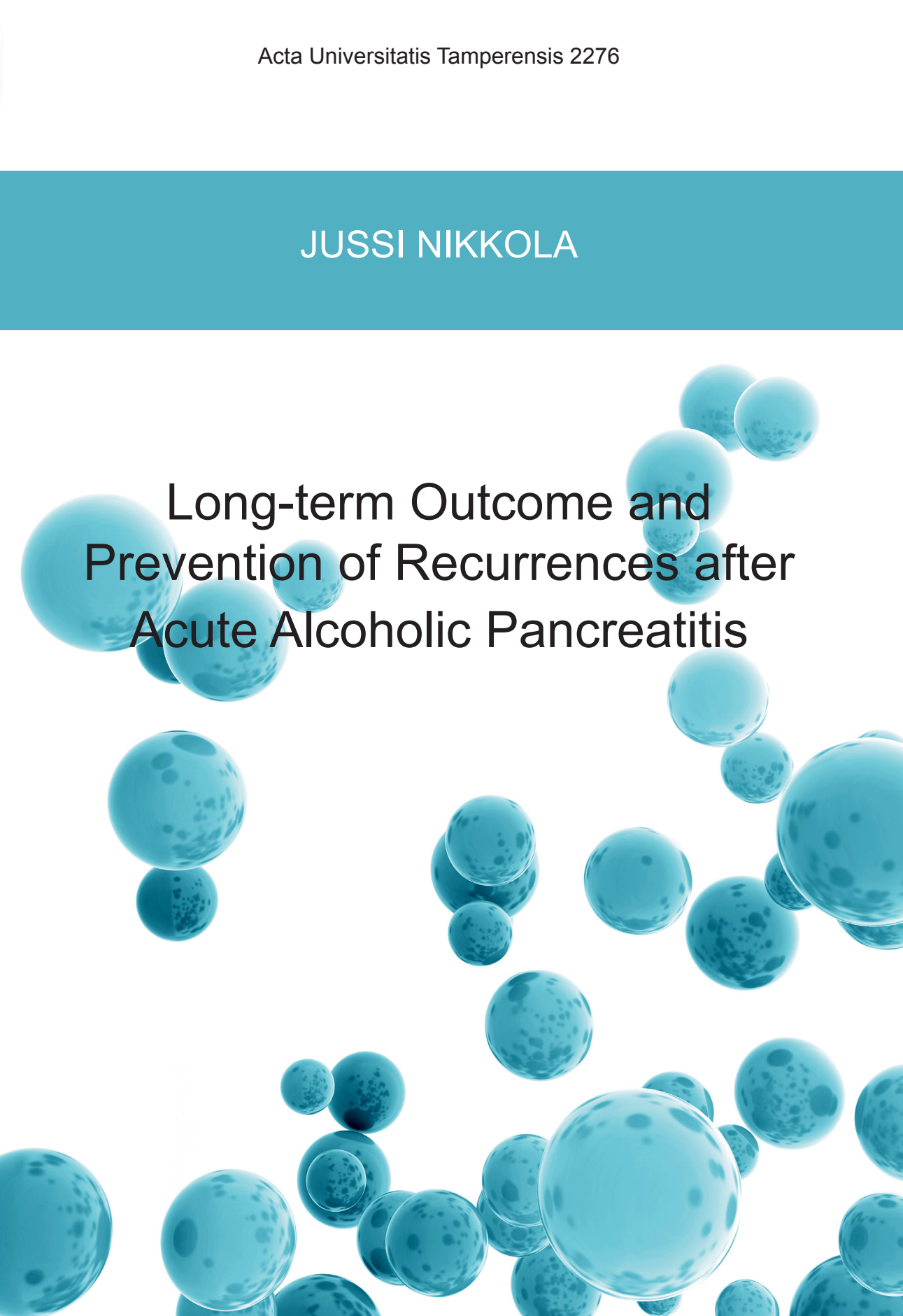


JUSSI NIKKOLA

Long-term Outcome and  
Prevention of Recurrences after  
Acute Alcoholic Pancreatitis

The background of the cover is white, featuring a decorative pattern of numerous blue, semi-transparent spheres of varying sizes. These spheres are scattered across the page, with some appearing larger and more prominent than others, creating a sense of depth and movement. The spheres have a subtle texture and are rendered with soft shadows, giving them a three-dimensional appearance.



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Long-term Outcome and  
Prevention of Recurrences after  
Acute Alcoholic Pancreatitis



ACADEMIC DISSERTATION

To be presented, with the permission of  
the Faculty council of the Faculty of Medicine and Life Sciences  
of the University of Tampere,  
for public discussion in the small auditorium of building M,  
Pirkanmaa Hospital District, Teiskontie 35, Tampere,  
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UNIVERSITY OF TAMPERE

JUSSI NIKKOLA

Long-term Outcome and  
Prevention of Recurrences after  
Acute Alcoholic Pancreatitis

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University of Tampere, Faculty of Medicine and Life Sciences  
Tampere University Hospital, Department of Gastroenterology and  
Alimentary Tract Surgery  
Finland

*Supervised by*

Docent Juhani Sand  
University of Tampere  
Finland  
Associate Professor Johanna Laukkarinen  
University of Tampere  
Finland

*Reviewed by*

Docent Leena Kylänpää  
University of Helsinki  
Finland  
Docent Perttu Arkkila  
University of Helsinki  
Finland

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# Abstract

Acute pancreatitis (AP) is one of the most common reasons for immediate gastrointestinal hospital admissions. Two of the most common etiologies are excessive alcohol consumption and gallstones. Biliary pancreatitis rarely relapses when gallstone disease is treated appropriately. However, in acute alcoholic pancreatitis (AAP), relapses of the disease are common and recurrent acute pancreatitis (RAP) develops in 33-46% of patients, and further chronic pancreatitis (CP) in 12-16%. The data on the development of pancreatic dysfunction after an initial episode of AP are controversial, however, and it is not clear what kind of consequences a single episode of AP may have for later pancreatic function and morphology.

The aim of this dissertation was to assess the incidence and risk factors for pancreatic dysfunction and chronic morphological changes after AAP and to explore ways to prevent RAP.

The effects of a single episode of AAP on pancreatic dysfunction were studied in 77 patients in a prospective long-term follow-up lasting for 10.5 years in median. Pancreatic function was assessed at 1 to 2-year intervals. Endocrine dysfunction (prediabetes or diabetes) developed in half of the patients and exocrine dysfunction (persistently low fecal elastase-1) in one fourth. RAP was a major risk factor for endocrine dysfunction. Pancreatogenic diabetes mellitus developed in 20% of the patients and only in patients with RAP.

Morphological changes seen in the pancreas were evaluated with secretin stimulated magnetic resonance cholangiopancreatography (S-MRCP). In a follow-up extending for up to nine years, chronic changes were observed in 47% of the patients and were more prevalent in patients with RAP and non-mild first AAP. Pancreatic dysfunction was associated with chronic changes.

The impact of abstinence from alcohol on recurrence of AAP was studied using a prospective study design. Abstinence protected against RAP and also against developing new-onset diabetes.

The current status of brief interventions (BIs) and substance abuse treatment in patients with AAP was assessed in patients treated in Pirkanmaa Hospital District, Finland in 2010 – 2012. Abstinence as the goal for substance abuse treatment was

mentioned in only one third of these patients' discharge summaries. In-hospital BI seemed not to have been provided for about one third of patients. On the other hand, in-hospital BI itself did not appear to reduce the later occurrence of RAP. In addition, young age at presentation of first AAP and higher Alcohol Use Disorders Identification Test (AUDIT) points were significant risk factors for RAP.

The conclusion of this thesis is that pancreatic insufficiency is likely to develop in patients who have recovered from their first AAP episode. RAP is the most important risk factor for the development of pancreatic endocrine insufficiency, pancreatogenic diabetes and chronic morphological pancreatic changes. Pancreatic function should be actively monitored after AAP and especially in patients with RAP. Alcohol abstinence protects against RAP and should thus be recommended to all AAP patients. Identification of the drinking problem and more effective means to organize the follow-up care for routine intervention are needed in order to effectively prevent recurrent attacks.

# Tiivistelmä

Akuutti haimatulehdus on yleisimpiä vatsanalueen päivystyksellistä sairaalahoitoa vaativia sairauksia. Yleisimmin taudinaiheuttajana on runsas alkoholinkäyttö tai sappikivet. Akuutin alkoholiperäisen haimatulehduksen sairastaneista potilaista uusiutuva haimatulehdus kehittyy jopa noin puolelle potilaista ja krooninen haimatulehdus 12-16%:lle. Tutkimustulokset haiman vajaatoiminnan kehittymisestä haimatulehduksen jälkeen ovat olleet ristiriitaisia. Aiemmin ei ole ollut luotettavasti selvillä, millainen vaikutus ensimmäisellä haimatulehduksella on haiman toimintaan ja rakenteellisten haimamuutosten kehittymiseen pitkällä aikavälillä.

Tämän tutkimuskokonaisuuden tarkoituksena oli selvittää haiman vajaatoiminnan ja haimassa nähtävien poikkeavien kuvantamismuutosten kehittymistä pitkäaikaisseurannassa ensimmäisen akuutin alkoholiperäisen haimatulehduksen jälkeen sekä tutkia näille poikkeavuuksille altistavia riskitekijöitä. Lisäksi tavoitteena oli arvioida haimatulehduspotilaan päihdehoidon toteutumista ja keinoja uusiutuvan haimatulehduksen ehkäisemiseksi.

Haiman toiminnan muutoksia ensimmäisen alkoholiperäisen haimatulehduksen jälkeen arvioitiin etenevässä pitkäaikaisseurannassa 77 potilaan kohortissa, jossa seuranta-ajan mediaani oli 10,5 vuotta. Haiman toimintaa seurattiin laboratoriokokein 1-2 vuoden välein. Endokriininen haiman vajaatoiminta (esidiabetes tai diabetes) kehittyi seurannassa puolelle potilaista ja eksokriininen vajaatoiminta (pysyvästi matala ulosteen elastaasi-1) neljäsosalle. Uusiutuva haimatulehdus todettiin tärkeimmäksi riskitekijäksi endokriinisen vajaatoiminnan kehittymiselle. Haimatulehduksesta johtuva haimaperäinen diabetes todettiin seurannan aikana kehittyvän 20%:lle ja vain niille potilaille, joilla oli aiempi uusiutuva haimatulehdus.

Haiman rakenteellisten muutosten kehittymistä arvioitiin niin ikään etenevässä pitkäaikaisseurannassa. Magneettikuvauksella nähtäviä kroonisia haimamuutoksia todettiin yhdeksän vuoden seurannassa 47%:lla akuutin alkoholiperäisen haimatulehduksen sairastaneista potilaista. Kroonisia haimamuutoksia todettiin merkitsevästi enemmän potilailla, jotka olivat sairastaneet uusiutuvan haimatulehduksen.

Etenevässä pitkäaikaisseurannassa tutkittiin alkoholista pidättäytymisen vaikutusta uusiutuvan haimatulehduksen sekä haiman vajaatoiminnan kehittymiseen. Tutkimuksessa todettiin alkoholista pidättäytymisen suojaavan uusiutuvalta haimatulehdukselta ja diabeteksen kehittymiseltä.

Akuutin alkoholiperäisen haimatulehduksen sairastaneiden potilaiden päihdehoidon toteutumista tutkittiin Pirkanmaan sairaanhoitopiirissä vuosina 2010 – 2012 hoidettujen potilaiden sairaskertomuksista. Tutkimuksessa todettiin, että vain noin kolmasosassa potilaiden epikriiseistä mainittiin alkoholista pidättäytymisen tärkeys uusiutuvan haimatulehduksen ehkäisemiseksi. Osastohoitojakson aikainen alkoholi-interventio (mini-interventio) näyttäisi jäävän kokonaan toteutumatta noin kolmasosalla potilaista. Toisaalta, ensimmäisen hoitojakson aikaisen alkoholi-interventio ei yksinään todettu vähentävän uusiutuvan haimatulehduksen kehittymistä seurannassa. Potilaan nuori ikä ja korkeat AUDIT-pisteet (Alcohol Use Disorders Identification Test) olivat merkitseviä riskitekijöitä uusiutuvan haimatulehduksen kehittymiselle.

Yhteenvedona tässä tutkimuskokonaisuudessa todettiin haiman vajaatoiminnan kehittymisen olevan yleistä potilailla, jotka ovat aiemmin sairastaneet akuutin alkoholiperäisen haimatulehduksen. Uusiutuvan haimatulehduksen todettiin olevan tärkein riskitekijä haiman endokriinisen vajaatoiminnan, erityisesti haimaperäisen diabeteksen ja kroonisten haiman kuvantamismuutosten kehittymiselle. Tutkimustulosten perusteella voidaankin suositella, että haiman toimintaa seurataan aktiivisesti laboratoriotarkastuksella, etenkin, jos taustalla on uusiutuva haimatulehdus. Lisäksi alkoholista pidättäytymisen todettiin suojaavan täysin uusiutuvalta haimatulehdukselta. Alkoholiongelman tunnistamiseen ja päihdeongelman haimatulehduspotilaan jatkohoidon järjestämiseen tulisi kiinnittää enemmän huomiota, jotta uusiutuvat haimatulehdukset voitaisiin ehkäistä.



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# List of original publications

This thesis is based on the following original publications, which are referred in the text by their Roman numerals I-IV:

- I. Nikkola J, Rinta-Kiikka I, Rätty S, Laukkarinen J, Lappalainen-Lehto R, Järvinen S, Seppänen H, Nordback I, Sand J. Pancreatic morphological changes in long-term follow-up after initial episode of acute alcoholic pancreatitis. *J Gastrointest Surg.* 2014;18(1):164–70.
- II. Nikkola J, Laukkarinen J, Lahtela J, Seppänen H, Järvinen S, Nordback I, Sand J. The long-term prospective follow-up of pancreatic function after the first episode of acute alcoholic pancreatitis: recurrence predisposes one to pancreatic dysfunction and pancreatogenic diabetes. *J Clin Gastroenterol.* 2017;51(2):183–90.
- III. Nikkola J, Rätty S, Laukkarinen J, Seppänen H, Lappalainen-Lehto R, Järvinen S, Nordback I, Sand J. Abstinence after first acute alcohol-associated pancreatitis protects against recurrent pancreatitis and minimizes the risk of pancreatic dysfunction. *Alcohol Alcohol.* 2013;48(4):483–6.
- IV. Nikkola J, Laukkarinen J, Huhtala H, Sand J. The intensity of brief interventions in patients with acute alcoholic pancreatitis should be increased, especially in young patients with heavy alcohol consumption. *Alcohol Alcohol.* 2017;doi:10.1093/alcalc/agx023. (Epub ahead of print).

# Abbreviations

AAP	Acute alcoholic pancreatitis
ADA	American diabetes association
AP	Acute pancreatitis
AUDIT	Alcohol use disorders identification test
BI	Brief intervention
BMI	Body mass index
CARS	Compensatory acute response syndrome
CCK	Cholecystokinin
CDT	Carbohydrate-deficient transferrin
CI	Confidence interval
CLDN2	Claudin-2
CP	Chronic pancreatitis
CRP	C-reactive protein
CECT	Contrast enhanced computed tomography
DM	Diabetes mellitus
ERCP	Endoscopic retrograde cholangiopancreatography
EUS	Endoscopic ultrasonography
FE-1	Fecal elastase-1
FPG	Fasting plasma glucose
HbA1c	Glycosylated hemoglobin A1c
HR	Hazard ratio
ICD-10	International statistical classification of diseases and health related problems 10 <sup>th</sup> revision
IGT	Impaired glucose tolerance
IL	Interleukin
MODS	Multiple organ dysfunction syndrome
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
OGTT	Oral glucose tolerance test
OR	Odds ratio

PEI	Pancreatic exocrine insufficiency
PP	Pancreatic polypeptide
PRSS1	Protease, serine, 1
RCT	Randomized controlled trial
SIRS	Systemic inflammatory response syndrome
S-MRCP	Secretin stimulated magnetic resonance cholangiopancreatography
RAP	Recurrent acute pancreatitis
SADD	Short alcohol dependence data
SPINK1	Serine protease inhibitor Kazal type 1
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
T3cDM	Type 3c diabetes mellitus
TNF	Tumor necrosis factor
US	Ultrasonography
WHO	World Health Organization





# Introduction

Acute pancreatitis (AP) is a complex inflammatory disorder of the pancreas, one of the leading gastrointestinal reasons for hospital admissions and is increasing in incidence (Peery et al. 2012; GBD 2015 Disease and Injury Incidence and Prevalence Collaborators 2016). Two main etiological factors are excessive alcohol consumption and gallstones together causing approximately 80% of morbidity. The pathophysiology of the mechanisms which trigger the acute attack are still poorly understood, but regardless of the initiating process, the course of the acute disease is similar even with different main etiologies (Frossard et al. 2008). Intra-acinar activation of pancreatic enzymes leads to autodigestion of the pancreas and systemic inflammatory reaction, the intensity of which determines the severity of the disease. In 80% of cases the disease is mild and self-limiting and responds well to conservative fluid-resuscitation treatment (Banks and Freeman 2006).

After biliary AP early cholecystectomy, or, if not feasible, endoscopic sphincterotomy, is recommended. This usually prevents disease relapse and thus allows good recovery (Bakker et al. 2011, 2014; Tenner et al. 2013). However, in acute alcoholic pancreatitis (AAP), recurrent attacks develop in 33-46% of patients (Appelros and Borgström 1999; Pelli et al. 2000; Gullo et al. 2002a, 2002b; Gislason et al. 2004; Lund et al. 2006; Lankisch et al. 2009; Takeyama 2009; Yadav et al. 2012b; Ahmed Ali et al. 2016) and chronic pancreatitis (CP) in 12-16% of patients (Lankisch et al. 2009; Yadav et al. 2012b).

Certain risk factors for progression to recurrent acute pancreatitis (RAP) and CP have been identified and some risk factors, such as alcohol consumption and smoking may even act synergistically to potentiate the risk (Pelli et al. 2008; Lankisch et al. 2009; Yadav et al. 2012b; Ahmed Ali et al. 2016).

Pancreatic function after AP has been studied with varying results. Endocrine dysfunction presenting as prediabetes or diabetes may develop in up to 40% of patients (Das et al. 2014b). Exocrine dysfunction is typically seen during convalescence after AP, but usually improves thereafter in most patients (Pelli et al. 2009; Sand and Nordback 2009).

According to a preliminary follow-up study, abstinence from alcohol may protect against RAP (Pelli et al. 2008). In Finland a randomized controlled study

was performed to study the impact of alcohol interventions in preventing alcohol-associated RAP. Repeated semi-annual interventions reduced the development of RAP by 50% in a two-year follow-up compared to interventions provided only during hospitalization (Nordback et al. 2009).

While the natural development of AP has attracted a lot of attention, there is a significant lack of knowledge on the consequences of an AP attack. Studies on pancreatic dysfunction are often short-term and include mixed etiologies, which makes it hard to achieve reliable results.

The purpose of this thesis was to study the incidence of and risk factors for pancreatic dysfunction and morphological changes in the pancreas after the first episode of AAP has resolved. In addition, we aimed to investigate if abstaining from alcohol alters the natural course of the disease. Furthermore, we wanted to assess the efficacy of brief interventions performed to reduce alcohol consumption, provided to patients during hospitalization for the first AAP and if they reduce the development of RAP.

# 1 Review of the literature

## 1.1 Anatomy and physiology of the human pancreas

The pancreas is a retroperitoneal organ located posteriorly to the stomach and transverse colon. It is a vital organ for the regulation of glucose homeostasis (endocrine pancreas) and participates in nutrient digestion (exocrine pancreas) and was first described by Herophilus (335-280 BC) (Beger et al. 2008).

The exocrine pancreas accounts for the majority of pancreatic mass and consists of lobules containing acinar and ductal cells. Fat and connective tissue form septas around these lobules. The acinar cells produce digestive enzymes (such as trypsin, amylase, lipase, chymotrypsin, carboxypeptidase, nucleases, elastase, cholesterolesterase and colipase), needed for digestion and further absorption of nutrients. Most of these enzymes are secreted as proenzymes or zymogens (such as trypsinogen) and activated normally in the duodenum by enteropeptidases and active trypsin. Protease inhibitors in the intestinal mucosa protect against the harmful effects of proteolytic enzymes on mucosa. Ductal cells produce electrolyte and bicarbonate rich fluid, which neutralizes gastric acid and facilitates the transportation of enzymes to the duodenum. Exocrine function is under hormonal and neural regulation. Secretion is regulated by gastrointestinal hormones (e.g. secretin, gastrin, cholecystokinin (CCK)) and cholinergic stimulation (Chandra and Liddle 2009; Townsend et al. 2012).

Pancreatic fluid is secreted to the pancreatic ducts and collected in the main pancreatic duct (ductus Wirsung), which enters the duodenum via the major papilla of the pancreas (papilla Vater) and an accessory pancreatic duct (ductus Santorini), which enters the duodenum via the minor papilla of the pancreas (Türkvatan et al. 2013; DiMagno and DiMagno 2016). The common bile duct enters the duodenum together with the main pancreatic duct in the papilla Vater (Townsend et al. 2012). The sphincter of Oddi is a smooth muscle in the distal pancreatic duct controlling the secretion (Sand et al. 1994; Laukkarinen et al. 2002).

The endocrine pancreas composes about 2% of the pancreatic mass and consists of pancreatic islets or islets of Langerhans distributed throughout the pancreas. These islets include insulin producing  $\beta$ -cells, glucagon producing  $\alpha$ -

cells, pancreatic polypeptide producing PP-cells, somatostatin producing  $\delta$ -cells and ghrelin producing  $\epsilon$ -cells. These hormones are secreted straight into the bloodstream (Beger et al. 2008).

Insulin is a peptide hormone that decreases blood glucose. Its secretion is increased as the blood glucose level rises. Gut hormones such as glucose-dependent insulintropic peptide (GIP), glucagon-like peptide-1 (GLP-1), amino acids, CCK, glucagon and post-prandial parasympathetic stimulation increase the secretion (Townsend et al. 2012; Fu et al. 2013). Glucagon is a counter-acting hormone to insulin. Its secretion is increased by hypoglycemia, adrenergic stimulation, amino acids (arginine and alanine in particular), CCK and inhibited by insulin, somatostatin and elevated blood ketone bodies and fatty acids (Townsend et al. 2012; Fu et al. 2013).

## 1.2 Etiologies and epidemiology of acute pancreatitis

Acute pancreatitis (AP) is most commonly associated with biliary disease or excessive alcohol consumption. These two main etiological factors account for approximately 80% of morbidity. There are differences between countries and regions in terms of the most common etiology. The annual incidence of AP ranges from 12 to 73 per 100,000 persons (Table 1). Alcohol is typically a more common etiology in men and especially in younger age groups ( $\leq 54$  years) and has shown an increasing trend (5-6% per year between 1999 and 2010) (Roberts et al. 2013). In countries like Finland, Germany, Poland and Hungary, higher proportions of alcohol versus gallstone etiology have been reported (Jaakkola and Nordback 1993; Gullo et al. 2002a; Bogdan et al. 2012) and in the United States the two main etiologies are reported to be equally prevalent (Fagenholz et al. 2007).

Seasonal variation for AAP has been reported in some studies. According to Roberts et al., admissions were significantly increased in the last weeks of December and first weeks of January (after Christmas and New Year) (Roberts et al. 2013). In a Finnish study peak incidences were found in July and August (Räty et al. 2003) suggesting a relationship between heavy alcohol consumption and AAP during or shortly after the vacation season. During a 20-year period (1987-2007) annual alcohol consumption in Finland increased from 8.2 to 10.2 liters per inhabitant. Simultaneously the overall incidence of AAP increased, but it was not possible to demonstrate an irrefutable connection between alcohol consumption and AAP (Sand et al. 2009).

AP can also result as a complication of endoscopic retrograde cholangiopancreatography (ERCP) and procedure-related complication rates between 2-6% have been reported (Andriulli et al. 2007; Silveira et al. 2009; Ukkonen et al. 2016). Other possible etiologies include hypertriglyceridemia, autoimmune disease, hypercalcemia, drugs (e.g. azathioprine, furosemide, valproic acid, tetracycline), ischemia, trauma, and infections (e.g. Epstein-Barr virus, cytomegalovirus and certain parasites) (Badalov et al. 2007; Forsmark et al. 2016). Autoimmune pancreatitis is classified as type 1 (systemic IgG4-associated disease with high risk of relapse) or type 2 (duct-centric with low risk of relapse), both forms usually responding to corticosteroid treatment (Madhani and Farrell 2016). Any factor causing pancreatic ductal obstruction may potentially cause AP: pancreatic tumors, pancreas divisum (controversial) or sphincter of Oddi dysfunction (Forsmark et al. 2016). Cystic fibrosis and other hereditary genetic factors may cause AP, the most studied genetic loci in hereditary pancreatitis are cystic fibrosis trans-membrane conductance regulator (CFTR) mutations and protease, serine 1 (PRSS1) (Etemad and Whitcomb 2001; Whitcomb 2013). Despite careful diagnostics, in some cases an etiological factor may not be found and etiology is classified as idiopathic in about 10% of patients (Guda et al. 2011).

**Table 1.** Incidence rates of acute pancreatitis and prevalence of the two main etiologies

<b>Study</b>	<b>Country</b>	<b>Years</b>	<b>Incidence (per 100 000)</b>	<b>Alcohol etiology</b>	<b>Gallstone etiology</b>
Appelros and Borsgröm 1999	Sweden	1985-1994	23.4	31.8%	38.4%
Birgisson et al. 2002	Iceland	1998-1999	32	32%	42%
Bogdan et al 2012	Poland	2005-2010	64.4	49%	27%
Eland et al. 2000	Netherlands	1985-1995	12.4 – 15.9	N/A	N/A
Fagenholz et al. 2007	USA	1988-2003	57 (40 – 73)	45%	45%
Floyd et al. 2002	Denmark	1981-2000	30	N/A	N/A
Frey et al. 2006	USA	1994-2001	33.2 – 43.8	20.3%	32.6%
Gislason et al. 2004	Denmark	1986-1995	30.6	19%	48.5%
Jaakkola and Nordback 1993	Finland	1970-1989	46.6 – 73.4*	N/A	N/A
Lankisch 2002	Germany	1988-1995	19.7	32%	40%
Lankisch 2009	Germany	1987-2006	13.1	30%	42%
Lindkvist et al. 2004	Sweden	1985-1999	18 – 34	25%	42%
McKay et al. 1999	Scotland	1984-1995	32	N/A	N/A
Roberts et al. 2008	England	1998-2005	22	7%	27%
Roberts et al. 2013	Wales	1999-2010	30	22%	37%
Sandzen et al. 2009	Sweden	1988-2003	27 – 33	N/A	N/A
Shen et al. 2012	Taiwan	2000-2009	36.9	N/A	N/A
Spanier et al. 2013	Netherlands	2000-2005	14.7	N/A	N/A
Tinto et al. 2002	Great Britain	1989-2000	19.3	N/A	N/A
Vidarsdottir et al. 2013	Iceland	2010-2011	40	23%	42%

N/A, not applicable

\*First and recurrent attacks

## 1.3 Acute alcoholic pancreatitis

### 1.3.1 Pathophysiology

The exact mechanism of the pathophysiology of AP remains poorly understood. Regardless of the etiology, different triggers can initiate the process of intra-acinar pancreatic trypsin activation leading to an activation cascade of other digestive pancreatic enzymes and autodigestion of the gland and surrounding tissues (Lankisch et al. 2015). The concept of autodigestive injury was first suspected by Hans Chiari in 1896 (Beger et al. 2008). Pancreatic injury leads to local inflammation involving neutrophils and macrophages, leading to the release and activation of proinflammatory mediators (cytokines), such as Tumor Necrosis Factor  $\alpha$  (TNF- $\alpha$ ) and Interleukins (IL) 1 $\beta$ , 6 and 8 (Mayer et al. 2000; Nieminen et al. 2014).

Alcohol is metabolized by the pancreas via oxidative and non-oxidative pathways, producing acetaldehyde, reactive oxygen species (ROS) and fatty acid ethyl esters (FAEE) as metabolites. Alcohol and its metabolites have direct and indirect toxic effects on pancreatic cells, leading to an intracellular imbalance of enzymes and calcium, fragility of organelles and production of extracellular matrix proteins (Apte et al. 2010). Simultaneous activation of transcription factors like nuclear factor  $\kappa$ B (NF- $\kappa$ B) promotes these changes (Rakonczay et al. 2008). With an appropriate trigger, a cascade leading to AP is initiated (Apte et al. 2010; Raghuwansh and Saluja 2012). Alcohol consumption may also modify inflammatory response (increase monocyte TNF- $\alpha$  production) and complicate the course of the disease once initiated (Szabo et al. 2007).

### 1.3.2 Clinical course

In most patients, the pancreatic inflammatory reaction is controlled and self-limiting. It is mainly restricted locally to the pancreas and peripancreatic tissues and is described as mild acute interstitial (edematous) AP. These patients usually respond well to intravenous fluid resuscitation and the inflammation resolves within days or weeks (Banks and Freeman 2006).

However, 10-20% of patients develop a more severe disease, where local inflammation progresses uncontrollably to hyperinflammation, clinically described

as systemic inflammatory response syndrome (SIRS) and local morphologic complications (necrosis and fluid collections) develop. Necrosis is detected in imaging studies in 5-10% of patients with AP (necrotizing AP) (Banks et al. 2013). Amplified inflammatory response in systemic circulation leads to capillary leakage and distant organ injury via impaired perfusion and possible multi-organ dysfunction syndrome (MODS) in 20-80% of patients with severe disease (Bhatia 2005; Kylänpää et al. 2010). This proinflammatory phase usually lasts one week and mortality in this early phase is predominantly caused by MODS (Phillip et al. 2014). To control the generalized hyperinflammation a compensatory anti-inflammatory response syndrome (CARS), including anti-inflammatory cytokines, develops simultaneously with the onset of pro-inflammatory reaction (Phillip et al. 2014). The late phase of AP (after first week) is associated with persistent inflammation and local complications in severe disease, in which excessive CARS may lead to immunosuppression further predisposing to bacterial infections (Kylänpää-Bäck et al. 2001b; Shen et al. 2011; Mayerle et al. 2012).

Severe disease is associated with high mortality of 10-30% (Banks and Freeman 2006). Death from severe AP occurs either early (during the first two weeks) from disease onset due to MODS or later, usually resulting from bacterial infection complications (Blum et al. 2001; Banks et al. 2013) and the mortality doubles if both are present (Petrov et al. 2010).

### 1.3.3 Risk factors

In 1878 the German physician and pathologist Nikolaus Friedreich proposed that alcohol might be associated with a general chronic interstitial pancreatitis using the term “drunkard’s pancreas” (Beger et al. 2008). Although the exact mechanism of how alcohol causes AP and reason why only a minority, about 3-5% of heavy alcohol drinkers (Lankisch et al. 2002b; Yadav et al. 2007), ever develop AP is still unclear, alcohol is considered an acknowledged risk factor for AP.

A dose-response relationship has been described (Kristiansen et al. 2008; Irving et al. 2009) and a threshold level of over 40 grams of alcohol per day increases the risk for AP according to meta-analysis (Samokhvalov et al. 2015). Kristiansen et al. found that beer consumption of  $\geq 14$  drinks per week was associated with higher risk of AP, but no association was found with spirits or wine (Kristiansen et al. 2008). On the other hand, a Swedish study reported a linear association between



the amount of spirits consumed on a single occasion and AAP, but no association in beer or wine drinking (Sadr Azodi et al. 2011).

Alcohol consumption is difficult to study and may change drastically in individual during year or month. Duration and pattern of drinking have yielded controversial results about the risk of AAP. During the Munich Oktoberfest, no significant increase in AAP was detected (Phillip et al. 2011). In a study by Nordback et al., most of the patients who developed AAP presented with their first symptoms during withdrawal from binge drinking (Nordback et al. 2005).

Despite numerous studies, the amount, type and duration of alcohol consumption required to initiate AP is uncertain. It is more than likely that other environmental and/or genetic risk factors combine with alcohol to initiate AAP.

AAP is more common in men, which may be explained by genetic predisposition, such as X-chromosome linked claudin-2 (CLDN2) risk allele (Whitcomb et al. 2012). The typical age for the presentation of first attack of AAP is between 30-60 years (Lankisch et al. 2002a; Yadav et al. 2009).

Smoking has been demonstrated to be an independent risk factor for non-gallstone related AP and duration of smoking seems to increase the risk (Lindkvist et al. 2008; Tolstrup et al. 2009; Sadr-Azodi et al. 2012).

Abdominal adiposity (waist circumference over 105cm) is associated with increased risk for both gallstone and non-gallstone related AP (Sadr-Azodi et al. 2013). According to three retrospective population-based studies, type 2 diabetes mellitus (T2DM) increases the risk for AP between 1.5 and three-fold (Noel et al. 2009; Girman et al. 2010; Lai et al. 2011) and simultaneous alcoholism potentiates the risk (Lai et al. 2011). Unfortunately, the etiology of AP was not assessed in these studies and only one study (Noel et al. 2009) used multivariable modeling adjusted with smoking and alcohol consumption as variables. The risk of patients with T2DM developing AAP remains to be ascertained and the association is complex since diabetes may result from AP itself or be a manifestation of underlying CP.

#### 1.3.4 Clinical picture and diagnosis

Typical clinical signs associated with AP include epigastric or left upper quadrant pain radiating to the back in about half of patients and this may be belt-like around the upper abdomen. The onset of pain is typically sudden, but may also begin as gradually increasing. Pain is usually constant and may be intense. Nausea and

vomiting are typically present. In severe cases patients may present with respiratory distress, agitation, anuria or shock. Palpation of the abdomen usually shows tenderness but this may range from mild distress to peritonistic abdomen. Thus the clinical signs and pain evaluation may be misleading (Whitcomb 2006).

Diagnosis of AAP is based on anamnestic information, clinical signs, laboratory markers, imaging study findings and the exclusion of other etiologies for acute abdomen and other etiologies for AP besides alcohol consumption. AP should be suspected in all patients with acute onset epigastric pain (Whitcomb 2006).

According to the revised Atlanta classification, a diagnosis of AP can be established when two out of the three following features are present: (i) typical pain associated with AP, (ii) serum lipase or amylase levels three times over the upper normal range and (iii) typical imaging findings associated with AP are present in abdominal imaging: contrast enhanced computer tomography (CECT), magnetic resonance imaging (MRI) or ultrasonography (US) (Banks et al. 2013).

When pancreatic acinar cells are injured, enzymes are released into the circulation. Two of the most commonly used laboratory markers used to detect AP are serum amylase and lipase activity (Matull et al. 2006). Amylase usually rises a few hours after the onset of symptoms and returns to normal in 3-5 days. Amylase levels may, however, be normal at the onset of the disease in 19% of patients (Clavien et al. 1989; Winslet et al. 1992). Serum lipase has been reported to have higher sensitivity and specificity than amylase and to remain elevated for a longer period (Keim et al. 1998). Amylase may be elevated in other conditions such as macroamylasemia, diseases of the salivary glands, various abdominal or gynecological diseases associated with inflammation (e.g., peptic ulcer disease, mesenteric ischemia, appendicitis, cholecystitis and salpingitis) or in patients with renal dysfunction (Swensson and Maull 1981; Townsend et al. 2012). Pancreas-specific amylase samples may be obtained to eliminate salivary-type amylase (Yadav et al. 2002). The severity or further course of AP cannot be determined by serum amylase or lipase levels (Lankisch et al. 1999). Urinary trypsinogen-2 dipstick test (Kemppainen et al. 1997) offers an easy and rapid option as a screening test for AP with a sensitivity of 82-96% and specificity of 92-95% (Kylänpää-Bäck et al. 2002; Chang et al. 2012)

Biliary AP is most commonly diagnosed or excluded using US or magnetic resonance cholangiopancreatography (MRCP) evaluation. Repetition of US examination increases its sensitivity to detect gallstones (Bortoff et al. 2000). A history of excessive alcohol intake during the preceding two weeks is suggestive of AAP. The Alcohol Use Disorders Identification Test (AUDIT) is recommended

for determining alcohol consumption: points of  $\geq 8$  refer to harmful alcohol consumption (Saunders et al. 1993; Nordback et al. 2007). The best laboratory marker for detecting increased alcohol consumption in AAP seems to be carbohydrate-deficient transferrin (CDT) (Jaakkola et al. 1994), but it is not routinely used in practice in AAP patients. Most patients have a history of prolonged alcohol consumption, but not all. Typically patients have stopped drinking prior to the onset of symptoms (Nordback et al. 2005). Exact alcohol consumption is very challenging to estimate and no definitive criteria for alcohol as an etiology of AP exist. Alcoholic etiology may thus be determined as probable when heavy alcohol consumption is evident or possible when alcohol consumption is moderate (Nordback et al. 2007).

### 1.3.5 Classification and assessment of severity

In 1992, a consensus conference took place in Atlanta, Georgia, where clinical classifications for severity and complications of AP were defined (Bradley 1993). AP was divided into two categories: mild (inflammation and edema, no systemic or local complications) and severe (systemic and/or local complications). A revision of the original criteria was made in 2012 (Banks et al. 2013).

The revised Atlanta criteria classify AP into three categories. In mild AP there is no organ failure, local or systemic complications. Moderately severe AP is defined by the presence of transient organ failure ( $<48\text{h}$ ) and/or local or systemic complications. Severe AP is defined by the presence of persistent organ failure ( $>48\text{h}$ ).

The most important local complications include acute peripancreatic fluid collections, pancreatic parenchymal or peripancreatic acute necrotic collections (ANCs), pseudocysts, and walled-off necrosis (WON). ANCs contain fluid and necrotic tissue and develop during the first four weeks (Thoeni 2012). Later (after four weeks) ANCs typically encapsulate and become so-called WON (Thoeni 2012). Acute peripancreatic fluid collections are associated with interstitial edematous pancreatitis; they usually resolve spontaneously and seldom develop into pseudocysts at least four weeks after the initial attack (Banks et al. 2013).

Systemic complications are defined as development of organ failure ( $\geq 2$  points in modified Marshall scoring system (Marshall et al. 1995)) or exacerbation of pre-existing co-morbidity (Banks et al. 2013).

Assessment of the severity of AP in the early stages remains a challenge. It is crucial, and should be made as early as possible to differentiate patients with a potentially severe course of disease and admit them to intensive care surveillance. A variety of scoring systems for predicting severity has been established including patient-based and laboratory parameters and also single laboratory markers such as C-reactive protein (CRP), hematocrit, procalcitonin, trypsinogen activation peptide, angiopoietin-2, creatinine may be useful in assessing severity of the disease (Puolakkainen et al. 1987; Kylänpää-Bäck et al. 2001a; Beger and Rau 2007; Mayerle et al. 2012). Novel markers like circulating cytokines IL-6 and hepatocyte growth factor (HGF) (Nieminen et al. 2014), or soluble urokinase-type plasminogen activator receptor (suPAR) (Nikkola et al. 2017) may in the future be beneficial for the early diagnosis of severe AP. Plasma IL-10 and decreased plasma calcium levels have shown prognostic value in predicting organ failure in severe AP (Mentula et al. 2005). Probably the most used clinical prognostic scoring systems are Ranson score (Ranson et al. 1974), Acute Physiology, and Chronic Health Evaluation (APACHE-II) score (Knaus et al. 1985) and Bedside Index for Severity in AP (BISAP) (Wu et al. 2008). Various CT scoring systems such as Balthazar grade and CT severity index (Balthazar et al. 1985, 1990) have also been developed.

### 1.3.6 Radiological imaging in AP

If the diagnosis of AP is uncertain, if another serious condition needs to be excluded or life-threatening complications in severe AP need to be immediately detected, diagnostic imaging studies are needed when the patient presents at the emergency department (Shyu et al. 2014). To detect necrosis, a standard CT can be performed in early acute phase without intravenous contrast medium to avoid nephrotoxicity and still provide adequate diagnostic value (Mentula and Leppäniemi 2014). US is used as a complementary study to detect gallstones (Tenner et al. 2013). Later in the course of the disease (one week after diagnosis), if severe AP is suspected and the patient's condition does not begin to improve, a CECT study is performed to assess the extent of necrosis and detect pancreatic or peripancreatic collections (Banks et al. 2013).

MRCP will give information on pancreatic ductal integrity and biliary stasis (gallstones) in patients with AP and significantly elevated liver enzymes (Freeman et al. 2012). ERCP with sphincterotomy, stone removal and/or stent placement

may be needed to restore flow in biliary stasis or suspected cholangitis (Fogel and Sherman 2014).

### 1.3.7 Treatment strategies

After confirmation of the diagnosis and initial assessment of disease severity, the cornerstone of treatment is early and tailored intravenous fluid resuscitation to maintain adequate organ perfusion (Puolakkainen et al. 1998). Lactated Ringer's solution should be preferred over normal saline solution since it seems to decrease SIRS (Wu et al. 2011) and be more favorable to acid-base balance (Sakka 2009). Adequate fluid resuscitation should be early initiated with a bolus infusion of 20 ml/kg in the emergency department and a total volume of ~2500-4000ml of fluid administered during the first 24 hours (Bakker et al. 2014). According to a recent multicenter study, early moderate to aggressive fluid resuscitation (>500ml during the first 4 hours) decreased the need for invasive interventions, but did not reduce organ failure, local complications or mortality, mainly because patients with more severe disease require more aggressive fluid administration to maintain organ perfusion, thereby causing reverse causation bias (Singh et al. 2016). Urine output, vital signs, markers for hypovolemia (hematocrit and creatinine) and physical examination should be assessed repeatedly and fluid resuscitation appropriately tailored. In severe AP patients require intensive-care surveillance (Working Group IAP/APA Acute Pancreatitis Guidelines 2013). Effective analgesia is usually provided by opiate based drugs. Enteral nutrition should be enabled as soon as possible to reduce infectious complications. Antibiotics should be administered only when there is a clear suspicion of infection (infected pancreatic necrosis or extrapancreatic infection) and surgical, endoscopic or radiological interventions should be delayed for as long as possible (Working Group IAP/APA Acute Pancreatitis Guidelines 2013). Gas bubbles in CECT and bacterial growth in US-guided fine needle aspirate indicate infected pancreatic necrosis, but a negative result may not suffice to rule out infection (Banks et al. 2013; Mentula and Leppäniemi 2014). If suspected, increased intra-abdominal pressure (IAP) is monitored in severe AP and elevated IAP is recommended to be treated conservatively if possible in a stepwise approach (Kirkpatrick et al. 2013)

## 1.4 Brief interventions

Brief interventions (BIs) are short talks usually ranging from 5 to 20 minutes with one or more sessions conducted to reduce harmful alcohol consumption (Connor et al. 2016). BIs should be motivational, include advice, feedback on personal risks, information and material on the harmful effects of drinking, information of alcohol support services and encourage patients to set goals to reduce their alcohol consumption (McQueen et al. 2011). Patients' own responsibility and autonomy to make decisions should be emphasized (Heinz and Wilwer 2003). Early identification of alcohol risk users with questionnaires eliciting excessive alcohol consumption (AUDIT) and dependency (Short Alcohol Dependence Data, SADD) is important and the results may be used to guide the conversation in BI (Raistrick et al. 1983; Saunders et al. 1993).

The effectiveness of BIs has been shown both in the hospital environment and in general practice to reduce alcohol consumption in heavy drinkers and the results from a single BI may last about a year (Kaner et al. 2007; McQueen et al. 2011; O'Donnell et al. 2014). BIs have also associated with reduced mortality in follow-up (Rehm and Roerecke 2013). Extended length of BI does not seem to significantly improve the outcome (Kaner et al. 2007), but more than one BI session may be needed to reduce alcohol consumption (Mdege et al. 2013; Simioni et al. 2015). The cost-effectiveness of BIs has been reported in four-year follow-up (Fleming et al. 2000). BIs given by nurses seem to be most efficient in reducing alcohol consumption according to a meta-analysis (Platt et al. 2016).

According to a large meta-analysis, the results on the efficacy of BIs given in emergency departments have yielded varying results but are generally favorable (Schmidt et al. 2016) and cost-effective (Gentilello et al. 2005).

For patients with screening-identified alcohol dependency, more effective measures than just BIs are usually needed (Saitz 2010).

Patients hospitalized due to alcohol-associated diseases are usually motivated to reduce drinking (Lau et al. 2010). After AAP, most patients (96%) are willing to stop or reduce their drinking and about 40% of them succeed (Lappalainen-Lehto et al. 2013).

## 1.5 Progression of alcoholic pancreatitis

### 1.5.1 Recurrent acute pancreatitis

According to various studies AAP progresses to RAP in 33-46% of patients (Appelros and Borgström 1999; Pelli et al. 2000; Gullo et al. 2002a, 2002b; Gislason et al. 2004; Lund et al. 2006; Lankisch et al. 2009; Takeyama 2009; Yadav et al. 2012b; Ahmed Ali et al. 2016). Of the first recurrences, 80% occur within the first four years (Pelli et al. 2000). RAP infrequently occurs in biliary AP, but is possible if cholecystectomy is not performed (Frey et al. 2006; Yadav et al. 2012a).

RAP is diagnosed and managed using the same criteria and treatment principles as for first AAP. After AAP or in CP, patients typically present with exacerbations (abdominal pain) of the disease not to be confused with RAP if the diagnostic criteria are not fulfilled (Guda et al. 2011). RAP may also develop in patients with diagnosed CP (Guda et al. 2011).

#### 1.5.1.2 Risk factors

Young age at the time of first attack (<45 years) and mild first AAP attack were associated with multi-recurring pancreatitis according to a retrospective study (Pelli et al. 2000). In another study patients with more severe first AAP had higher risk for RAP (Bertilsson et al. 2015). Young age has been associated with higher recurrence rate in two other studies (Yadav et al. 2014; Ahmed Ali et al. 2016).

In prospective studies, continuous alcohol consumption or alcohol dependence (as depicted by less reduced SADD points (Pelli et al. 2008), use of other sedatives besides alcohol (Pelli et al. 2008) and persistent pancreatic pseudocysts (Pelli et al. 2009) have been found to be independent risk factors for progression to RAP.

In a retrospective Dutch study smoking was found to be an independent risk factor for RAP in AAP patients (Ahmed Ali et al. 2016).

### 1.5.1.3 Prevention of recurrent attacks

According to a two-year follow-up, abstinence may protect against RAP (Pelli et al. 2008). There are numerous guidelines on the treatment of AP, but none include specific recommendations for treating the problem itself: heavy alcohol consumption and alcohol dependency. In Finland a randomized prospective trial showed that repeated motivational talks against high alcohol consumption at 6-month intervals reduced the recurrence of AAP by 50% in a two-year follow-up compared to a single intervention during hospitalization (Nordback et al. 2009). Cessation of smoking seems to protect against AP, and should thus probably be recommended to patients to prevent RAP (Sadr-Azodi et al. 2012).

## 1.5.2 Chronic pancreatitis

Alcohol consumption is the leading cause of CP in developed countries, causing approximately 70-90% of cases (Steer et al. 1995; Coté et al. 2011; Levy et al. 2014) and usually prolonged (5-15 years) heavy alcohol consumption is required (Witt et al. 2007). The incidence of CP varies between 4-13 / 100,000 persons (Levy et al. 2014). Rates for progression from AAP to CP between 11% and 36% have been reported (Yasuda et al. 2008; Lankisch et al. 2009; Takeyama 2009; Nøjgaard et al. 2011a; Yadav et al. 2014; Bertilsson et al. 2015; Ahmed Ali et al. 2016).

Unlike in AP or RAP, in CP, definitive irreversible damage to the pancreatic tissue is evident when fibrotic tissue replaces normal pancreatic parenchyma. CP is clinically characterized by chronic abdominal pain, malabsorption resulting from exocrine pancreatic dysfunction and leading to weight loss, possible endocrine pancreatic dysfunction, and exacerbations of the disease (Etemad and Whitcomb 2001). However, not all patients develop symptoms or pancreatic dysfunction (Majumder and Chari 2016).

CP has been associated with 5-fold increased mortality compared to matched controls and is an acknowledged risk factor for pancreatic cancer (Lowenfels et al. 1993; Bang et al. 2014). CP accompanied by diabetes increased the risk for pancreatic cancer to 33-fold compared to healthy controls (Liao et al. 2012).



### 1.5.2.1 Pathogenesis

The development of CP is a complex and multifactorial inflammatory process including environmental, metabolic and genetic factors (Yadav and Whitcomb 2010). Initially AP and CP were concerned as two different conditions, later it was demonstrated that AP can progress to CP (Sarnar and Cotton 1984; Sarles 1991).

Different theories for pathogenesis have been proposed which may partly explain the pathogenesis of CP. In the protein plug theory, increased secretion of proteins from acinar cells induces plug and later stone formation in the pancreatic ducts, leading to ulcerations, inflammation and other findings consistent with CP (Sarles 1986). The toxic-metabolic hypothesis suggests that alcohol poses direct toxic effects on acinar cells inducing progressive lipid deposition, necrosis and fibrosis (Bordalo et al. 1977). In the oxidative stress hypothesis, bile (including free radicals) is refluxed to the pancreatic ducts inducing pathological intracellular events in acinar cells leading to inflammatory response and fibrosis (Braganza 1983).

In 1946 Comfort et al. proposed that RAP episodes predispose to CP (Comfort et al. 1968). Later the “necrosis-to-fibrosis” hypothesis was presented by Klöppel & Maillet, in which continuous attacks of AP cause CP with necrosis-fibrosis sequence (Klöppel and Maillet 1993). This hypothesis was validated when Amman & Muellhaupt investigated the development of CP and found that the number and severity of RAP episodes were significantly associated with the development of future alcohol-associated CP (Ammann and Muellhaupt 1994).

Since AP patients (and especially patients with hereditary AP) can progress to CP with minimal detectable necrosis a “sentinel acute pancreatitis event” or “SAPE” hypothesis for development of CP was proposed (Whitcomb 1999). In this model risk factors (e.g. alcohol) exert stress on the pancreas and lower the threshold for initial AP. Acute pancreatitis initiates acute inflammatory response and later anti-inflammatory response, which limits the injury and promotes healing. Pancreatic stellate cells are activated in the healing process to produce collagen. Continuous exposure to risk factors (e.g. alcohol and tobacco) or genetic predisposition (e.g. PRSS1 mutation in hereditary pancreatitis) may initiate RAP episodes in which acute inflammatory response is countered by enhanced anti-inflammatory response, which stimulates the development of fibrosis (Whitcomb 1999).

CP may also develop after severe AP in case of extensive necrosis and/or pancreatic ductal obstruction (Yadav and Whitcomb 2010).

### 1.5.2.2 Diagnosis

CP is a progressive heterogeneous disorder with many difficulties in diagnosis and treatment. Eventually CP will progress to extensive pancreatic fibrosis and calcification, but in its early stages CP may be difficult to diagnose and the process may take years (Ammann et al. 1996). In alcoholic CP diagnosis is made approximately 2.5-4.5 years after onset of symptoms associated with CP (Beger et al. 2008). Other morphological features include ductal abnormalities and strictures, pseudocysts and pancreatic atrophy (Majumder and Chari 2016). Diagnosis relies on pancreatic imaging studies and laboratory findings indicating pancreatic dysfunction together with typical symptoms of CP. Histological biopsy findings of pancreatic fibrosis would be the most definitive tool for diagnosis, although extremely invasive and due to irregular distribution of chronic changes may yield false negative results (Catalano et al. 2009; Duggan et al. 2016).

Different criteria to determine CP have been developed, and there is no consensus on which should be used. The Marseille criteria of 1963 and updates to these in 1984 and 1988 were based on the morphological characteristics of CP (Sarner and Cotton 1984; Sarles et al. 1989), likewise the later Cambridge classification (ductal changes) and Rosemont criteria (Sarner and Cotton 1984; Catalano et al. 2009). Lünenburg and Mayo Clinic scores were based on morphological features, functional abnormalities and imaging findings (Layer et al. 1994; Lankisch 1999).

The M-ANNHEIM classification system categorizes CP according to possible multi-factorial etiologies or risk factors: alcohol consumption, nicotine use, nutritional factors, hereditary factors, efferent duct factors (obstruction, strictures, congenital abnormalities, sphincter of Oddi dysfunction), immunological factors and miscellaneous factors (hypercalcemia, drugs, etc.). The M-ANNHEIM diagnostic criteria classify CP as definitive, probable or borderline. Definitive CP is diagnosed when typical clinical history is accompanied by one or more of the following: pancreatic calcifications, ductal lesions, persistent exocrine insufficiency or histological findings of CP. Probable CP refers to a typical clinical picture combined with either mild ductal alterations, recurrent or persistent pseudocysts and pathologic finding in exo- or endocrine pancreatic function. Borderline CP is defined as typical clinical picture but absence of findings indicative of probable or definitive CP (Schneider et al. 2007).

### 1.5.2.3 Imaging of chronic changes

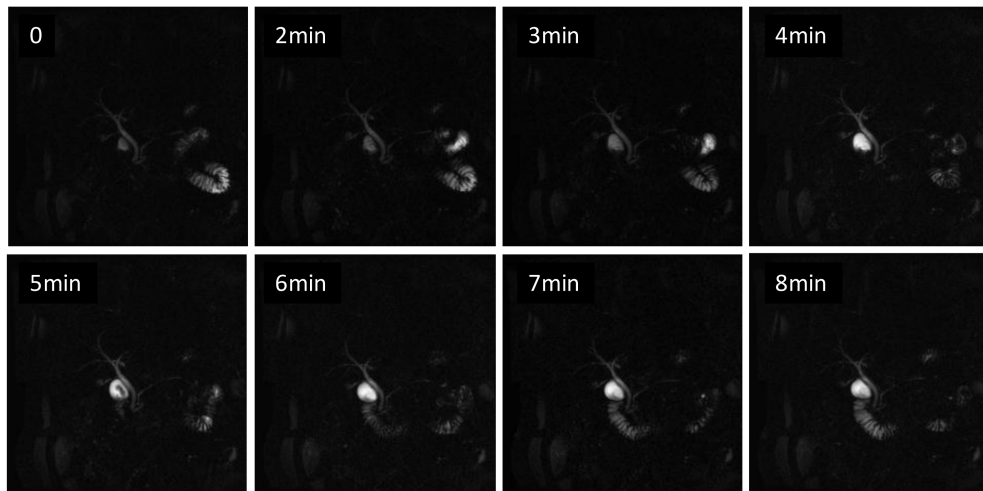
CECT, MRI, ERCP, and endoscopic ultrasound (EUS) are used to evaluate parenchymal and ductal abnormalities in the pancreas. CECT is readily available and used for the initial evaluation of CP and associated complications. Calcifications, atrophy, dilated main pancreatic duct, and mass-effect causing dilatation (tumor or mass) can be visualized in CECT (Kim and Pickhardt 2007). EUS has been considered sensitive in detecting minimal parenchymal changes, but its availability is limited, diagnostics is operator-dependent and poor correlation to histopathological CP has been reported (Trikudanathan et al. 2016). ERCP is best suited for ductal anatomy assessment, offering simultaneous therapeutic options, but should not be used solely to obtain a diagnosis of CP (Duggan et al. 2016). MRI is a non-invasive technique compared to EUS or ERCP and excellent in diagnosing pancreatic ductal variations accompanied with iv-administered secretin (Mariani et al. 2009; Thevenot et al. 2013). Complications associated with CP can also be visualized in MRI (Table 2). In secretin stimulated magnetic resonance cholangiopancreatography (S-MRCP), secretin increases the secretion of bicarbonate rich fluid from the pancreas but also acts on the biliary tree and sphincter of Oddi (transient tone increase) to a smaller extent, causing delayed emptying of the ducts, and thereby enhancing the visibility of the morphology of the main pancreatic duct and side branches (Choueiri et al. 2010; Balcı 2011). CECT or EUS have been reported to identify small calcifications better than MRI, but MRCP with secretin stimulation provides better visualization of ductal anatomy as well as information on pancreatic exocrine function (Figure 1) (Choueiri et al. 2010). Table 2 presents the most common chronic pancreatic changes that can be seen in S-MRCP (Table 2). The sensitivity of S-MRCP for early chronic pancreatitis has been reported to be 92%, the specificity 75%, and the diagnostic yield for mild CP is up to four-fold compared to that of MRCP without secretin stimulation (Zhang et al. 2003; Czako 2007; Testoni et al. 2009). S-MRCP findings correlate well with the histopathological findings of CP (Trikudanathan et al. 2015).

**Table 2.** Chronic changes and complications in the pancreas seen in S-MRCP

S-MRCP finding	Comment
Fibrosis* (and chronic inflammation)	Loss of normal high T1 signal (decreased amount of protein-rich fluid), decreased enhancement (loss of vascular supply)
Atrophy*	Diminished pancreas size/thickness, decreased enhancement
Pseudocysts	
Decreased ductal distension after secretin administration	Impaired duct compliance (early finding in CP)
Side branch dilatation	Due to fibrosis in side branch–main duct junction
Ductal abnormalities	Main duct dilatation, strictures, tortuousness, discontinuity, loss of normal tapering
Calcification	Poor identification in MRI (may be suspected when filling defects in the ducts is seen)
Exocrine response	Duodenal filling (grades 0-3)
Obstructive processes	Neoplasms (e.g. adenocarcinoma, MCN, IPMN), choledocholithiasis
Ductal anomalies	Pancreas divisum, pancreas annulare
Other complications	Pseudoaneurysm, fistula, vein thrombosis, biliary dilatation

MCN, mucinous cystic neoplasm; MRI, magnetic resonance imaging; IPMN, intraductal papillary mucinous neoplasm, S-MRCP, secretin stimulated magnetic resonance cholangiopancreatography

\*subtle changes may be associated with aging



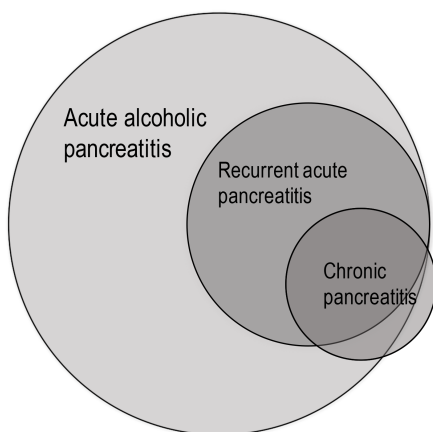
**Figure 1.** Normal secretin response in S-MRCP. Normal pancreatic duct dilatation is visible 4 minutes after secretin administration and then returns to normal size. Normal duodenal filling is detected

#### 1.5.2.4 Risk factors

Persistent alcohol consumption increases the risk for CP (Irving et al. 2009; Takeyama 2009) and CP mainly occurs in the setting of AAP rather than biliary AP (Lankisch et al. 2009). Smoking is a well known risk factor for CP (Lankisch et al. 2009; Yadav et al. 2012b) and increases the risk 2-fold according to a meta-analysis (Alsamarrai et al. 2014). Smoking also seems to accelerate the progression from AP to CP (Maisonneuve et al. 2005). These findings were validated in a meta-analysis (Sankaran et al. 2015) and a cumulative risk of alcohol consumption and smoking has been identified (Ahmed Ali et al. 2016). Cessation of smoking may delay the development of pancreatic calcifications (Talamini et al. 2007).

RAP is strongly associated with the development of CP (Yadav et al. 2012b; Bertilsson et al. 2015). In a recent meta-analysis of 14 studies, the rate for AP to progress to CP was 10% and the rate for progression in patients with RAP was 36% (Sankaran et al. 2015) (Figure 2). The risk of transition was greater in patients with heavy alcohol consumption and smoking.

Genetic factors may also predispose to CP, mutations in CFTR, CTRC, SPINK1, PRSS1, CLDN2 and CASR genes have been associated with developing CP after AAP (Sharer et al. 1998; Witt et al. 2000; Muddana et al. 2008; Rosendahl et al. 2008; Whitcomb et al. 2012). The same mutations probably predispose to RAP as well, but there is a lack of prospective studies to demonstrate the true meaning of genetic predisposition in progression of AAP.



**Figure 2.** RAP predisposes to CP, but in some patients CP may develop after first AAP or in rare cases be the first manifestation of the disease (modified from Yadav & Lowenfels, 2013)

## 1.6 Chronic morphological changes

Acute fluid collections and necrotic collections develop fairly early in the course of AP. Acute fluid collections are detected in a third of patients during first AP and are associated with necrosis and more severe disease (Lankisch et al. 2012). Within three months they usually either disappear or present as pseudocysts in about a fourth of those patients who initially had acute fluid collections (Lankisch et al. 2012).

Pseudocysts are considered a late complication of the acute disease and may be associated with CP. After AP it usually takes over four weeks from disease onset for a pseudocyst to develop. They are defined having well defined and circumscribed granulation tissue wall, homogenous fluid with amylase activity and are considered to develop from leakage of pancreatic juice from the pancreatic ductal system to the surrounding tissues (Klöppel and Maillet 1993; Banks et al. 2013). Persistent pseudocysts are associated with alcohol etiology of AP and more severe disease and are seen in 10-30% of patients in one to two years after AP (Pelli et al. 2009; Lankisch et al. 2012). In long-lasting alcoholic CP pseudocysts are seen in about half of patients in autopsy (Ammann et al. 1996). The preferred treatment for pseudocysts is endoscopic transpapillary or transmural drainage and stent placement (Weckman et al. 2006). Small, asymptomatic pseudocysts do not require drainage or follow-up (Lankisch et al. 2012).

Dilatation of the main pancreatic duct and side branches are early signs of CP. Other ductal changes, such as strictures and calculi, develop later in the course of the disease (Sarner and Cotton 1984; Choueiri et al. 2010).

Unevenly located fibrosis containing inflammatory cells is a common early feature in CP (Klöppel and Maillet 1993). In advanced CP, fibrous inflammatory tissue spreads, the pancreatic ducts become distorted and atrophy of the pancreas develops (Klöppel and Maillet 1993). Fibrosis in the head of the pancreas may obstruct bile and pancreatic juice flow to the duodenum or even cause duodenal obstruction, thus complicating endoscopic treatment (Klöppel 2007). In autopsy study fibrosis was detected in 68% of CP patients' pancreas and its presence was correlated to pancreatic dysfunction (diabetes and low fecal chymotrypsin) (Ammann et al. 1996). Aging is associated with reduction in the size of the pancreas, but more rapid atrophy is associated with CP (Hansen et al. 2013).

Pancreatic calcifications are commonly associated with CP (specificity of 67-100% depending on the location) but may also be detected in patients with pancreatic tumors or cystic changes (Campisi et al. 2009). These gradually develop

during the course of the disease (after 14 years in up to 80-91%) and develop earlier in alcoholic CP than in other forms (Layer et al. 1994; Müllhaupt et al. 2005). In autopsy calcifications are seen in over 70% of patients with long-lasting (mean of 12 years) alcoholic CP (Ammann et al. 1996).

Morphological changes seen in advanced CP are known, but their development after initial AP has scarcely been studied. In the only available study, overall one half of the patients with AAP were found to have developed chronic changes in the pancreas in S-MCRP during a two-year follow-up (Pelli et al. 2009).

## 1.7 Pancreatic dysfunction

Pancreatic endocrine dysfunction ranges from minor hyperglycemia associated with impaired glucose tolerance (IGT) and early type 2 diabetes mellitus (T2DM) to severe hyperglycemia and life-threatening ketone-acidosis and inability to transport glucose into the cells due to insulin deficit (Arkkila and Gautier 2003).

Diabetes is a disease group characterized by chronic hyperglycemia. In type 1 diabetes mellitus (T1DM) pancreatic  $\beta$ -cells are destroyed in an autoimmune process causing absolute insulin deficiency. It accounts for 5-10% of diabetes cases. T2DM is characterized by relative insulin deficiency and insulin resistance. It is typically part of metabolic syndrome. T2DM accounts for 90-95% cases with diabetes (American Diabetes Association 2014).

There is controversy over the development of pancreatic dysfunction after AP. Many studies include patients with different etiologies and severities. More studies focus on patients with severe (necrotizing) AP or patients treated with surgery. Follow-up times are often short and the criteria for pancreatic dysfunction, CP, RAP and severity of AP differ. Diagnostic tests for pancreatic dysfunction likewise differ and the type of the new diabetes is rarely if ever classified.

### 1.7.1 Endocrine dysfunction

According to various studies, diabetes after AP develops in 5-54% of patients (Table 3) and much higher percentages have been reported, especially in patients with necrotizing AP treated with necrosectomy. New prediabetes or IGT develops to 5-44% of patients according to different studies (Table 3).

Recently Das and colleagues conducted a systematic review and meta-analysis of 24 prospective studies on pancreatic function after AP (Das et al. 2014b). They found that new diabetes mellitus (DM) develops in 23% and new prediabetes in 16% of patients after AP. In total 37% of patients develop either DM or prediabetes. Severity of AP, etiology, patient's age or gender were not associated with risk of developing endocrine pancreatic dysfunction.

The percentage of patients with CP developing DM may be up to 46-83% (Ammann et al. 1996; Malka et al. 2000; Wang et al. 2011; Pan et al. 2016). In a Danish retrospective follow-up study patients with CP were at 5-fold risk of diabetes compared to the controls (Bang et al. 2014). By comparison, after partial pancreatic resection (pancreaticoduodenectomy or distal pancreatectomy) new diabetes has been shown to develop in 18-31% depending on the procedure (Burkhart et al. 2015).



**Table 3.** Development of pancreatic dysfunction after acute pancreatitis in long-term follow-up studies

Reference	N	D (y)	Endocrine insufficiency		Exocrine insufficiency	Etiology			Severity			
			Diabetes	Prediabetes or IGT		Alcohol	Biliary	Other	Mild	Mode rate	Severe	Operated
Andersson et al. 2010	40	3.5	23% (40% in AAP)	33%	3% (FE-1)	25%	50%	25%	65%		35%	
Appelros et al. 2001*	35	7	42%	11%	26% (method N/A)	N/A					100%	
Doepel et al. 1993	37	6.2	54% (88% in AAP)		N/A	76%	8%	16%			100%	100%**
Eriksson et al. 1992	36	6.2	53%	11%	N/A	78%	6%	16%	44%		56%	36%
Gupta et al. 2009	30	2.6	20%	20%	40% (FFE)	33%	40%	27%	100%		100%	25%
Halonen et al. 2003*	145	5.5	43%		N/A	78%	22%				100%	
Ho et al. 2015*	12284	1-9	5% (7% in AAP)		46% (49% in AAP) (ES)	47%	53%		94%		6%	
Malecka-Panas et al. (2002)	82	4.7	16% (36% DM/IGT in AAP)	5%	N/A	44%	35%	21%	66%		34%	
Pelli et al. 2009	54	2	11%	26%	9% (FE-1)	100%			75%		25%	
Symersky et al. 2006	34	4.6	N/A	35%	65% (FFE/u-PABAr)		76%	24%	65%		35%	
Takeyama et al. 2009	714	13	13% (21% in AAP)		N/A	39%	17%	44%	56%			
Tsiotos et al. 1998	44	5	36%		14% (FFE)	11%	39%	50%			100%#	
Uomo et al. 2010	40	15	16%		0% (FE-1)		70%	30%			100%	
Vujasinovic et al. 2014	100	2.7	14%		21% (31% in AAP) (FE-1)	42%	36%	22%	67%	15%	18%	
Winter Gasparoto et al. 2015	16	2.9	31%	44%	6% (FFE)	25%	63%	12%			100%	13%
Xu et al. 2012	65	2.4	N/A		59% (FE-1)	11%	77%	12%	42%		58%	8%
Yasuda et al. 2008	45	4.6	39%		N/A	51%	22%	27%			100%	

N, number of patients; D, duration of follow-up in years; AAP, acute alcoholic pancreatitis; ES, enzyme supplementation; FE-1, fecal elastase 1; FFE, fecal fat excretion; IGT, impaired glucose tolerance; N/A, not applicable; u-PABAr, urinary 4-aminobenzoic acid recovery

\*Retrospective follow-up, \*\*Peritoneal lavage, #Severe, necrotizing

## 1.7.2 Pancreatogenic diabetes

Pancreatogenic diabetes or type 3c diabetes mellitus (T3cDM) or secondary diabetes is classified as resulting from diseases of the exocrine pancreas by the American Diabetes Association (ADA) and World Health Organization (WHO) (Alberti and Zimmet 1998; World Health Organization (WHO) Consultation 2006; American Diabetes Association 2014). Most typically it results from pancreatitis, but may also result from pancreatic tumors, trauma, pancreatic surgery, certain viral infections (e.g. congenital rubella, coxsackievirus B, cytomegalovirus) or any other reason causing pancreatic damage (American Diabetes Association 2014). CP accounts for 80-85% of pancreatogenic diabetes and pancreatic cancer accounts for 8-15% (Price et al. 2010; Ewald et al. 2012).

The prevalence of pancreatogenic diabetes is estimated to be up to 5-10% in patients with DM (Cui and Andersen 2011). Ewald and colleagues reclassified 1,868 patients with diagnosed DM treated in a tertiary center and found a prevalence of 9.2% for pancreatogenic diabetes and that it was commonly misclassified as T2DM (Ewald et al. 2012).

The proposed diagnostic criteria for pancreatogenic diabetes were introduced only recently and are presented in Table 4 (Ewald and Bretzel 2013). For the diagnosis of pancreatogenic diabetes all major criteria must be present.

The development of pancreatogenic diabetes is a complex process and the clinical picture may be complicated due to underlying disease and pancreatic exocrine insufficiency (PEI). There is no prospective data on the development of pancreatogenic diabetes after AP. The exact pathophysiology of the disease is not known and it differs from T1DM and T2DM. In its extreme (e.g. long-lasting CP or after total pancreatectomy), pancreatogenic diabetes is often termed “brittle diabetes” due to the destruction or malfunction of both pancreatic  $\alpha$ - and  $\beta$ -cells. This in turn leads to persistent hyperglycemia resulting from unsuppressed hepatic glucose production (decreased hepatic insulin sensitivity due to decreased pancreatic polypeptide regulation of insulin receptors), exaggerated peripheral insulin sensitivity and blunted glucagon response to hypoglycemia (Slezak and Andersen 2001; Cui and Andersen 2011). While the loss of pancreatic parenchyma due to necrosis leads to DM, most patients presenting with DM after AP may not have necrosis or have only minimal necrosis, which may implicate mechanisms

other than necrosis, e.g. inflammation, in the development of pancreatogenic diabetes (Das et al. 2014b).

**Table 4.** Proposed diagnostic criteria for pancreatogenic diabetes (Ewald & Bretzel, 2013)

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<b>Major criteria</b>
Pancreatic exocrine insufficiency
Pathological pancreatic imaging findings
Absence of autoimmune markers associated with type 1 diabetes mellitus
<b>Minor criteria</b>
Impaired incretin secretion (e.g. GLP-1, pancreatic polypeptide)
No excessive insulin resistance (e.g. HOMA-IR)
Impaired pancreatic $\beta$ -cell function (e.g. HOMA-B, C-peptide/glucose ratio)
Low serum levels of lipid soluble vitamins (A, D, E and K)

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GLP-1, glucagon-like peptide-1; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA-B, homeostatic model assessment for  $\beta$ -cell function

### 1.7.3 Exocrine dysfunction

Pancreatic exocrine insufficiency (PEI) refers to diminished or absent intestinal intraluminal availability of pancreatic enzymes, clinically presenting as steatorrhea, diarrhea, malnutrition, and weight loss in advanced stages. Pancreatic parenchymal destruction in CP is the most common cause of PEI, but it may also result from various other reasons like cystic fibrosis, pancreatic tumors, surgical procedures (e.g. gastrectomy) or diabetes (Keller and Layer 2005). In CP the clinical symptoms of PEI usually take over 10 years to develop (Löhr et al. 2013) and it has been traditionally considered that steatorrhea does not develop until pancreatic lipase secretion is reduced to <10% of normal, but it decreases more rapidly than protease secretion (DiMagno et al. 1973).

Fecal elastase 1 (FE-1) test has become the first-line test of choice for diagnosing PEI with high sensitivity and specificity (93% and 93% respectively) for moderate to severe PEI, while being simple and non-invasive (Löser et al. 1996; Leeds et al. 2011). Elastase-1 is a proteolytic pancreatic enzyme accounting for about 6% of pancreatic enzyme secretion. It is not degraded in the intestine and FE-1 measurement correlates well with pancreatic enzyme secretion (amylase, lipase and trypsin) (Stein et al. 1996). Other tests like fecal fat quantification or  $^{13}\text{C}$ -mixed triglycerides breath test may yield more reliable results in mild or moderate PEI, but are not widely used (Lindkvist 2013). Dilatation response and duodenal filling in S-MRCP have shown correlation with the exocrine reserve of the

pancreas, but are not used in clinical practice to detect exocrine dysfunction (Schneider et al. 2006; Balci et al. 2010; Manfredi et al. 2012). Secretin-cerulein test was considered a gold standard for detecting PEI due to its direct nature, but it is time-consuming, invasive, due to duodenal tube aspiration of pancreatic fluid, and not routinely available (Lindkvist 2013).

While endocrine pancreatic function typically deteriorates after AP, exocrine function usually improves during and shortly after the convalescence period (Sand and Nordback 2009). In a previous Finnish prospective study, the prevalence of PEI as determined by persistently low FE-1, decreased from 39% to 9% in two years of follow-up after AAP (Pelli et al. 2009).

Again, the development of PEI varies between different studies depending on diagnostic tests and characteristics of study populations. In long-term follow-up studies 0% to 65% of patients reportedly develop PEI (Table 3).

## 1.8 Understanding the natural history and treatment of pancreatitis

The incidence of AP is rising and high recurrence rates after first AAP have been reported (Pelli et al. 2000; Peery et al. 2012). Since the pathogenesis of AP, RAP and CP is complex and poorly understood, the possible treatment strategies are mainly supportive and preventative, aiming to reduce the impact of risk factors to prevent disease progression. Various guidelines for treatment of AP have been developed, but no specific recommendations for any follow-up protocols or treatment of alcohol problem itself in AAP have been presented in any of these reports (UK Working Party on Acute Pancreatitis 2005; Banks and Freeman 2006; Sekimoto et al. 2006; Forsmark and Baillie 2007; Tenner et al. 2013; Working Group IAP/APA Acute Pancreatitis Guidelines 2013). Preventative efforts are mentioned in only one guideline (Forsmark and Baillie 2007).

Alcohol problems may create severe morbidity, mortality, economic losses and social deprivation. Efforts to reduce alcohol consumption and raise awareness of alcohol related diseases are the key in decreasing health-care costs and improving the quality of life of patients and their significant others (World Health Organization 2014; Connor et al. 2016). A severe disease – such as AAP – may be taken as a good opportunity to intervene and change the direction of life (Nordback et al. 2009; Lappalainen-Lehto et al. 2013).

Follow-up times in the available clinical studies on AP are limited and studies have not adjusted for different variables. Even though complications in advanced CP are known, long-term studies to adequately determine the progression of AP are lacking. Good clinical studies may help to shed light on the grey area between AP and CP and to understand the mechanisms involved in the development of pancreatic dysfunction, RAP and CP from a clinical perspective.

## 2 Aims of the study

The aim of this academic doctoral dissertation was to investigate the natural course of pancreatic function and morphology after the first episode of AAP, and the prevention of recurrent attacks of the disease. The specific aims were to study:

- I. The long-term development of pancreatic morphological changes seen in S-MRCP after first AAP and risk factors for chronic changes.
- II. The long-term effects of an episode of AAP on pancreatic function and risk factors for pancreatic dysfunction.
- III. The impact of alcohol abstinence on the recurrence of AAP and development of pancreatic dysfunction.
- IV. The current status of brief interventions provided to patients during hospitalization for AAP and RAP and the impact of in-hospital brief interventions on disease recurrence.

## 3 Materials and methods

### 3.1 Studies I-III

#### 3.1.1 Study population

The patient cohort for Studies I-III was originally registered prospectively as a part of a randomized controlled trial (RCT), where patients were randomized to receive alcohol interventions either at initial hospitalization only (n=61) or repeated alcohol interventions at six month-intervals (n=59). The results from the RCT with a two-year follow-up were published in 2009 (Nordback et al., 2009). Thereafter the patients continued within a prospective follow-up until December 31, 2013.

Out of the 120 patients suffering their first attack of AAP between January 2001 and March 2005 originally recruited for the prospective follow-up study, six were later excluded due to detection of another AP etiology (n=3) or earlier AAP episode. Thus the final study population consisted of 114 patients.

#### 3.1.2 Follow-up protocol

Details of the first AAP and patient characteristics were registered prospectively. The prospective follow-up consisted of repeated interviews, laboratory tests and S-MRCP studies. Interviews were conducted by a study nurse, who also sent the patients invitations to participate in the laboratory and imaging studies. Interviews and laboratory studies took place annually for the first five years and at two-year intervals thereafter.

During the follow-up interviews alcohol consumption, smoking habits and BMI were studied. Electronic medical records were reviewed for clinical course, readmissions, imaging study reports, laboratory tests (also tests ordered by primary care physicians), histology reports, surgical reports, and mortality. RAP episodes were diagnosed using the same criteria as for the first AAP. Causes of death were obtained from Statistics Finland.

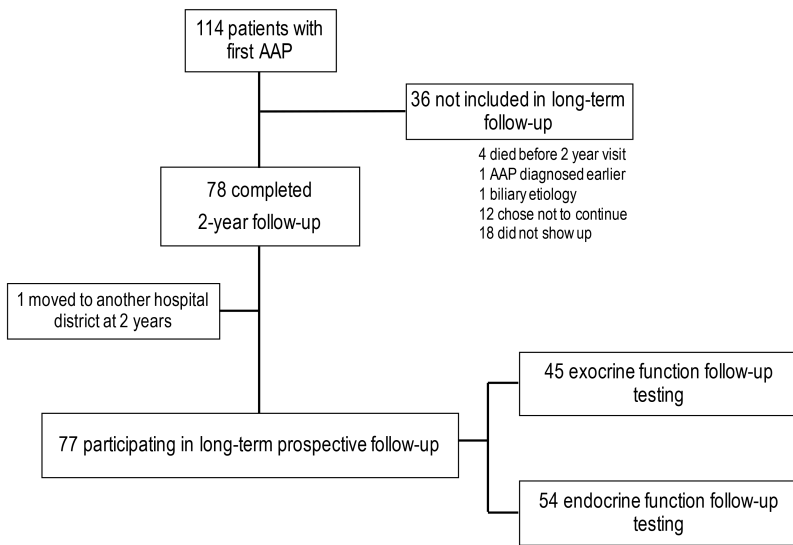
Persistent heavy alcohol consumption was suspected if a patient reported heavy alcohol consumption from the preceding 2 months (converted into drinks/week; in men  $\geq 24$  drinks/week, and in women  $\geq 16$  drinks/week) at any time point during follow-up.

I) Forty-four of the patients initially recruited volunteered to take part in the S-MRCP follow-up arm of the study. It was agreed to evaluate pancreatic morphology with S-MRCP at 3 months, and at 2, 7, and 9 years after hospitalization.

II) To study pancreatic function after AAP, all patients who participated in the prospective follow-up for at least for two years were included in Study II for further analysis. One of these patients moved to another hospital district at two years and was thus excluded from long-term follow-up, which included 77 patients in total (Figure 3). Endocrine and exocrine function were evaluated more closely in 54 and 45 patients respectively as described in flow-chart in Figure 3. Follow-up covered 460 and 397 patient-years for endo- and exocrine pancreatic function respectively.

III) In Study III, 18 patients who managed to maintain abstinence for at least one and a half years after first AAP were included in the follow-up. Abstinence was determined as self-reported alcohol consumption of  $< 24$  grams per month for the preceding two months, AUDIT points  $< 8$  and SADD points  $< 9$ . Laboratory markers indicating high alcohol consumption were also evaluated (CDT,  $\gamma$ -glutamyl transferase and red blood cell corpuscular volume).





**Figure 3.** Flow-chart of patients included in the follow-up program for detailed testing for pancreatic function (Study II)

### 3.1.3 Diagnosis and classification of AAP

AP was diagnosed when a patient met at least two out of the three diagnostic criteria: (1) typical abdominal pain, (2) serum amylase >3 times the upper limit of normal, (3) characteristic findings for AP from abdominal imaging studies. Alcohol etiology was determined when a patient or family members reported and/or the AUDIT test indicated heavy alcohol consumption. Other etiologies were excluded by history, transabdominal US, CECT or MRI, liver chemistry and serum calcium and lipid measurements. Patients with previous episodes or symptoms of pancreatitis or signs indicative of CP were excluded from the study.

The updated Atlanta criteria were published in 2013 (Banks et al. 2013), thus the severity of AAP in the patients in Studies I and II was retrospectively reassessed using the updated version. In Study III the original version was used (Bradley 1993).

### 3.1.4 Laboratory tests

Fasting plasma glucose (FPG, normal range 3.9-5.5 mmol/l) and plasma glycosylated hemoglobin A1C (HbA1c, normal value <5.7% or <39 mmol/l) were used to measure the endocrine function of the pancreas. Oral glucose tolerance test (OGTT, normal 2h value <7.8 mmol/l) was performed for non-diabetic patients, later accompanied by glucagon C-peptide test (normal rise in 6 min value >0.90 nmol/l compared to baseline) if patient did not refuse. Exocrine pancreatic function was measured using FE-1 concentration (normal value >200 µg/g or >150 µg/g in study III) and plasma concentrations of vitamins A (normal range 1-3 µmol/l for adults) and E (normal range 12-42 µmol/l for adults).

### 3.1.5 Diagnosis and criteria for pancreatic dysfunction and CP

Diagnosis of diabetes was based on a 2-hour glucose value  $\geq 11.1$  mmol/l in OGTT, an HbA1c value  $\geq 6.5\%$ , or FPG  $\geq 7.0$  mmol/l according to ADA and WHO criteria (World Health Organization (WHO) Consultation 2006; American Diabetes Association 2014). T2DM was diagnosed in diabetic patients who had normal or elevated fasting C-peptide levels and BMI  $\geq 30$  kg/m<sup>2</sup>.

A diagnosis of pancreatogenic diabetes was considered when the patient had (1) diagnosed diabetes, (2) morphological chronic changes in pancreatic imaging studies, and (3) exocrine insufficiency (persistently low FE-1 values <200 µg/g). In cases of missing FE-1, the diagnosis of pancreatogenic diabetes was based on the clinical picture of diabetes (obvious problems with glycemic control necessitating emergency department visits, steatorrhea, and the need for insulin therapy), together with tests indicating impaired  $\beta$ -cell function (glucagon C-peptide test) and nutritional deficiencies (low serum lipid-soluble vitamins A and E).

Prediabetes was diagnosed when 2-hour plasma glucose was  $\geq 7.8$  mmol/l and <11.1 mmol/l in OGTT (impaired glucose tolerance), FPG 5.6 to 6.9 mmol/l (impaired fasting glucose), or HbA1c 5.7% to 6.4% (American Diabetes Association 2014).

Exocrine dysfunction was categorized as a persistently low FE-1 (<200 µg/g or <150 µg/g in study III) value during follow-up.

A patient was diagnosed with CP according to M-ANNHEIM criteria (Schneider et al. 2007) when a typical clinical picture was combined with findings associated with CP in the imaging studies, findings indicating pancreatic dysfunction and a need for pancreatic enzyme replacement therapy.

### 3.1.6 Morphological changes and imaging modalities

S-MRCP studies conducted according to the study plan were assessed by the same experienced radiologist, who was unaware of patients' clinical details.

The MRI modality used was 1.5 T Signa Horizon (GE Medical Systems, Milwaukee, WI, USA) with a phased-array torso coil. Fat-saturated T2-weighted Fast Spin Echo and T1-weighted Spin Echo sequences were first obtained in the axial plane to assess the position and morphology of the pancreas, followed by the heavily T2-weighted fat-saturated Single Shot Fast Spin Echo MRCP sequence in the coronal plane obtained radially at 15° intervals, without and repeatedly at 1-min. intervals up to 9 min from the injection of 100 IU secretin pentahydrochloride (Secrelux; Sanochemia Diagnostics, Neuss, Germany).

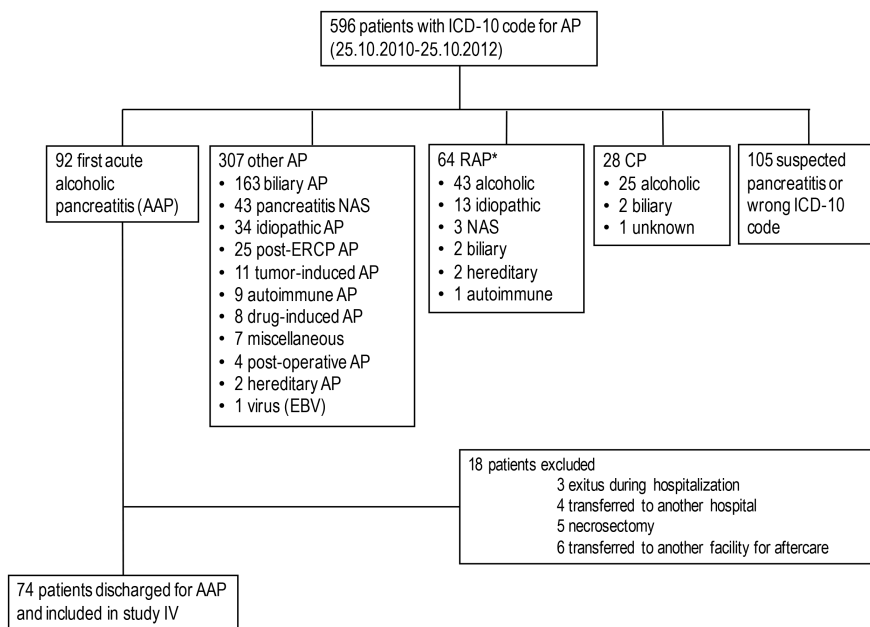
Pancreatic morphology was classified as normal, including acute changes or including chronic changes. Acute changes included pancreatic or peripancreatic edema. Chronic changes included abnormal secretin response (poor constriction or poor dilatation for secretin), pancreatic cyst, strictures, parenchymal changes, calcifications and atrophy. Parenchymal changes were noted when there was a diffuse decrease in signal intensity in T1-weighted images. The pancreatic parenchyma signal was compared to the signal of the spleen or peripheral muscles. Another criterion for parenchymal changes was the presence of segmental dimensional changes without general parenchymal atrophy. Changes in glandular shape were also interpreted as a parenchymal change.

## 3.2 Study IV

### 3.2.1 Study population

To study brief interventions (BIs) provided during hospitalization for AAP and RAP patients treated in Pirkanmaa Hospital District, Tampere, Finland, all primary diagnosis codes for acute pancreatitis (ICD-10 code K85) were obtained retrospectively from hospital databases for the time period October 25<sup>th</sup> 2010 to October 25<sup>th</sup> 2012. Overall 596 patients with the discharge code were obtained. Electronic medical records were thoroughly studied and only patients suffering their first episode of AAP were included for further analysis. Figure 4 presents patient selection for Study IV. The most common etiology for first AP was biliary

(41%) and the second was alcohol (23%), RAP was most commonly associated with alcohol etiology (67%) (Figure 4). Diagnosis and severity assessment of AP was performed using the same principles as for Studies I-III. Patients who had been operated on during first AAP and patients transferred to another hospital or facility for treatment or aftercare (and were not able to receive BIs in the study hospitals) were excluded from the study. Most patients were treated in Tampere University Hospital, a tertiary referral center, but the hospital district also included two smaller regional hospitals (Valkeakoski and Vammala hospitals). If other etiologies had not been excluded and alcohol use was not verified, AP was categorized as “not further specified”.



**Figure 4.** Flow-chart of patient selection in Study IV. \*First AP prior to 25.10.2010. AAP, acute alcoholic pancreatitis; AP, acute pancreatitis; CP, chronic pancreatitis; EBV, Epstein-Barr virus; ERCP, endoscopic retrograde cholangiopancreatography; NAS, non aliter specificatus; RAP, recurrent acute pancreatitis

### 3.2.2 Follow-up methods

Development of RAP and CP were evaluated from electronic medical records using the criteria described above and follow-up extended up to February 20<sup>th</sup> 2016.

All medical records were thoroughly evaluated and recorded BIs performed during hospitalization for initial AAP and first RAP episode studied. We studied whether BI was provided by doctor, nurse or social worker. AUDIT points and smoking status were also registered. Discharge papers were evaluated for recommendations regarding alcohol abuse, follow-up visits or counseling.

A study questionnaire was sent to patients with a valid Finnish mail address. Patients were asked about BIs during their initial hospitalization, their goals for alcohol consumption after hospital discharge and if they had succeeded in achieving those goals, information received on AAP in total, overall help received in reducing substance abuse, planned follow-up visits and substance abuse treatment services.

### 3.3 Statistics

In the univariate analysis, Fisher's exact test (I-IV),  $\chi^2$  test (I-IV), Student's t-test (IV) and binary logistic regression analysis (I, II, IV) were used for bivariate comparisons.

In Studies II and IV the Kaplan-Meier methodology was used to calculate cumulative incidences and the log-rank test to compare the risk between groups. Significant variables were included in the multivariate analysis, which were performed using Cox regression or logistic regression analysis.

In Study IV, McNemar's test was used to compare RAP patients' BIs during initial and first RAP hospitalization and a receiver operating characteristic (ROC) analysis was performed to calculate the area under the curve (AUC) for the AUDIT test to predict RAP. Sensitivity and specificity were determined using the Youden index.

P-values <0.05 were considered to be statistically significant. Statistical testing was performed using SPSS (version 21; IBM Corporation, Armonk, NY).

### 3.4 Descriptive data on patients

Demographics of patients included in Studies I-IV are presented in Table 5.

**Table 5.** Descriptives of patients in Studies I-IV during initial hospitalization of first AAP

	<b>Study I</b>	<b>Study II</b>	<b>Study III</b>	<b>Study IV</b>
Number of patients	44	77	18	74
Male	41 (93%)	69 (90%)	18 (100%)	70 (95%)
Age at entry, years	47 (25-68)	48 (25-71)	47 (27-71)	48 (20-70)
Smokers	30 (68%)	48 (62%)	11 (61%)	36 (49%)
Smoking, cigarettes/day*	10 (2-50)	20 (2-50)	16 (6-23)	
Heavy smokers (≥20/day)	14 (32%)	27 (35%)	6 (33%)	
BMI	27.8 (21-35)	27.7 (19-38)	30.1 (24-35)	
Obesity (BMI ≥30)	12 (37%)	21 (27%)	10 (56%)	
DM before	5 (11%)	5 (6%)	2 (11%)	
DM during hospitalization	3 (7%**)	4 (6%**)	1 (6%**)	
Self-estimated alcohol intake (grams / two months)	2880 (768-11425)	3216 (288-15456)	4320 (768-9216)	
Heavy alcohol consumption (self-reported)#	25 (58%)	70 (92%)	12 (71%)	
AUDIT	20 (5-32)	21 (5-38)	22 (7-37)	19 (5-38)
SADD	14 (0-33)	12 (0-36)	15 (1-31)	
Severity##				
Mild	29 (66%)	53 (69%)	17 (94%)	48 (65%)
Moderate	11 (25%)	20 (26%)		22 (30%)
Severe	4 (10%)	4 (5%)	1 (6%)	4 (5%)
Hospital stay, days	7 (3-41)	7 (2-30)	9 (4-41)	6 (2-49)
Needed surgery	0	0	0	0

AAP, acute alcoholic pancreatitis; AUDIT, Alcohol Use Disorders Identification Test; BMI, body mass index; SADD, Short Alcohol Dependence Data

Data given in numbers (%) or median (range)

\*Of smokers

\*\*Diabetes diagnosed before excluded

#In males ≥24 drinks / week, in females ≥16 drinks / week (calculated from self-reported alcohol intake per two months)

##According to the original (Study III) or revised Atlanta criteria (Studies I, II and IV)

### 3.5 Ethical aspects

Studies I-IV were approved by the ethics committee of Tampere University Hospital (R00126 (I-III) and R13167 (IV)). All patients approved attendance by providing informed consent.

## 4 Results

### 4.1 Pancreatic morphology and dysfunction after first episode of AAP

#### 4.1.1 Morphology (I)

In Study I, out of the 44 patients who underwent baseline S-MRCP, 36 patients attended the long-term follow-up to study the development of chronic pancreatic changes. Chronic morphological changes were detected in 47% of patients who participated in S-MRCP at seven years. The most typical chronic findings were pseudocyst (in 36%), parenchymal changes (in 28%) and atrophy (in 28%). Pancreatic morphology at different time-points is presented in Figure 5. There were no new changes in the pancreas in the attending patients between 7 and 9 years. Chronic changes detected in baseline S-MRCP would show in later imaging studies.

Seventy-five per cent of the patients with severe first attack and 86% of the patients with moderate first attack had chronic changes at seven years. Patients with mild first attack had fewer chronic changes in S-MRCP at seven years than did patients with moderate and moderate and severe first attack together (32% vs. 86% and 82%,  $p=0.03$  and  $p=0.01$ ). Severity of initial attack was not statistically significantly associated with the development of new chronic changes during follow-up.

Of the patients with only acute findings at 3 months, 60% resolved to normal in 7 years, but the rest (40%) showed chronic changes later on and half of these patients had RAP ( $p=0.044$ ). Figure 6 describes the case of a patient who had only acute imaging findings at baseline, but after suffering a RAP episode, chronic changes (pseudocyst and atrophy) developed.

RAP developed in 22% of the patients (mean 22 (2-60) months from the initial attack). Patients with RAP episodes had significantly more often chronic S-MRCP changes in the pancreas compared to non-RAP patients (88% vs. 36%,  $p<0.02$ ). New chronic changes developed in 39% of the patients; in 86% of patients with

RAP and in 28% of patients without RAP (OR=15.8, 95% CI 1.6-152,  $p=0.017$ ) and the result remained in the multivariate analysis (adjusted for smoking, sex and severity of initial attack).

Four patients were diagnosed with clinical CP and all had previous RAP episode or episodes. New chronic findings in follow-up were detected in all CP patients and three out of these four patients were smokers.

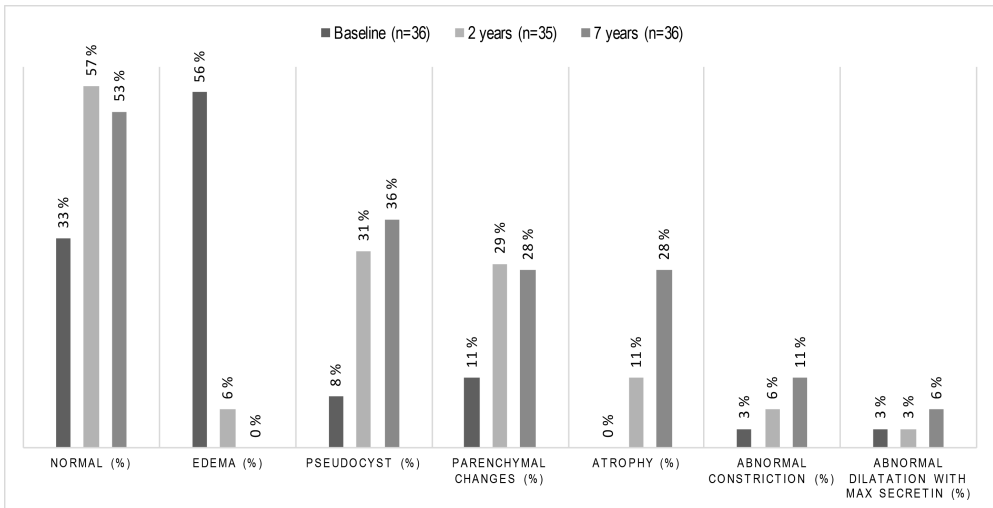
Smoking and obesity were not significantly associated with development of chronic morphological changes. Almost 70% of all the patients were smokers: 83% (5/6) of the patients who initially had only acute findings but later developed chronic findings were smokers, but there was no statistically significant difference from non-smokers.

Six patients maintained abstinence through follow-up (mean 8.7 (7-9.1) years). One of these patients (17%) developed pancreatic atrophy at the age of 63, the rest did not develop new chronic changes and of the non-abstinent patients without RAP, 18% (4/22) developed new chronic changes.

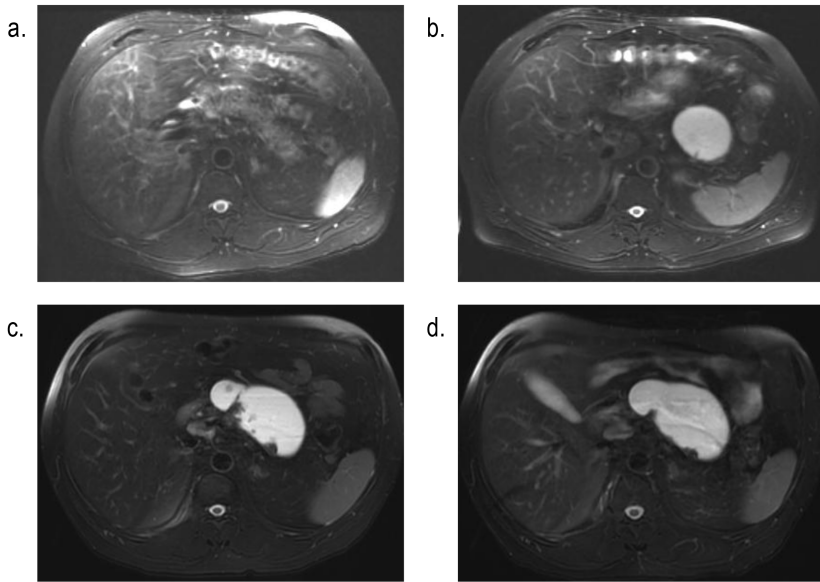
There were three patients in the S-MRCP study who developed new pancreatogenic diabetes (Study II). All these patients had pseudocyst(s), parenchymal changes, atrophy and abnormal constriction to secretin in seventh year S-MRCP. T2DM was not associated with increased chronic morphological changes.

Of the patients who participated in endocrine pancreatic function follow-up (Study II) and had new abnormal endocrine function (prediabetes or diabetes), 47% (7/15) had chronic changes in seventh year S-MRCP compared to 13% (1/12) in patients with normal endocrine function ( $p=0.038$ ). Of the patients with PEI in Study II, 88% (7/8) had abnormal S-MRCP at seven years compared to 20% (5/25) with normal exocrine function ( $p=0.001$ ).





**Figure 5.** S-MRCP imaging findings at baseline, 2 years and 7 years in patients who participated in long-term follow-up



**Figure 6.** Follow-up images of a patient with mild first AAP with one RAP episode at 19 months. Fat saturated T2-weighted FSE images in axial plane at 3 months (a) shows acute inflammation and edema in peripancreatic tissue. At 2 years (b), 7 years (c) and 9 years (d), a large pseudocyst is seen accompanying general parenchymal atrophy

## 4.1.2 Pancreatic function (II)

In Study II, changes in pancreatic function after first AAP and risk factors for dysfunction were evaluated in 77 patients who participated in long-term follow-up (Figure 3). Development of new diabetes and CP and risk factors were studied in the whole patient cohort. DM was diagnosed prior to first AAP in 6% and during hospitalization in 6% of patients.

During a median follow-up of 10.5 (3.1-12.9) years RAP developed in 35% and CP was diagnosed in 12% of the patients. The first RAP episode developed at a median of 2.2 (0.1-10.4) years after initial AAP and 74% of first RAP episodes occurred during the first four years. The first RAP episode was mild in 70% and moderate in 30%.

New DM developed in 34% of the patients. Pancreatogenic diabetes developed in 19% (13/68) of the non-diabetic patients and only in patients who had suffered previous RAP episode or episodes (OR 39, 95% CI 4.6-327.1, vs. non-RAP patients, Table 6). T2DM developed in 15% and was associated with obesity (OR=5.9; 95% CI, 1.2-27.9, for BMI  $\geq$ 30). Cumulative development of diabetes is presented in Figure 7.

A regression analysis of the possible effect of different risk factors for pancreatogenic diabetes is presented in Table 6. In univariate and multivariate analysis, RAP was significantly associated with developing new pancreatogenic diabetes. Pancreatogenic diabetes was diagnosed in a median of 1.9 (0.3-6.7) years after the first RAP and 4.3 (1.9-10.2) years after the first AAP.

**Table 6.** Risk factors for pancreatogenic diabetes

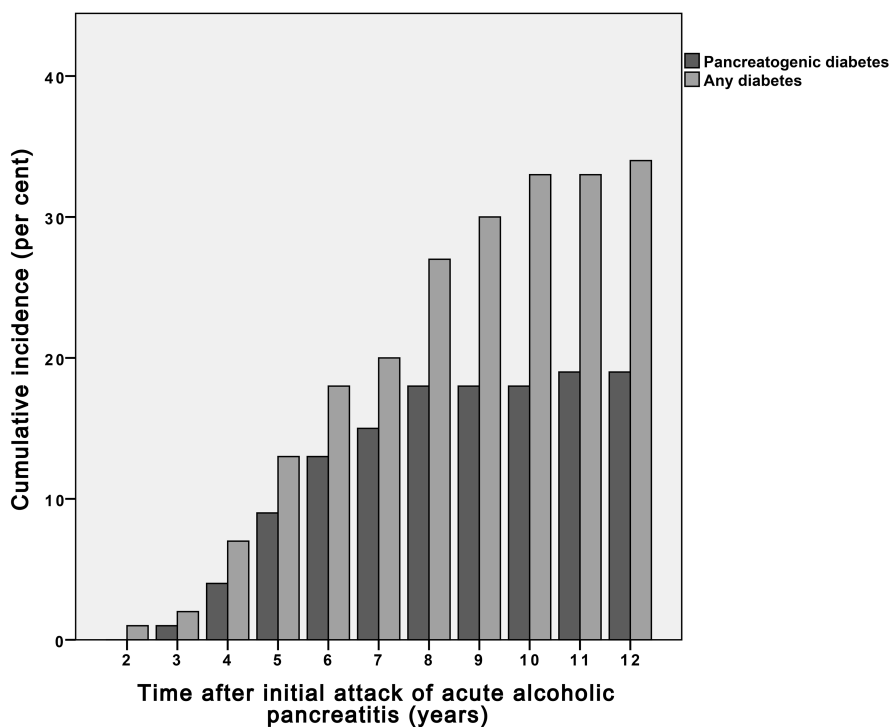
	Pancreatogenic diabetes n = 13	No pancreatogenic diabetes n = 55	OR	95% CI	P-value
RAP	13 (100%)	13 (24%)	39*	4.6-327.1	<0.001
Smoking	7 (54%)	34 (62%)	0.7	0.2-2.4	0.60
Heavy smoking	6 (46%)	15 (27%)	2.3	0.7-7.9	0.19
Obesity (BMI ≥30)	2 (15%)	16 (29%)	0.4	0.1-2.2	0.32
Severity of initial attack			0.5	0.2-1.9	0.35
Mild	8 (62%)	41 (75%)			
Moderate or severe	5 (38%)	14 (25%)			
Persistent heavy alcohol consumption** (vs. no)	6 (46%)	20 (37%)	1.5	0.4-4.9	0.55

Diabetes diagnosed before or during hospitalization excluded. Heavy smoking means ≥20 cigarettes per day

CI, confidence interval; RAP, recurrent acute pancreatitis

\*Result remained in multivariate analysis

\*\*In males ≥24 drinks / week, in females ≥16 drinks / week at some point during follow-up (calculated from self-reported alcohol intake per two months) compared to patients with moderate alcohol consumption or abstinence



**Figure 7.** Cumulative incidence of diabetes after first episode of AAP

New prediabetes or diabetes developed in 55% of patients who were non-diabetic after first AAP. RAP predisposed to developing new endocrine dysfunction and persistently low FE-1 values were associated with new endocrine dysfunction as depicted in the regression analysis in Table 7. All patients with normal endocrine function also had normal FE-1 values.

PEI developed in 24% of the patients and all these patients also had endocrine dysfunction (prediabetes or diabetes). Overall 40% of patients with diabetes or prediabetes had PEI (OR=10.8, 95% CI 1.2-102, P=0.037). Of the patients with PEI, 45% had RAP episodes (versus 18% in patients with normal exocrine function), but the association was not statistically significant (p=0.10).

Smoking, heavy alcohol consumption and severity of initial AAP were not associated with risk of pancreatic dysfunction. Obesity (BMI ≥30) was associated with T2DM (OR=5.9, 95% CI 1.2-27.9), but not with pancreatogenic diabetes.

**Table 7.** Predictors of pancreatic endocrine dysfunction

	<b>New abnormal finding* n = 26 (55%)</b>	<b>Normal endocrine function n = 21 (45%)</b>	<b>OR</b>	<b>95% CI</b>	<b>P-value</b>
RAP	12 (46%)	2 (10%)**	8.1#	1.6-42.3	0.013
Low FE-1	8 (40%)	0	10.5#	1.1-96.6	0.038
CP	3 (12%)	0			
Severity of initial attack			3.2	0.7-13.7	0.12
Mild	17 (65%)	18 (86%)			
Moderate or severe	9 (35%)	3 (14%)			
Smoking	15 (58%)	14 (67%)	1.5	0.4-4.8	0.53
Heavy smoking	6 (23%)	9 (43%)	2.5	0.7-8.7	0.15
Obesity (BMI ≥30)	7 (27%)	6 (29%)	0.9	0.3-3.3	0.90
Persistent heavy alcohol consumption##	12 (46%)	6 (29%)	2.1	0.6-7.3	0.22

Diabetes diagnosed before or during hospitalization excluded

Heavy smoking means ≥20 cigarettes per day

CP, chronic pancreatitis; RAP, recurrent acute pancreatitis; FE-1, fecal elastase-1

\*Pancreatogenic diabetes (7), T2DM (6) or prediabetes (13)

T2DM, type 2 diabetes mellitus

\*\*Both were "late" recurrences (8.3 and 9.4 years)

#result remained in multivariate analysis

##In males ≥24 drinks / week, in females ≥16 drinks / week at some point during follow-up (calculated from self-reported alcohol intake per two months) compared to patients with moderate alcohol consumption or abstinence

## 4.2 Abstaining from alcohol and brief interventions

### 4.2.1 Impact of abstinence on natural course of AAP (III)

Study III aimed to assess if abstaining from alcohol would prevent the development of RAP and pancreatic dysfunction. None of the 18 abstinent patients developed RAP while maintaining abstinence. The mean follow-up time for abstinence was 5.15 (1.83-9.13) years. Of the non-abstinent patients in the study population, 34% developed RAP ( $p < 0.001$ ).

Of the non-diabetic abstinent patients, none developed new DM during follow-up. Two patients (13%, 2 out of 15) were diagnosed with new prediabetes (one IGT and one IFG).

One patient (6%) had persistently low FE-1 values in follow-up referring to PEI, the rest of the patients had values  $>150 \mu\text{g/g}$  (and  $>200 \mu\text{g/g}$ ) in follow-up while abstinent. Vitamin A and E concentrations were normal in follow-up in all patients.

### 4.2.2 Brief interventions (IV)

In Study IV, the means and frequency of BIs given for AAP and RAP patients in hospital daily practice were evaluated and whether BIs protect against RAP. Of the 74 patients included in Study IV, 95% were male and median age at first AAP attack was 48 (20-70) years (Table 5). During hospitalization for first attack of AAP, BIs provided (by a doctor, nurse or social worker) were recorded in 72% of patients' electronic medical records (Table 8). Thirty-seven per cent of patients' discharge records included recommendations for abstinence or reducing alcohol consumption and AUDIT points were registered for 37% of the patients (Table 8).

During follow-up (median 4.2 (0.2-6.1) years), RAP episodes developed in 32% of patients and first RAP developed in a median of 13.2 (2.0-52.3) months after the initial AAP. BIs during initial hospitalization did not reduce the development of RAP when compared to patients with no recorded BIs (72% vs. 71%,  $p = 0.60$ ). Table 8 describes the number of BIs performed by different health care professionals and differences between non-RAP and RAP patients.

During hospitalization for first RAP episode 71% of patients received BIs but fewer patients received multiple interventions than during their hospitalization for first AAP (42% vs. 8.3%,  $p=0.039$ ).

Completed study questionnaires were received from 27% of patients by mail. Of the responders, 94% (16/17) reported having received BIs (71% from doctors, 71% from nurses, 6% from social workers) during their initial hospitalization. All patients wanted to reduce their alcohol consumption after first AAP: half (9/17) had abstinence as a goal and the rest aimed at moderate drinking. Sixty-five percent (11/17) felt they had succeeded and 24% (4/17) reported having partly succeeded in achieving their set goals. RAP developed in 35% in this subgroup with no difference in BIs provided during initial hospitalization or patient-set goals for alcohol reduction.

**Table 8.** BIs during initial hospitalization for AAP among all patients and patients who did or did not develop RAP

	All patients n = 74	non-RAP patients n = 50	RAP patients n = 24	p-value
AUDIT points registered	27 (36.5%)	17 (34.0%)	10 (41.7%)	0.61
BI against substance abuse given by				
Doctor	24 (32.4%)	14 (28.0%)	10 (41.7%)	0.29
Nurse	33 (44.6%)	23 (46.0%)	10 (41.7%)	0.81
Social worker	24 (32.4%)	15 (30.0%)	9 (37.5%)	0.60
Any	53 (71.6%)	36 (72.0%)	17 (70.8%)	0.92
Multiple*	25 (33.8%)	15 (30.0%)	10 (41.7%)	0.43
Abstinence mentioned in discharge papers	27 (36.5%)	18 (36.0%)	9 (37.5%)	0.90
Counseling for substance abuse recommended	27 (36.5%)	15 (30.0%)	12 (50.0%)	0.094
Social worker recommended but patient refused	7 (9.5%)	4 (8.0%)	3 (12.5%)	0.68

AAP, acute alcoholic pancreatitis; AUDIT, Alcohol Use Disorders Identification Test; BI, brief intervention; RAP, Recurrent Acute Pancreatitis

\*Interventions from two or three different health care professionals (doctor, nurse, social worker)

## 4.3 Risk of recurrent attacks and mortality (II and IV)

### 4.3.1 Risk for RAP

The overall incidence rates for RAP were 35% and 32% in Studies II and IV respectively. In Study IV, younger age (OR=0.96, 95% CI 0.92-1.00) and higher AUDIT points ( $p=0.044$ , OR=5.6 95% CI=1.02-30.9 for  $\geq 20$  points) were associated with higher risk for RAP (Table 9). Pseudocyst diagnosed after initial AAP was associated with RAP but was not a statistically significant risk factor ( $p=0.056$ ). Smoking, duration of initial hospitalization and severity of initial AAP were not predictors of RAP (Table 9).

In the ROC analysis, the AUDIT test had the best sensitivity and specificity (0.70 and 0.71 respectively) for predicting RAP at a cut-off value of 20 points.

**Table 9.** Risk factors for RAP (Study IV)

	<b>RAP n = 24</b>	<b>non-RAP n = 50</b>	<b>OR</b>	<b>95% CI</b>	<b>p-value</b>
AUDIT points $\geq 20$	7 (70.0%)	5 (29.4%)	5.6	1.02-30.9	0.048
Age, years, mean (SD)	41.4 (10.6)	47.6 (12.6)	0.96	0.92-1.00	0.045
Severity of initial AAP					
Mild	16 (66.7%)	32 (64.0%)	1.13	0.40-3.14	0.82
Non-mild	8 (33.3%)	18 (36.0%)			
Smoking	13 (54.2%)	23 (46.0%)	1.39	0.52-3.68	0.51
Pseudocyst	6 (25.0%)	4 (8.0%)	3.8	0.97-15.2	0.056
Duration of hospitalization, days, mean (SD)	8.5 (9.3)	7.5 (4.6)	1.02	0.95-1.10	0.53

AAP, acute alcoholic pancreatitis; AUDIT, Alcohol Use Disorders Identification Test; OR, odds ratio; RAP, Recurrent Acute Pancreatitis; SD, standard deviation

Non-mild = moderately severe and severe acute alcoholic pancreatitis combined

### 4.3.2 Mortality

In Study II the mortality rate in patients who had survived their first AAP was 12% at follow-up and in Study IV also 12%. RAP was a significant risk factor for higher mortality in Study II (HR 4.0, 95% CI 1.4-11.0, Table 10, Figure 8). Smoking, heavy smoking, pancreatogenic diabetes and higher age were independent risk factors for mortality in multivariate analysis (Table 10).

Causes of death in Study II were related to accidents in 56% (9/16) of the patients (56% alcohol-associated and 44% non-alcohol-associated accidents or intoxications). Nineteen per cent of the patients died from gastroenterological diseases (1 RAP, 1 alcoholic hepatitis, 1 esophageal ulcer) and 19% from malignancy (1 pancreatic ductal adenocarcinoma, 1 colon cancer, 1 non-follicular (diffuse) lymphoma). In one patient, the cause of death was unknown.

**Table 10.** Predictors of mortality (Study II)

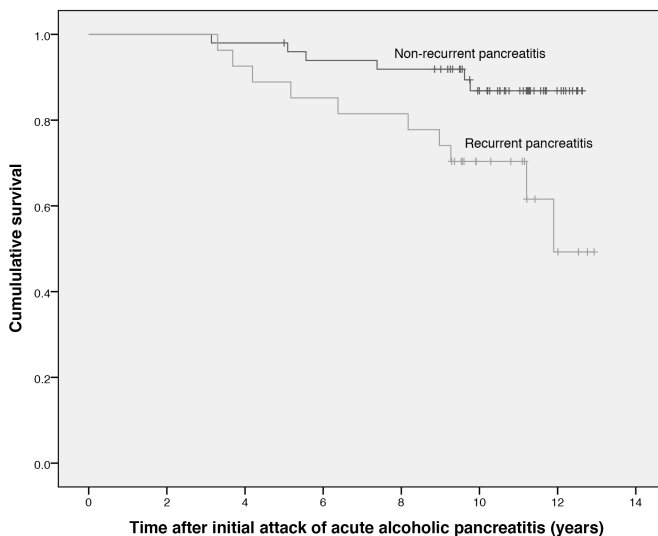
	Univariate analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
RAP	3.5	1.3 to 9.6	0.016	4.0	1.4 to 11.0	0.008
Smoking	1.6	0.5 to 4.5	0.42	3.17	1.13 to 8.89	0.028
Heavy smoking	2.1	0.8 to 5.6	0.14	4.4	1.4 to 13.6	0.006
Obesity (BMI ≥30)	0.8	0.3 to 2.5	0.70	0.6	0.2 to 1.9	0.39
Pancreatogenic diabetes	3.7	1.3 to 10.6	0.016	4.9	1.6 to 15.4	0.006
Age	1.05	1.0 to 1.1	0.058	1.07	1.01 to 1.13	0.021
Persistent heavy alcohol consumption*	1.1	0.4 to 2.9	0.91	1.2	0.4 to 3.6	0.72

RAP, recurrent acute pancreatitis; BMI, body mass index

Heavy smoking means ≥20 cigarettes per day

CI, confidence interval; RAP, recurrent acute pancreatitis

\*In males ≥24 drinks / week, in females ≥16 drinks / week at some point during follow-up (calculated from self-reported alcohol intake per two months) compared to patients with moderate alcohol consumption or abstinence



**Figure 8.** Kaplan-Meier curves for cumulative survival (mortality) in patients with recurrent vs. non-recurrent pancreatitis (Study II) (log-rank: p=0.01)



## 5 Discussion

AP has a wide spectrum of severities and the natural course of the disease in acute attack and thereafter is dynamic with various factors having an effect. The results on pancreatic dysfunction and morphology after AP have been controversial and there are relatively few prospective studies on the natural course of the disease. Follow-up studies so far have not distinguished pancreatogenic diabetes from other types of DM. Studying disease development after AAP and follow-up of patients with AAP is challenging, but interesting. It is important to know the consequences of a serious illness which has the potential to recur.

With a prospective follow-up model, we managed to determine the development of pancreatic dysfunction and chronic morphological changes after AAP more precisely. The present study adds valuable information to what is known about the consequences of AAP. We have also delved into the underlying problem, namely excessive alcohol consumption. Prevention of RAP and pancreatic dysfunction and even of the development of CP serve to reduce high morbidity and health care costs.

### 5.1 Morphology

In Study I, chronic morphological findings seen in S-MRCP were detected in half of the patients. Patients with mild first attack assessed with the updated Atlanta criteria had fewer chronic changes in follow-up, while over 80% of patients with severe or moderate first attack had chronic findings. Chronic morphological pancreatic changes increased with recurrent episodes of acute pancreatitis and new changes developed in 90% of patients with RAP compared to 30% without RAP. Smoking or obesity were not associated with the development of chronic changes. However, smoking was highly prevalent in patients with chronic findings and thus requires further investigation.

S-MRCP pathology was compared to the findings from Study II and endocrine dysfunction and PEI were significantly associated with chronic changes seen in the

pancreas. All patients with pancreatogenic diabetes were found to have multiple chronic S-MRCP findings.

The findings from Study I support the sentinel acute pancreatitis event (SAPE) hypothesis regarding pancreatitis, in which RAP episodes probably drive chronic inflammation and activation of pancreatic stellate cells predisposing to development of chronic morphological changes (Whitcomb 1999). Patients who had normal imaging findings at baseline (three months after discharge) did not develop chronic changes unless they suffered RAP episodes. Two fifths of the patients who still had only acute changes (edema) three months after discharge developed chronic findings and the rest resolved to normal in long-term follow-up. Chronic changes at baseline were seen in later studies. Pseudocyst at three months was categorized as chronic change, since acute fluid collections have previously been reported to resolve or develop into pseudocysts at three months (Lankisch et al. 2012). In our preliminary two-year S-MRCP follow-up no risk factors for the development of chronic pancreatic morphology could be identified (Pelli et al. 2009).

So far no prospective long-term follow-ups of the natural course in pancreatic morphology after acute pancreatitis patients have been published. Study I concludes that chronic morphological changes are common after AAP and develop especially in RAP patients and are commonly seen in patients with non-mild first episode. If a patient with history of pancreatitis presents with abdominal symptoms, MRCP or other imaging studies may be justified to reveal possible underlying pathology.

## 5.2 Endocrine and exocrine dysfunction

In a recent meta-analysis prediabetes or diabetes were found to develop in 37% and diabetes in 25% of patients after AP. Severity and etiology did not correlate with the development of dysfunction (Das et al. 2014b). Meta-analysis is comprehensive, but still suffers from methodological heterogeneity among the studies included. The follow-up times in the individual studies were not long and half of the studies included only patients with severe AP.

Study II adds valuable information to the current knowledge on pancreatic function after AAP. RAP was a very strong risk factor for endocrine dysfunction and the development of pancreatogenic diabetes. All in all, we found that half of the patients developed new endocrine dysfunction (prediabetes or diabetes) and

20% developed pancreatogenic diabetes. The percentages of those developing endocrine dysfunction are close to those reported by Das et al., but they were not able to study the impact of RAP on dysfunction. However, since AAP is the etiology most likely to recur, it may be that patients with AAP are at higher risk of endocrine dysfunction.

Das and colleagues also conducted a systematic review and meta-analysis on PEI after AP including eight studies and pooling together 234 patients (Das et al. 2014a). They found a pooled prevalence of 29% for PEI after AP and that 40% of patients with endocrine pancreatic dysfunction also had PEI (41% in prediabetic and 39% in diabetic patients). Of the studies included, only one had patients with different severities (Andersson et al. 2010), the other 88% (7/8) had only patients with severe AP, mostly necrotizing AP treated with necrosectomy. The etiology of AP was biliary in 45% and alcohol in 22%.

In Study II, PEI (persistently low FE-1 values) was detected in a fourth of the patients. Of the patients with prediabetes or diabetes 40% had PEI, showing a statistically significant association between endocrine and exocrine dysfunction.

Endocrine and exocrine pancreas are closely linked. Insulin has trophic effects on exocrine pancreas and effects on enzyme secretion which may explain the association between PEI and endocrine dysfunction (Czako et al. 2009). Other possible explanations might be diabetic angio- or neuropathy or inflammatory alterations (Andrén-Sandberg and Hardt 2008; Hardt and Ewald 2011).

Pancreatogenic diabetes developed rather early in follow-up. It was diagnosed in a median of four years after first AAP and two years after first RAP. It is assumed that pancreatic dysfunction develops late in the course of CP, but that may be due to a lack of prospective studies and these are first prospective long-term results investigating the development of pancreatogenic diabetes.

Overall 12% of patients in Study II developed CP, which is in line with two other long-term follow-up studies (Lankisch et al. 2009; Yadav et al. 2012b). Only 19% of patients with RAP developed CP. This is less than previously reported by Lankisch et al. or Yadav et al. in patients with alcoholic RAP developing CP (41% and 32% respectively) (Lankisch et al. 2009; Yadav et al. 2012b). This may be due to the criteria used by Lankisch et al. (Lüneburg and Mayo criteria), where RAP gives additional points to CP diagnosis or by relying solely on hospital database coding for diagnosis of CP as done by Yadav et al. In this thesis, RAP was not found to be a significant risk factor for CP, but is associated with complications typical in CP. Also, we used fairly strict criteria for CP in our study.

Smoking was not found to be a risk factor for pancreatic dysfunction, RAP or CP, probably because smoking was highly prevalent. Many studies have associated smoking with the risk of RAP and CP (Lankisch et al. 2009; Yadav et al. 2012b; Alsamarrai et al. 2014). One explanation may be that studies have included mixed etiologies and since alcohol consumption is extremely difficult to analyze and smoking is highly prevalent in heavy alcohol consumers, their separate effects are hard to adjust. The impact of smoking on pancreatic dysfunction and morphology thus requires further investigation and discontinuation of smoking should be encouraged in all patients with AAP, RAP and especially in CP, since smoking cessation has been demonstrated to decrease disease progression in CP (Talamini et al. 2007).

In conclusion, we found that endocrine pancreatic dysfunction is common after AAP, and RAP is important risk factor for endocrine dysfunction and pancreatogenic diabetes. PEI develops in a fourth of patients and is associated with endocrine dysfunction. Overall 50% of RAP patients developed pancreatogenic diabetes, 69% developed any DM and 86% developed DM or prediabetes. Prevention of RAP is crucial in order to avoid the development of endocrine dysfunction. Pancreatic function should be screened for after the first episode of AAP and especially in patients with multiple episodes. Patients with findings indicative of abnormal endocrine function should be screened to assess possible exocrine dysfunction and vice versa.

### 5.3 What can be done to prevent RAP?

While dozens of guidelines concerning the treatment of acute pancreatitis have been published, preventive measures to reduce RAP and alcohol consumption are rarely if ever mentioned (UK Working Party on Acute Pancreatitis 2005; Banks and Freeman 2006; Sekimoto et al. 2006; Tenner et al. 2013; Working Group IAP/APA Acute Pancreatitis Guidelines 2013).

Study III showed that abstinence is infrequently (only in 15% of patients) achieved after AAP, but it seems to offer excellent protection against disease progression since none of the abstinent patients developed RAP episodes. None of the abstainers were diagnosed with DM and only one had atrophy in S-MCRP, which is also seen in normal aging pancreas (Sato et al. 2012), while the rest had normal morphology. Nevertheless, it should be borne in mind that the sample size was rather small. In a study by Halonen et al., a third of the patients chose

abstinence after severe AAP, and these patients were able to get back to work and achieve good quality of life, while continuing alcohol consumption led to increased mortality (Halonen et al. 2003).

In Study IV, there was a significant lack of BIs provided during hospitalization for AAP and RAP. Only 70% of patients with first AAP received documented BI during their first hospitalization. In-hospital BI itself did not reduce the development of RAP. These results are comparable with those reported in the study by Beagon et al., where hospital policy was to refer all AAP patients to a social worker, but only 56% were so referred and 31% received documented BI. There was no difference in the development of RAP whether or not social worker BI was provided (Beagon et al. 2015). Even more dramatic results were reported in a Swedish study, where only 20% of AAP patients were offered BI during hospitalization (Bertilsson et al. 2015).

Although single BIs have been reported to be effective in reducing alcohol consumption (McQueen et al. 2011), recent meta-analyses have emphasized the importance of multiple interventions (Mdege et al. 2013; Simioni et al. 2015). These findings corroborate the results of repeated interventions in reducing the development of RAP after AAP (Nordback et al. 2009).

The quality of BIs could not be addressed in Study IV, although BIs provided by social workers who are more trained to perform BIs than other medical personnel, did not yield better results. Nevertheless, the content of BIs should be standardized and hospital staff routinely trained to perform BIs for patients with alcohol-associated disease.

There may be several other reasons for the results of Study IV besides the quality of BIs. First, due to the retrospective nature of the study, BIs may have been provided more frequently to patients with obvious alcohol problems and thus probably higher risk for RAP. Secondly, since the BIs performed were studied from electronic medical records, the number of recorded BIs may have been underestimated. On the other hand, since only a third of patients' discharge summaries included recommendations for abstinence, it seems that alcohol problems may often be neglected. Third, some people may assume that during a serious illness like AAP with challenges in somatic treatment, it is not the right place to perform BIs or simply to have time to perform them. Treatment of patients with alcohol problems is considered frustrating and challenging and patients' compliance with treatment may be lacking, which is probably reflected in finding that significantly fewer patients received multiple interventions during hospitalization for RAP. However, patients hospitalized due to alcohol-associated

diseases are usually motivated to reduce alcohol consumption (Lau et al. 2010) and the majority of patients are willing to reduce their drinking (Lappalainen-Lehto et al. 2013) suggesting that AAP might serve as leverage for changing drinking habits.

Different risk factors for alcoholic RAP have been identified. These include younger age, mild first episode, pseudocysts, smoking, other sedatives besides alcohol consumption, more severe addiction problem (Pelli et al. 2000, 2008, 2009; Ahmed Ali et al. 2016) and probably also genetic factors (Whitcomb et al. 2012). Previous findings concerning pseudocysts and younger age were validated in Study IV. AUDIT was found to have fair specificity and sensitivity to predict RAP with a cut-off value of 20 points. Since AUDIT is a universally used and validated test, it should be performed on all AAP patients as well as other patients with alcohol-related diseases.

A care pathway protocol for AAP patients in Tampere University Hospital was established in 2010, which recommends BIs, AUDIT testing, social worker visits in all AAP patients during hospitalization and follow-up visits to primary health care. It was notified that this protocol was not sufficiently utilized and none of the patients were recommended or scheduled for follow-up visits.

In conclusion, no safe limit for alcohol consumption after AAP can be set and abstinence should be recommended to all patients since it protects against RAP. Single BIs during hospitalization are insufficient to reduce RAP in AAP patients. Patients with AAP require tailored and more extensive follow-up models to reduce alcohol consumption and prevent RAP. AUDIT should be used as a tool to assess the risk of RAP. Overall, there is a significant lack of interventions in alcohol problems in patients hospitalized due to AAP or its future recurrences. Follow-up visits to primary health care after discharge would probably produce good results and cost-effectiveness as described before (O'Donnell et al. 2014). If possible, appointments should be prearranged. General practitioners must be made aware of the importance of BIs in AAP patients.

## 5.4 Strengths and limitations of the study

All patients in the prospective follow-up program (Studies I-III) were motivated to participate and may have been more willing to reduce their alcohol consumption, which may have resulted in fewer RAP episodes than in an unselected population. One limitation is also that smoking habits prior to first AAP were not studied. The number of patients in follow-ups was not high, but patients were well selected and

stratified with thorough follow-up enabling validated and reliable results. The follow-up time was also long enough to make justified conclusions and differentiate pancreatogenic diabetes from other types of DM. We defined RAP with the same criteria as first AP. Some studies lack this definition and patients with exacerbations of disease (abdominal pain) may be included as RAP episodes. Patients with complications necessitating surgical or other interventional procedures were excluded. This exclusion was intended to enable us to investigate the natural healing process after AP.

Our criteria for pancreatogenic diabetes were fit to meet the criteria proposed by Ewald & Bretzel (Ewald and Bretzel 2013), except that antibodies associated with T1DM were not included in the study protocol, since this work was a prospective follow-up initiated in 2001, when pancreatogenic diabetes was a less known topic. Anti-glutamic acid decarboxylase (GAD) antibodies, typically associated with autoimmune based T1DM, were obtained in 5/13 of the patients with pancreatogenic diabetes and were all negative. Many of these patients had multiple RAP episodes and were heavy alcohol abusers and might thus not have been committed to further studies. Also, the clinical picture of diabetes was complicated with problems in glycemic control in many patients, necessitating emergency visits and, with a history of RAP these patients were probably considered to have “certain” pancreatogenic diabetes. If glucagon-C-peptide test after diagnosis of DM revealed insulin deficiency (C-peptide elevation of 0.30 mol/l) this was suggestive of pancreatogenic diabetes along with other criteria. All patients with pancreatogenic diabetes eventually needed insulin replacement therapy.

One strength of the studies composing this thesis is that the etiology of AP and the development of pancreatic dysfunction were individually evaluated and based on validated criteria instead of relying solely on ICD-10 coding. However, symptoms associated with CP were not routinely elicited and our diagnosis of CP had to rely on clinician based diagnoses in electronic medical records. Thus the development of CP is probably underestimated in these studies. All CP diagnoses were studied to be in accordance with M-ANNHEIM criteria. Although the M-ANNHEIM is probably the most suitable of the current guidelines on diagnosing CP, no generally accepted criteria exist. We think that low FE-1 values alone do not justify a diagnosis of CP, since they are also seen in diabetic patients without CP.

## 5.5 Future prospects

A new mechanistic definition for CP has recently been proposed by Whitcomb et al., where CP is characterized as pathologic fibro-inflammatory syndrome and persistent pathologic responses, which develop in response to parenchymal injury or stress in patients with environmental and/or genetic risk factors (Whitcomb et al. 2016). Criteria based on this new definition may be of importance in the future in order to make early diagnosis of CP. The current diagnostic criteria for CP are mainly based on morphology, describing symptoms and features, and a diagnosis can be made in only in the advanced stages. In light of this thesis pancreatogenic diabetes may develop earlier in the course of the disease, RAP may have a specific role in the pathogenesis, since it leads to pancreatic dysfunction and morphological changes and this could be explained by genetic risk factors probably acting together with environmental factors. In the future, biomarkers or genetic testing may identify those patients who will develop RAP and CP earlier. Options may even emerge to delay the pathological inflammatory process.

The prevalence and importance of pancreatogenic diabetes have been underestimated and the disease is typically misclassified as T2DM (Ewald et al. 2012). Criteria for pancreatogenic diabetes have only recently been proposed (Ewald and Bretzel 2013), but they need to be further validated. PEI complicates glucose control in pancreatogenic diabetes impairing incretin function, but this may be improved by pancreatic enzyme replacement therapy. Pancreatogenic diabetes may also promote fibrosis, since hyperglycemia causes activation of pancreatic stellate cells (Nomiya et al. 2007). Increased tissue pressure (Jalleh et al. 1991; Watanabe et al. 2004) and reduced pancreatic microcirculation (Schilling et al. 1999) associated with progression of pancreatitis have also been shown to activate stellate cells.

The findings of this thesis emphasize the importance of recognizing pancreatogenic diabetes in patients after AAP and RAP and of performing adequate testing on suspected patients. Patients with pancreatogenic diabetes have the same angiopathic complications of elevated blood glucose as do patients with T1DM and DM increases pancreatic cancer risk in CP and overall mortality in pancreatitis (Gullo et al. 1990; Ziegler et al. 1994; Levitt et al. 1995; Nøjgaard et al. 2011b; Liao et al. 2012). More prospective studies focusing on detecting pancreatogenic diabetes and basic studies to understand its pathogenesis are needed to further understand the meaning of this entity.



In future, the development of pancreatic dysfunction, RAP and CP after AAP will be prevented by focusing on treating the etiology, that is, heavy alcohol consumption and developing efficacious substance abuse treatment with abstinence as the goal. Along with follow-up care programs with repeated interventions for AAP patients, anti-craving drug therapy as a part of the treatment should be assessed.

## 6 Conclusions

The conclusions of this thesis are:

- I. Chronic morphological pancreatic changes in S-MRCP are observed in half of the patients in long-term follow-up after first AAP and are associated with pancreatic dysfunction. RAP and non-mild first episode are risk factors for chronic changes.
- II. Pancreatic endocrine dysfunction develops in half and exocrine dysfunction in one fourth of the patients after AAP. Pancreatogenic diabetes develops in 20%. RAP is a risk factor for endocrine dysfunction and pancreatogenic diabetes. Pancreatic function should thus be actively screened for after AAP, and especially in patients with RAP.
- III. Abstinence protects against RAP and against new-onset diabetes and should be recommended to all patients with AAP.
- IV. Only 70% of AAP patients received documented brief intervention during their initial hospitalization. The in-hospital brief intervention by itself is not sufficient to reduce RAP. Young patients with high AUDIT scores are especially at high risk of developing RAP and should thus be included in more intense follow-up care programs.

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## 9 Original publications

