
Hypertriglyceridemia	3%
Calcifications	70%
Ductal lesion	87%
Pseudocysts	57%
Recurrent AP	87%
PEI (pre-op *vs* post-op)	34% *vs* 67%
Diabetes (pre-op *vs* post-op)	32% *vs* 56%
Opiate use (pre-op *vs* post-op)	73% *vs* 37%
Primary benefit from surgery	70%
Death	27%
Years after surgery	5.5 (0-16)
Age of death	51 (41-63)

B

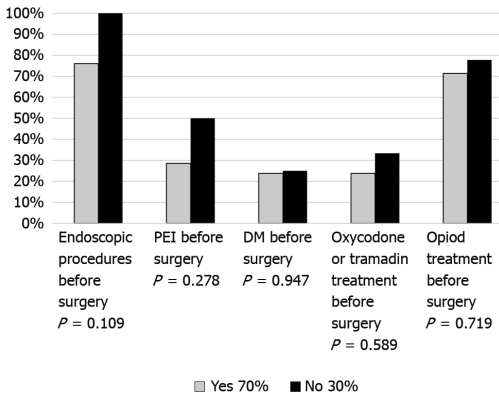
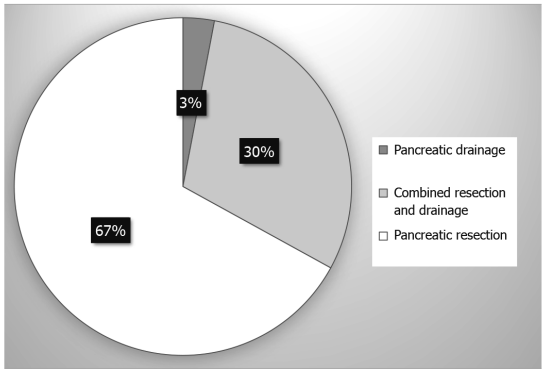


Figure 2 Demographics and outcome of chronic pancreatitis surgery. A: Demographics of the surgical chronic pancreatitis patients; B: Surgical chronic pancreatitis patients grouped based on pain relief approximately one year after surgery. AP: Acute pancreatitis; PEI: Pancreatic exocrine insufficiency; DM: Diabetes mellitus.

Pancreatic exocrine insufficiency (PEI) was present in 34% of the patients preoperatively and in 67% postoperatively. Diabetes was seen in 32% of the patients preoperatively and in 56% postoperatively. When comparing CP patients who had surgery (n = 25) to the Finnish general CP cohort who did not have pancreatic surgery (n = 195) and had a median time after diagnosis of 5-43 years, the frequency of PEI was similar (surgery group 67% *vs* nonsurgical group 63%, P = 0.679). Also, the frequency of diabetes was the same in CP patients not undergoing pancreatic surgery (61%) as in patients undergoing surgery (56%; P = 0.586). Seventy-three percent of the patients were on opioids before surgery and 37% after surgery (P = 0.004). Opioid use for the control group was not recorded (Figure 4).

Endoscopic retrograde cholangiopancreatography was performed on 83% of the patients prior to surgery. Twenty percent had already undergone prior pancreatic surgery for pancreatic pseudocyst complications. When comparing these parameters to the Finnish general CP cohort, significantly more endoscopic procedures (83% *vs* 27%, P < 0.0001) and recurrent AP (87% *vs* 67%, P = 0.007) were seen in these surgically treated CP patients than in the overall CP patients in the control group (Figure 4).

A



B

Pancreatic surgery in Finland for CP in 2000-2008	*n*
Distal resection	16
Pancreaticoduodenectomy	4
Puestow combined with caudal resection	3
Frey (duodenum perserving pancreatic head resection)	4
Beger (duodenum-preserving pancreatic head resection)	2
Puestow (lateral pancreaticojejunostomy)	1

Figure 3 Distribution of chronic pancreatitis surgery in Finland. A: Type of surgery for chronic pancreatitis. Most operations involved a pancreatic resection (pancreaticoduodenectomy or a distal resection); B: Type of surgical operations in detail. CP: Chronic pancreatitis.

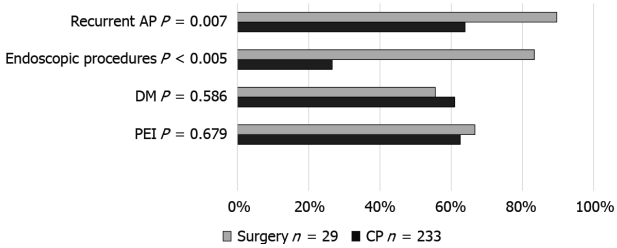


Figure 4 Surgical chronic pancreatitis patients compared to control population, which included nonsurgical chronic pancreatitis patients from the Finnish chronic pancreatitis cohort from 2014 to 2015 (*n* = 233). There was more recurrent acute pancreatitis and prior endoscopic procedures in the chronic pancreatitis patients who underwent surgery. Pancreatic insufficiency and diabetes were similar between the groups. CP: Chronic pancreatitis; AP: Acute pancreatitis; PEI: Pancreatic exocrine insufficiency; DM: Diabetes mellitus.

Out of the 21 patients asked to complete the questionnaires, eight (38%) returned the QoL questionnaires (QLQ-C30 and Pan-26) and the AUDIT questionnaire. There was no significant difference between the responders and nonresponders in gender, pancreatic calcifications, PEI, recurrent AP or alcohol-related etiology. All the patients who responded had a history of smoking and 63% continued smoking compared to 35% among the nonrespondent patients ($P = 0.003$).

Of the CP patients who responded, 88% reported that the surgery helped their pain and 63% were almost or entirely pain-free 14 (10-18) years after surgery. The AUDIT questionnaire median was 4 (0-28) points, and in the control CP population, the AUDIT score median was 3 (0-39) points ($P = 0.764$).

When comparing the QLQ-C30 and PAN26 responses to the Finnish general CP cohort (Figure 5) the nonsurgery group had more pain, pancreatic pain and hepatic symptoms but this was not significant ($P = 0.869$, $P = 0.970$ and $P = 0.379$). Since all the responding CP patients undergoing surgery were smokers, we compared them to those in the Finnish general CP cohort who had been smoking.

DISCUSSION

Surgery for CP is rare and no nationwide data with long-term follow-up after surgery are available. Our aim was to find out how common CP surgery is and what the long-term effects on CP patients are. We found that surgery for CP is rare but seems to give long-term pain relief in CP and reduces opiate use.

Approximately three operations for CP pain were performed per year in the whole of Finland. We estimate that 0.6%-0.8% of CP patients undergo surgery for CP pain.

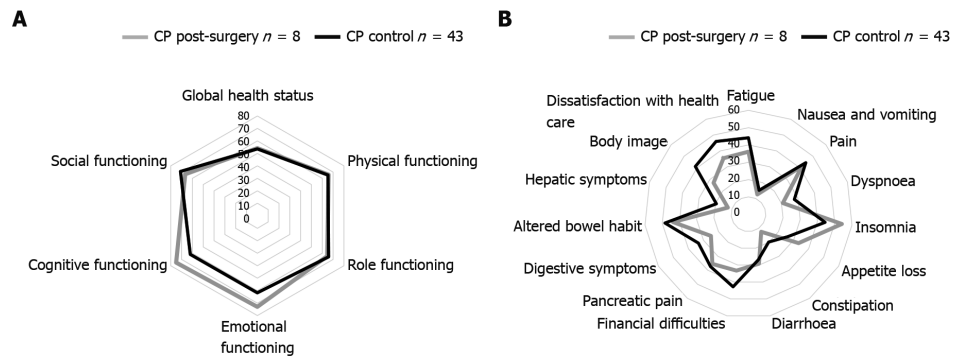


Figure 5 Quality of life in the chronic pancreatitis patients who underwent surgery, compared to control chronic pancreatitis patients. All patients who answered the quality of life (QoL) questionnaire in the surgical group were smokers. The control group consisted of Finnish chronic pancreatitis patients who did not have surgery and smoking contributing to their disease. A and B: QoL functioning (A) and symptom scores (B) had a tendency to be better in most parameters in the surgical group, but without significance. A higher score was better in the functioning scores (A), and a lower score was better in the symptoms scores (B). CP: Chronic pancreatitis.

Most of the surgical interventions in CP are for treatment of complications (such as pseudocyst infections, hemorrhage and bowel obstruction), or due to suspicion of malignancy. Overall, pancreatic surgery for CP is rare in Northern Europe: < 10%, compared to studies from North America and Hungary, reporting 20% pancreatic surgery in the CP population[26-28]. Most patients had already undergone endoscopic procedures; some of them multiple times. In our study, patients with no previous endoscopic procedures had better pain relief (64% *vs* 100%) even though the difference was not significant due to the number patients with no previous endoscopies. It seems that in Finland surgical procedures are only considered after endoscopic means have been already tried. Thirty-four percent already had preoperative PEI, indicating advanced CP. Retrospective studies have shown that pancreatic surgery for pancreatic duct decompression is more cost-effective than endoscopy[29,30].

During the time of the study, CP pancreatic surgery was spread over many hospitals in Finland, 13 in total — compared to five centers at present. Most of the patients underwent endoscopic procedures before the operation. The procedures performed were also heterogeneous. In our study there was no correlation in the timing of the surgery and primary pain relief but most of the operations were performed within 3 years of diagnosis (74%). A few retrospective studies have reported that earlier CP surgery (< 3 years after diagnosis) improves the outcome and is also safe. In a prospective, multicenter randomized controlled trial (ESCAPE trial), surgery was reported to produce better outcomes when performed early enough before endoscopic procedures. In CP, the pancreas tends to be harder due to fibrosis, which can lead to fewer postoperative pancreatic fistulas than in a soft normal pancreas. Compared to reports in Europe and North America, the low percentage of CP surgery in Finland suggests that CP patients are operated on too seldom in Finland, which could be due to advances in endoscopic procedures or to a high threshold for performing pancreatic surgery on a benign disease[31-35].

Most of the patients in our study used opioids before surgery, and surgery reduced the need for opioids. Perhaps when opioids are needed surgery should be considered. Thirty-six percent of the patients had opioids after surgery and this could be due to opioid tolerance and addiction. Preoperative opioid use, persistent pain (3 mo) and previous surgery have been shown to be risk factors for postoperative pain in abdominal surgery. Chronic use of opioids in abdominal pain such as in CP can cause hyperalgesia in which abdominal pain paradoxically may become more severe[36-39].

Half of the CP patients undergoing surgery were smokers and they took significantly more opioids before surgery. Smoking has been reported to impair the outcome of pancreatic surgery and QoL[40]. Cessation of smoking and opioid use should be considered before pancreatic surgery for CP.

There was no significant difference in PEI, diabetes or QLQ responses between CP patients undergoing surgery and a Finnish control CP group, even though it seems that the CP patients who underwent pancreatic surgery were a selected patient group with more severe pancreatitis, since they had significantly more endoscopic procedures (83% *vs* 27%, $P < 0.0001$) and recurrent AP (87% *vs* 67%, $P = 0.023$) than the

control CP group. Nonoperated and operated CP patients had approximately the same amount of PEI. Surprisingly, diabetes is more common in CP patients without pancreatic surgery. This could be due the decompressing surgery influencing the progression of pancreatitis and slowing pancreatic insufficiency[41,42].

The rate of idiopathic pancreatitis is high in patients who have surgery. In some cases, it could be due to the difficulty in differencing benign pancreatic masses and malignant tumors, which could affect the decision for surgery[43-45].

The strength of our study is that it involved all the CP patients in Finland. We made a broad selection and only included patients with CP diagnosis and surgery performed for CP pain. To the best of our knowledge, no national study on CP surgery had been published earlier. In spite of the small population, our study provides a valuable description of CP patients who undergo surgery for CP.

The limitations of this study were the small patient number and low response rate of 38%, which is approximately the same as in an earlier study[25]. We gathered the medical histories retrospectively, and one was lost because the patient was deceased, and the record had been deleted. Smoking and alcohol consumption were not always recorded accurately, so presumably these may have been more common.

CONCLUSION

Surgery for CP is rare in Finland, but seems to produce good long-term results. Opiate usage was reduced after surgery. Most of the patients had undergone endoscopic procedures before surgery. Complications after CP surgery were rare. More studies are needed on the timing of CP surgery to ensure maximum benefit for patients.

ARTICLE HIGHLIGHTS

Research background

Chronic pancreatitis (CP) may need invasive surgical interventions. There is no current knowledge of long-term outcomes and prevalence of surgery for CP.

Research motivation

We wanted to investigate the current state of pancreatic surgery in Finland for CP.

Research objectives

Our objective was to find long-term outcomes of patients who have pancreatic surgery for CP pain in Finland.

Research methods

We gathered all CP patients who had pancreatic surgery in Finland in 2000-2008 *via* the Finnish National Institute for Health and Welfare registry. We gathered information about the time of CP diagnosis, etiology of CP, previous CP treatments, type of current surgical therapy, postoperative complications, possible reoperations, and exocrine and endocrine pancreatic insufficiency.

Research results

We found that surgery for CP is rare in Finland but most patients (70%) are pain free after surgery. Opiate usage was less after surgery.

Research conclusions

CP surgery is rare and produces good long-term results in CP patients.

Research perspectives

Our study was limited because of the small number of patients but we provide a long 16-year follow-up and our study contains all of CP patients in Finland who had pancreatic surgery.

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III

Surgical Strategies for Chronic Pancreatitis in a 1,327- patient Scandinavian Baltic Pancreatic Club (SBPC) register

Mikael Parhiala, Anne Waage, Povilas Ignatavičius, Søren S Olesen, Jakob L Poulsen, Engjom Trond, Georg Dimcevski, Ingrid Nordaas, Amer Hadi, Evangelos Kalaitzakis, Asbjørn M Drewes, Camilla Nøjgaard & Johanna Laukkarinen

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Surgical strategies for chronic pancreatitis in a 1,327- patient Scandinavian Baltic pancreatic Club (SBPC) register

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ABSTRACT

Background: Chronic pancreatitis (CP) may cause intermittent or continuous pain and complications requiring invasive interventions. No specific recommendations for surgical interventions have been presented. Our aim was to determine the surgical treatment strategies for the treatment of CP in the Scandinavian and Baltic countries.

Methods: This multi-centre cross sectional study included 1327 CP patients from eight centres. The data was gathered from the Scandinavian Baltic Pancreatic Club (SBPC) database. Patients who underwent pancreatic surgery were analysed. The baseline CP population from the eight centres was used as a reference. The information registered included comorbidities, pancreatic function, previous interventions, time and type of surgery and the EORTC-30 quality of life (QOL) questionnaire.

Results: Overall, 95/1327 (7%) patients underwent pancreatic surgery. Fifty-one (54%) of these underwent pancreatic surgery for chronic pain (PSCP) and formed the final study group. Median follow-up time was two (range 0–8) years after surgery and seven (1–46) years after diagnosis. The most common surgical procedures were pancreatic resection combined with drainage (54%) followed by pancreatic resections (32%) and drainage procedures (14%). Postoperatively, 47% of the patients were pain free with or without pain medication while 16% had chronic pain episodes, this did not differ from the base CP population. In QOL questionnaires, PSCP patients reported the same QOL but worse social functioning and more symptoms compared to the CP population.

Conclusions: Pancreatic surgery for CP is rare: surgical procedures were performed on only 7% of the CP patients in the SBPC database. In half of the patients the indication was pain. Most of these patients underwent endoscopic procedures before surgery. Half of the patients reported being pain-free after surgery.

1. Introduction

Chronic pancreatitis (CP) causes sustained inflammatory changes in the pancreatic tissue leading to fibrosis and calcifications, which in turn can lead to pancreatic ductal strictures and

Abbreviations: CP, Chronic Pancreatitis; ERCP, Endoscopic retrograde cholangiopancreatography; PD, Pancreaticoduodenectomy; QoL, Quality of Life; EPI, Exocrine pancreatic insufficiency; PSCP, Pancreatic Surgery for Chronic Pain.

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dilation. Over time the pancreatic tissue loses function, leading to exocrine pancreatic insufficiency (EPI) and endocrine insufficiency. The main risk factors for CP are excessive alcohol consumption and smoking [1–4].

In CP patients, chronic pain is the leading symptom and cause of poor quality of life (QOL). Several theories have been proposed to explain the mechanism underlying pancreatic abdominal pain. High pancreatic ductal pressure may be related to pain although many other factors also come into play. Chronic inflammation can cause neuropathy and lead to irreversible sensitization of the central nervous system, causing patients to suffer continuous pain despite the disappearance of inflammation in the pancreatic tissue. Pancreatic ischaemia and oxidative stress have also been associated with pancreatic pain. Other causes of pain in CP patients can be attributed to complications such as pseudocysts and bile duct obstruction [5–12].

CP patients may need invasive endoscopic or surgical procedures, either for pain or to treat complications. Endoscopic procedures include pancreatic and bile duct stenting and pseudocyst drainage. Surgical interventions are intended to improve pancreatic drainage and to remove fibrotic and calcified tissue. The choice of surgery is based on the symptoms and imaging findings, involving resection, drainage, or a combination of these [13,14]. So far there are no specific recommendations for surgical interventions.

Our objective was to determine the surgical treatment strategies for the treatment of CP in the Scandinavian and Baltic countries.

2. Methods

This was a cross-sectional multicentre study including data from the Scandinavian Baltic Pancreatic Club (SBPC) database [15]. The data was collected from 2016 to the extraction date in 2019 and included data from eight centres across northern Europe. Among the patients included, 1327 met the M-ANNHEIM definitive diagnostic criteria, which include one or more of the following: pancreatic calcifications, moderate or marked ductal pancreatic ductal lesions according to the Cambridge classification, pancreatic exocrine insufficiency (pancreatic steatorrhea markedly reduced by pancreatic enzyme replacement therapy) or a typical histological specimen of the pancreas [16,17]. Patients who underwent pancreatic surgery and the base CP group were analysed (Fig. 1). The surgery group consisted of CP patients who underwent pancreatic surgery for CP pain. CP patients from the same eight centres who did not have any surgery were used as a basegroup. Patients undergoing emergency pancreatic surgery (for example, necrosectomy) or who had a gastroenteroanastomosis or a hepaticojejunostomy without pancreatic intervention were excluded from the final analysis.

The base population (n = 1327) consisted of CP patients without any surgical intervention from the same eight centres included in the SBPC database.

The data were registered by the respective centres and included type and year of surgery, indications and complications. From the SBPC database we gathered data on pancreatic function, endoscopic therapies, QOL, pain and CP aetiology. Exocrine pancreatic insufficiency (EPI) was characterized by the use of faecal elastase-1, faecal fat collection or a C13 mixed triglyceride breath test. EPI was defined according to previously published guidelines [18].

QOL was measured using the QLQ-C30 questionnaire. The EORTC scoring manual was used for the QLQ-C30 questionnaires and responses were scored from 0 to 100. A higher score on QOL/functioning indicates better quality of life as also does lower score on symptoms (e.g., pain or insomnia).

2.1. Ethical aspects

The study was approved by the Ethics Committee of Tampere University Hospital, Finland (ETL code R15187). Also each participating centre obtained a seperate approval from their local institutional review boards.

2.2. Statistical analyses

Data are presented as medians (range) or numbers (%) unless otherwise specified. The statistical analyses were performed using Pearson's Chi-Square or Fisher's exact test. The analysis of the continuous variables was done using Mann Whitney *U* test. The QLQ C30 responses were presented in a radar plot. A boxplot with whiskers was used to show the pain results and disease duration before surgery, the middle line indicating a median value, the box

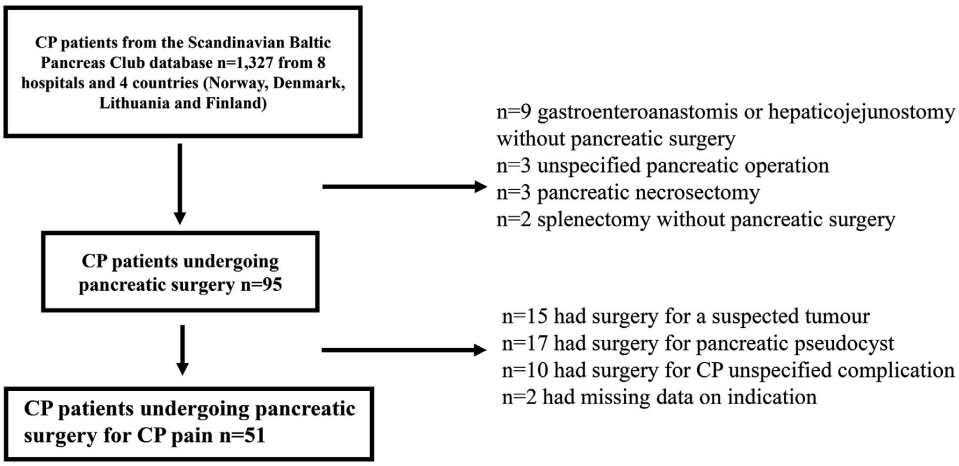


Fig. 1. Flowchart of CP surgery patients. The data were gathered from the Scandinavian Baltic Pancreas Club database and details concerning surgery were collected separately. The final study group was formed of CP patients undergoing surgery for pain n = 51.

indicating the interquartile range and whiskers the range. A p-value of under 0.05 was considered statistically significant. The IBM SPSS® (Armonk, NY) version 26 was used for all statistical analysis.

3. Results

Of the 1331 CP patients in the database, 95 (7%) patients underwent pancreatic surgery. Indication for surgery was pain in 51 (54%), complications to CP in 27 (28%) and suspected malignancy in 15 (16%) of the patients. In two (2%) patients' data on indication was lacking.

The 51 patients who underwent pancreatic surgery for chronic pain (PSCP group) formed the final study group and were analysed. The median follow-up time was two (range 0–8) years after surgery. The median age at the time of surgery was 48 (range 18–71) years and n = 17 (33%) of the patients were female. Surgery was performed a median of three years (0–28) after the diagnosis. Ductal lesions were present in 74% and pancreatic calcifications in 91% of the patients. Seventy-four-point five percent (74.5%) of the patients underwent endoscopic retrograde cholangiopancreatography (ERCP) prior to surgery. Pancreatic resection combined with drainage (n = 28 (54%), Frey, Berne and Beger procedures) was the most common procedure, followed by pancreatic resections alone (n = 17 (33%); pancreaticoduodenectomy, distal resections and total pancreatomies) and drainage alone (n = 7 (13%); Puestow/Partington-Rochelle and pseudocyst drainage) (Table 1 and Fig. 2). Post-operative diabetes was diagnosed in 39% and 41% had EPI.

Patients in the base group were older with a median age of 59 (range 15–109) vs. 51 (range 19–73) years. Idiopathic pancreatitis, calcifications and ductal dilation were more often diagnosed in the PSCP group. Endoscopic procedures were more often also performed in the PSCP group, 75% vs. 26%, (p = 0.000). Diabetes occurred equally in both groups but EPI was less common in the surgery group post-operatively. There was no difference in the number of patients with high pain scores and pain medication after surgery (Table 1).

Deaths were registered separately from all eight centres a median of 12 years after surgery (range 1–31) in 88% (45/51) of the patients. During this follow-up time, only one patient (2%) died of unknown causes one year after surgery.

3.1. Pain

After surgery, 16% of the patients suffered chronic pain episodes, 36% had recurring or intermittent pain episodes and 47% were pain free with or without medication. The patients with constant pain had longer disease duration before surgery than the CP patients without constant pain (11 (1–28) vs. 3 years, p = 0.034 (Fig. 3).

Of the 33 patients with data on pain medication two (range 1–7) years after surgery, 30% took strong pain medication (morphine, tramadol, buprenorphine), 6% had paracetamol or a nonsteroidal anti-inflammatory drug and 64% had no pain medication.

3.2. Quality of life (QLQ C30) responses

More than a half of patients (n = 31 (61%)) from the PSCP group completed the EORT QLQ C30 questionnaire. In the QLQ C30 responses, the PSCP group had worse social functioning (p = 0.028) but QOL and other functioning responses did not differ from those of the base CP population (n = 514). In symptom responses, the PSCP group reported more constipation, nausea and insomnia (p = 0.009, p = 0.002 and p = 001). (Fig. 4).

In the PSCP group, patients with prior ERCP (n = 25) had worse physical, role and social functioning (p = 0.017, p = 0.04 and p = 0.04) and more severe fatigue and pain symptom scores (p = 0.041 and p = 0.006) than patients without prior ERCP (n = 6).

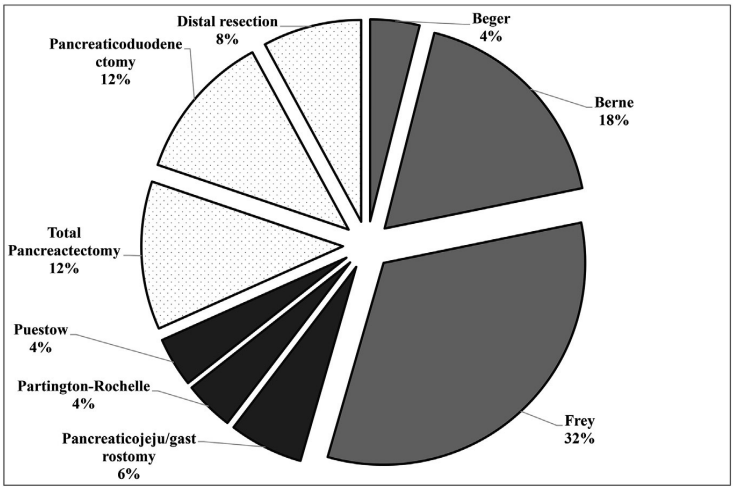
When comparing surgical procedures in the PSCP group, pancreatic drainage resulted in most patients with constant pain (p = 0.015). Patients with combined pancreatic resection and drainage had the least amount of constant pain (drainage 50%, resection 23% and combined 4%) p = 0.013 (Fig. 4). Total

Table 1
Demographic table of CP patients who underwent pancreatic surgery for pain. Pain and pancreatic insufficiency were measured post-operatively in the surgical group.

	Surgery for CP pain n = 51	All CP n = 1327	Surgery vs control p-value
Male/Female	67%/33%	67%/33%	p = 0.976
Age when surgery	48 (18–71 years)	N/A	
Age when visit	51 (19–73 years)	59 (15–109) years	p = 0.000
Time after diagnosis	6 (0–39 years)	3 (0–61 years)	p = 0.001
Aetiology			
Alcohol	60%	61%	p = 0.936
Nicotine	60%	69%	p = 0.231
Immunological	0%	2.3%	p = 0.308
Hereditary	6.7%	9.7%	p = 0.578
Efferent duct	0%	10%	p = 0.030
Unknown	30%	7.0%	p = 0.000
Calcification	91%	69%	p = 0.003
Ductal dilation	74%	57%	p = 0.031
Pseudocysts	41%	43%	p = 0.850
ERCP	75%	26%	p = 0.000
Biliary stenting	19%	12%	p = 0.039
Pancreatic stenting	33%	17%	p = 0.002

Pancreatic function and pain after surgery	Surgery for CP pain n = 44	Control CP group n = 1107	Surgery vs control p-value
Diabetes	39%	44%	p = 0.491
PEI	41%	60%	p = 0.019
No (post-operative) pain *	47%	47%	p = 0.940
Continious (post-operative) pain *	15.9%	16.4%	p = 0.926
Morphine*	21.2%	18.5%	p = 0.695
No pain medication*	64.0%	57.0%	p = 0.434

*Pain and pain medication was measured after surgery, except for the control group.



Drainage procedure	13%	n=7
Pancreatic resection	33%	n=17
Duodenum perserving pancreatic head resection	54%	n=28
Total	**100%**	**n=52**

Fig. 2. Type of pancreatic surgery performed with indication of chronic pancreatitis pain in the eight centres.

A.

										Surgery type		
	n		Female/ Male %	Surgery done time after diagnosis median (range)	Pancreatic main duct dilation	Pancreatic calcification	Alcohol	Smoking	Prior ERCP	Pancreatic drainage n=6	Pancreatic resection n=13	DPPHR n=25
Painless without medication or intervention	16	36%	38%/62%	3 (1-23) years	77%	92%	38%	46%	69%	17%	38%	40%
Painless with medication or intervention	5	11%	40%/60%	1 (1-8) years	67%	100%	75%	50%	80%	0%	15%	12%
All Painless	21	48%	38%/62%	3 (1-23) years	75%	94%	47%	47%	71%	17%	54%	52%
Recurring pain	16	36%	31%/69%	3(1-8) years	73%	93%	63%	75%	81%	33%	23%	44%
Constant pain	7	16%	29%/71%	**11 (1-28) years**	100%	86%	71%	57%	76%	**50%**	23%	**4%**
Constant pain vs recurring and painless	p-value	0.737	0.802	**0.034**	0.13	0.488	0.412	0.865	0.812	**0.0014**	0.4	**0.013**

B.

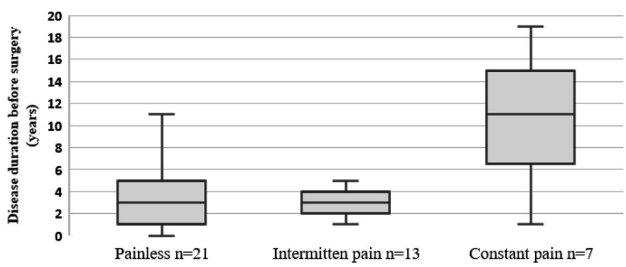


Fig. 3. A. Results of surgery in CP patients who underwent pancreatic surgery for pain. Duodenum perserving pancreatic head resections (DPPHR) seemed to have less pain. **B.** Patients with constant pain after surgery had a longer disease duration before surgery. Boxplot with whiskers with the middle line indicating a median value, the box indicating the interquartile range and whiskers the range.

pancreatectomy was performed on six patients, four with islet autotransplantation. One (17%) of these patients had opiate use and chronic pain.

Of the 15 patients undergoing surgery for a suspected tumour, 11 had completed the pain scores and EORTC QLQ-C30 responses. None of them had constant pain and 55% were pain free with or without medication. On EORTC QLQ-C30 responses they had a statistically better score in role functioning ($p = 0.029$), fatigue ($p = 0.049$) and pain ($p = 0.009$) than the base CP population.

4. Discussion

CP can lead to burdensome abdominal pain which may necessitate endoscopic treatment or pancreatic surgery. The optimal treatment and timing for CP remains uncertain. We aimed to ascertain the surgical treatment strategies in CP and to study QOL in these patients.

We found that pancreatic surgery for CP is rare: surgical procedures were performed on only 7% of the CP patients in the SBPC database. In most of the patients the indication was pain, and half of them reported being pain free after surgery.

The first surgical procedure reported for CP was pancreaticoduodenectomy (PD) While PD involves resecting the duodenum together with the pancreas a CP-specific duodenum preserving surgical technique has been developed, for example the Frey, Puestow, Berger and Berne modifications [19–25]. The Beger

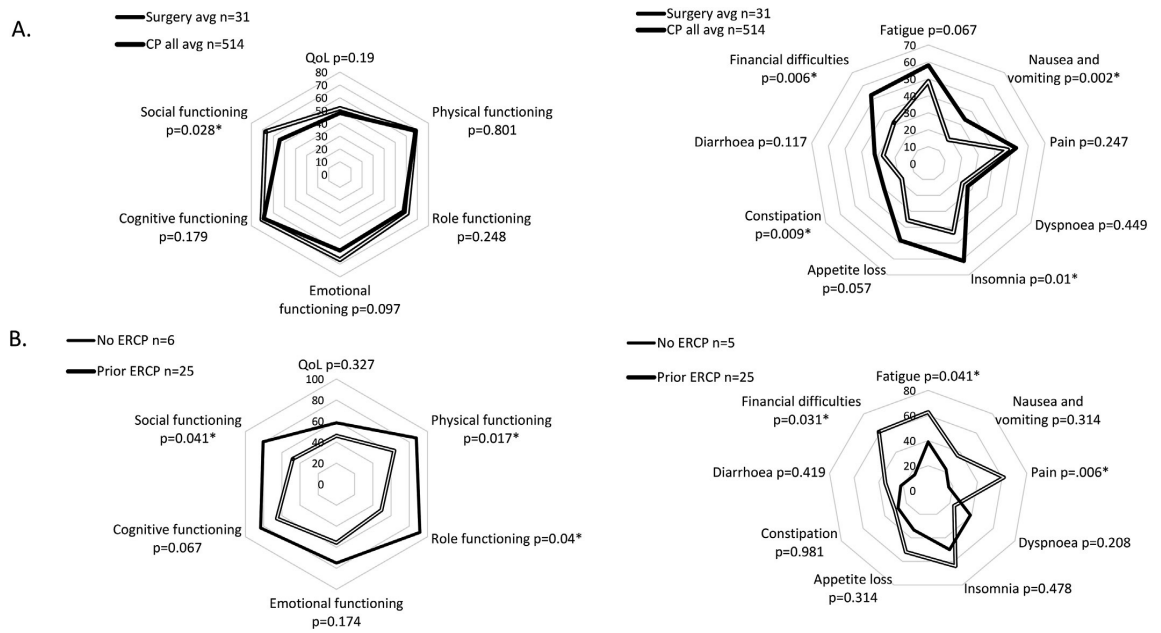


Fig. 4. EORTC C30-QOL and functioning in CP patients who had pancreatic surgery for pain. A higher score in QOL/functioning represents a better score A lower score in symptoms represents a better score. **A.** The surgery group appeared to have a similar QOL to the control group. **B.** The CP patients who did have any prior endoscopic procedures done before surgery had a better quality of life and fewer symptoms, e.g., pain.

procedure involves the resection of the pancreatic head and the pancreas is divided above the portal vein. In the Frey procedure the pancreatic head is opened and resected following a lateral jejunostomy. A Berne modification has subsequently been developed which involves carving out the inflamed pancreas mass from the head of the pancreas and does not involve dividing the pancreatic tissue [26–30].

In our study, combined pancreatic drainage and resection was most common (55%), Frey's procedure being the primary procedure of choice (33% of total). Pancreatic resection was done in 31% and drainage procedures in 14%. Numerous pancreatic surgery techniques are in use and there seems to be no predominant style. In the ESCAPE trial, 59% of the procedures were drainage and 37% were combined drainage and resection and in a Finnish cohort study pancreatic resection (70%) was the most common technique in CP with combined drainage and resection being (30%) while pure drainage procedures were very rare (1%). This differs from the meta-analysis by Ratnayake et al. where 67% of the procedures were combined pancreatic resections [31–33].

Presumably the difference in pancreatic surgery techniques is based on the surgeons' and clinics' own customs. The type of pancreatic surgery for CP should be determined by the anatomy of the afflicted pancreas. The international consensus guidelines recommend a Berne or Frey-type procedure over PD or Pylorus perserving-PD [34]. In patients with CP and a dilated main duct without an inflamed mass in the pancreatic head and no bile duct stenosis or portal vein stenosis, a lateral jejunostomy may suffice [35].

The selection of a surgical technique for patients with CP should be based on the anatomical characteristics of the pancreas to be operated on. In our study, CP patients with only pancreatic drainage for pain had more symptoms and post-operative pain than those patients who underwent resection or combined resection and drainage procedures. Patients with combined pancreatic resection and drainage procedures had the least amount of constant pain. Further studies are needed to determine the optimal strategies for surgical interventions.

In our study there was no difference in pain and pain medication between the base CP group and the PSCP group. We did not have access to detailed preoperative data. The PSCP group had a lower incidence of pancreatic insufficiency, possibly due to the inflammation subsiding slowly after surgery. Similar findings have been reported in earlier studies [30,31,36].

CP patients undergoing pancreatic surgery for pain had more pain post-operatively if they had already undergone ERCP. In our study CP patients who had undergone ERCP before surgery received more pain medication than patients who had not undergone ERCP prior to surgery. Moreover, no post-operative morphine was needed in patients undergoing their first surgery without prior endoscopic treatment and early surgery also seems to achieve better pain relief.

Similar results have been reported in other studies such as the Dutch ESCAPE trial, where an endoscopy-first approach resulted in more pain at 18 months while quality of life remained the same. In our study CP patients with no prior surgery had higher QOL scores [31]. Another Dutch randomized trial compared endoscopy and pancreatic surgical drainage [37]. In the two-year follow-up the surgical group were more pain free than patients treated with the endoscopic approach (40% vs. 16% respectively $p = 0.007$). A Czech randomized trial compared endoscopy to surgery and the surgical group had more painless (with or without pain medication) patients than the endoscopy group at five-year follow-up (surgery 32% vs. endoscopy 15% $p = 0.002$) [38]. In our study, 12% of the patients underwent total pancreatectomy for CP. These patients had approximately the same amount of constant post-operative pain and opiate use than the rest of the surgery group.

Our study has some limitations. We were not able to collect complete preoperative data from all the patients on pain, medication and QOL before the surgical interventions. Even though the SBPC register is the largest CP register in existence, surgical operations are rare, and thus the overall number of patients meeting our inclusion criteria is still fairly small. Although this is a cross-sectional study the numbers are too small for multivariate analyses. It should be noted that the time factors after surgery differ, not being consecutive causes limitations in the causality between surgery and outcomes. We assume that the surgery group have an altogether more severe disease spectrum than the conservatively managed population. The International Study Group of Pancreatic Surgery in 2020 released a standard for reporting details prior to and after surgery, including the use of opiates, pancreatic insufficiency and quality of life. According to this, the morphology of the pancreas and the outcome of surgery should also be reported. In the future adhering to these standards will result in a more reliable comparison of surgical outcomes and better care for CP patients [39].

There is preliminary data to suggest that pancreatic surgery for CP may not only slow down the inflammation but also delay the development of pancreatic insufficiency. In our population CP patients treated surgically for pancreatic pain had less EPI and endocrine insufficiency than the base population. Similar results have been reported in earlier studies [40,41].

More studies are needed to determine which CP patients benefit from surgery and when an endoscopic approach may suffice for pain relief.

We conclude that surgery for CP is rare. Surgical procedures were performed in only 7% of the CP patients in the SBPC database. In half of the patients the indication was pain. Most of these patients underwent endoscopic procedures before surgery. Half of the patients reported being pain free after surgery, either with or without pain medication. Patients who underwent a resection or combined resection and drainage seemed to achieve better pain and symptom control than the patients who underwent surgical drainage only. Further studies are needed to determine the optimal strategies for surgical interventions.

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PUBLICATION

IV

Endoscopic procedures and quality of life in chronic pancreatitis patients.

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Submitted