# Progression of Pancreas Morphology in Chronic Pancreatitis

*Exploration of New Potential MRI Biomarkers*

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# PROGRESSION OF PANCREAS MORPHOLOGY IN CHRONIC PANCREATITIS

EXPLORATION OF NEW POTENTIAL MRI BIOMARKERS

**BY**
**EMILY STEINKOHL**

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# PROGRESSION OF PANCREAS MORPHOLOGY IN CHRONIC PANCREATITIS

## EXPLORATION OF NEW POTENTIAL MRI BIOMARKERS

Ph.D. Dissertation
Emily Steinkohl

Dissertation submitted October, 2021

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# Curriculum Vitae

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**Publications**

1. **Steinkohl E**, Olesen SS, Hansen TM, Drewes AM, Frøkjær JB. T1 relaxation times and MR elastography-derived stiffness: new potential imaging biomarkers for the assessment of chronic pancreatitis. Abdom Radiol (NY). 2021; [Epub ahead of print].
2. **Steinkohl E**, Bertoli D, Hansen TM, Olesen SS, Drewes AM, Frøkjær JB. Practical and clinical applications of pancreatic magnetic resonance elastography: a systematic review. Abdom Radiol (NY). 2021 Oct; 46(10): 4744-4764.
3. Olesen SS, Hagn-Meincke R, Drewes AM, **Steinkohl E**, Frøkjaer JB. Pancreatic atrophy and exocrine insufficiency associate with the presence

of diabetes in chronic pancreatitis patients, but additional mediators are operative. Scand J Gastroenterol. 2021 Mar; 56(3):321-328.

4. **Steinkohl E**, Olesen SS, Drewes AM, Frøkjaer JB. Progression of pancreatic morphology in chronic pancreatitis is not associated with changes in quality of life and pain. Scand J Gastroenterol. 2020 Sep; 55(9):1099-1107.

5. **Steinkohl E**, Olesen SS, Drewes AM, Frøkjær JB. Response to Letter to the Editor: Treatment methods and age adjustment were important to evaluate morphological progression in chronic pancreatitis. Eur J Radiol. 2020 Jun; 127:108993.

6. Leere JS, Karmisholt J, Robaczyk M, Lykkeboe S, Handberg A, **Steinkohl E**, Frøkjær JB, Vestergaard P. Denosumab and cinacalcet for primary hyperparathyroidism (DENOCINA): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Diabetes & Endocrinology, Volume 8 (Issue 5), pp. 407-417, 2020 May.

7. **Steinkohl E**, Olesen SS, Mark EB, Hansen TM, Frandsen L, Drewes AM, Frøkjær JB. Progression of Parenchymal and Ductal Findings in Patients with Chronic Pancreatitis. Eur J Radiol. 2020 Apr; 125:108868.

8. Olesen SS, Phillips AE, Faghih M, Kuhlmann L, **Steinkohl E**, Frøkjær JB, Bick BL, Ramsey M, Hart P, Garg P, Singh VK, Yadav D, Drewes AM. Overlap and cumulative effects of pancreatic duct obstruction, abnormal pain processing, and psychologic distress on patient reported outcomes in chronic pancreatitis. [In press Gut].

9. **Steinkohl E**, Olesen SS, Hansen TM, Drewes AM, Frøkjær JB. Quantification of parenchymal fibrosis in chronic pancreatitis: relation to atrophy and pancreatic function. [Submitted to Magnetic Resonance Imaging].

10. Bertoli D, **Steinkohl E**, Mark EB, Brock C, Drewes AM, Frøkjær JB. Quantification of Gastric Emptying with Magnetic Resonance Imaging in Healthy Volunteers: A Systematic Review. [Submitted to Neurogastroenterology and Motility].

11. Borgbjerg J, **Steinkohl E**, Olesen SS, Akisik F, Bethke A, Bieliuniene E, Engjom T, Haldorsen IS, Kartalis N, Lisitskaya MV, Naujokaite G, Novovic S, Ozola-Zālīte I; Phillips AE, Swensson JK, Drewes AM, Frøkjær JB. Measurement variability of parenchymal- and ductal diameters in Chronic Pancreatitis: A SBPC Multi-Institutional and Multiobserver Study. [Submitted to Radiology].

# List of Papers

**The thesis is based on the following papers**

1. **Steinkohl E**, Olesen SS, Mark EB, Hansen TM, Frandsen LK, Drewes AM, Frøkjær JB. Progression of Parenchymal and Ductal Findings in Patients with Chronic Pancreatitis. Eur J Radiol. 2020 Apr; 125:108868.

2. **Steinkohl E**, Olesen SS, Drewes AM, Frøkjaer JB. Progression of pancreatic morphology in chronic pancreatitis is not associated with changes in quality of life and pain. Scand J Gastroenterol. 2020 Sep; 55(9):1099-1107.

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# Abbreviations

| | |
|---|---|
| ADC | Apparent diffusion coefficient |
| AP | Acute pancreatitis |
| AUC | Area under the curve |
| CP | Chronic pancreatitis |
| CT | Computed tomography |
| DWI | Diffusion-weighted imaging |
| EPI | Exocrine pancreatic insufficiency |
| ERCP | Endoscopic retrograde cholangiopancreatography |
| EUS | Endoscopic ultrasonography |
| FSF | Fat signal fraction |
| HC | Healthy control |
| MPD | Main pancreatic duct |
| MRCP | Magnetic cholangiopancreatography |
| MRE | Magnetic resonance elastography |
| MRI | Magnetic resonance imaging |
| PDFF | Proton density fat fraction |
| QOL | Quality of life |
| RAP | Recurrent acute pancreatitis |
| ROC | Receiver operating characteristic |
| ROI | Region of interest |
| SAPE | Sentinel AP event |
| SI | Signal intensity |

# English Summary

Chronic pancreatitis (CP) is associated with considerable morbidity in the Western World and has an annual incidence of approximately 10 per 100,000 inhabitants. CP is characterized by progressive destruction of the pancreas due to repeated inflammation with atrophy, pancreatic fibrosis, significant exocrine and endocrine function impairment, and severe chronic abdominal pain.

The leading cause is disproportionate long-term alcohol use, while nicotine, genetic, hereditary, environmental, and autoimmune factors are essential risk factors for developing CP. However, the detailed mechanisms behind the development and progression of CP are not well understood, and no adequate and curative treatment of established CP has so far been found. Therefore, there has been an increased focus on early detection and progression of CP.

A better understanding of the underlying mechanisms behind the development and progression of CP is necessary to suggest and evaluate new mechanism-based treatments. Moreover, it is essential to identify new methods to detect very mild structural damage and, as a result, diagnose CP in earlier stages; thus, early interventions can be undertaken to prevent the progression of CP as early as possible. This Ph.D. thesis aims to provide a deeper understanding of the development and progression of CP, and to apply and validate new non-invasive magnetic resonance imaging (MRI) methods to diagnose CP in earlier stages. Four papers compile this Ph.D. project.

Paper I and II were based on a longitudinal study that assessed morphological pancreatic changes over a four-year follow-up, using quantitative MRI. The morphological parameters of the pancreas included: gland volume, main pancreatic duct diameter, Cambridge classification, diffusion properties of the parenchyma as a proxy for fibrosis, and measurement of parenchymal fat infiltration. The main finding of this study showed a pronounced progression of the parenchymal-related parameters during the follow-up period. In contrast, the ductal-related parameters were stable and did not change over the period. Moreover, it was demonstrated that the disease burden was not connected to the morphological progression.

The remaining papers (III and IV) were based on a cross-sectional study in CP patients and healthy controls, where new potential MRI biomarkers for the diagnosis and staging of CP were obtained and evaluated. T1 relaxation time, magnetic resonance elastography (MRE)-derived stiffness, and proton density fat fraction, along with the morphological parameters from study I,

were used. Paper III aimed to determine the diagnostic performance of T1 relaxation time, MRE-derived stiffness, proton density fat fraction and gland volume. It was shown that T1 relaxation time and MRE-derived stiffness had a very high diagnostic performance in detecting different stages of CP and were superior to pancreatic gland volume and proton density fat fraction.

Finally, paper IV investigated the relationship between measurements with these new techniques and with pancreatic gland volume as a reference. It showed that MRE-derived stiffness and T1 relaxation times were related, whereas there only was a week association with the gland volume. The findings support the hypothesis that the modalities likely reflect aspects of fibrotic processes in CP and might be considered non-invasive biomarkers for quantifying early fibrotic changes in CP patients. Most interestingly, paper IV showed that a subgroup of CP patients with preserved exocrine and endocrine functions had fibrosis, as assessed by MRE and T1 mapping, despite a normal pancreatic volume, suggesting that both techniques might be more specific for the early parenchymal changes of CP than the loss of gland volume.

Overall, papers I and II provide a deeper understanding of the disease progression in CP, whereas papers III & IV propose new MRI biomarkers for use in diagnosing and staging the earlier stages of the CP disease. This knowledge contributes to improving insight into understanding the complex CP disease and points into the direction of a paradigm change in the diagnosis of early CP.

# Dansk Resumé

Kronisk pankreatit (KP) er forbundet med et ikke uvæsentlig antal af sygdomstilfælde i den vestlig verden og har en årlig forekomst på cirka 10 pr. 100.000 indbyggere. KP er karakteriseret ved progressiv ødelæggelse af bugspytkirtlen på grund af gentagne tilfælde af betændelse med atrofi, bindevævsdannelse (fibrose), signifikant svækkelse af eksokrine og endokrine funktioner. Den alvorligste komplikation ved KP er kroniske mavesmerter.

Øget alkoholforbrug er den dominerende årsag til udvikling af KP, mens tobaksrygning, genetiske, arvelige, miljømæssige og autoimmune faktorer også spiller en væsentlig rolle for udviklingen af KP. De detaljerede mekanismer bag udviklingen og progressionen af KP er ikke klarlagt, og der er hidtil ikke fundet nogen tilstrækkelig behandling af KP. Derfor har der været et øget fokus på tidlig diagnose og progression af KP.

En bedre forståelse af de underliggende mekanismer bag udviklingen og progressionen af KP- er nødvendig for at foreslå og evaluere nye mekanismebaserede behandlinger. Desuden er det vigtigt at identificere nye metoder til at detektere de meget lette strukturelle skader på bugspytkirtlen og som følge heraf diagnosticere KP i tidligere stadier; således man bedre kan gribe ind tidligt i processen for at forhindre progression af KP så tidligt som muligt.

Formålet med denne ph.d.-afhandling, er at give en bedre forståelse af udviklingen og progressionen af KP og at anvende samt validere nye ikke-invasive magnet resonans (MR) billeddannelsesmetoder i KP med henblik på at diagnosticere KP i tidligere stadier. Denne afhandling er baseret på en samling af fire originale artikler, som tager udgangspunkt i to studier.

Artikel I og II er baseret på et longitudinelt kohortestudie, der undersøgte morfologiske ændringer i bugspytkirtlen over en fireårig periode, ved brug af kvantitativ MR. De morfologiske parametre omfattede: bugspytkirtlens volumen, diameter af bugspytkirtel-gangen, Cambridge-klassifikation, diffusionsegenskaber i bugspytkirtel-vævet som en indikator for fibrose og måling af fedtinfiltration af vævet. Hovedresultatet af denne undersøgelse viste en udtalt progression af de parenkym-relaterede parametre over den fireårige periode. Derimod var de duktal-relaterede parametre stabile og ændrede sig ikke i løbet af perioden. Desuden blev det påvist, at sygdomsbyrden ikke var forbundet med de morfologiske progressioner.

De resterende artikler (III og IV) var baseret på et tværsnitsstudie hos KP-patienter og raske kontroller. I dette studie, blev nye potentielle MR-biomarkører til diagnose af KP evalueret. MRE (magnetic resonance

elastografi)-baseret stivhed, T1 relaksationstid og fedtfraktion baseret på protontæthed anvendt sammen med de morfologiske parametre fra studie I. MR målingerne i artikel III havde til formål at bestemme den diagnostiske ydeevne af T1 relaksationstid og MRE-baseret stivhed, fedtfraktion og kirtelvolumen til at påvise KP. Artikel III viste at, T1 relaksationstid og MRE-baseret stivhed havde en meget høj diagnostisk ydeevne og var bedre end bugspytkirtlens volumen og fedtfraktion.

Endelig undersøgte artikel IV det indbyrdes forhold imellem de nye teknikker og med bugspytkirtlens volumen som reference. Denne artikel viste en sammenhæng mellem MRE-baseret stivhed og T1 relaksationstid, hvorimod der kun var en svag sammenhæng med kirtelvolumen. Resultaterne understøtter hypotesen om, at metoderne sandsynligvis afspejler aspekter af fibrotiske processer i KP og derfor kan betragtes som ikke-invasive biomarkører til kvantificering af tidlige fibrotiske ændringer hos KP-patienter. Ydermere, viste artikel IV, at en undergruppe af KP-patienter med bevarede eksokrine og endokrine funktioner havde fibrose kortlagt ved brug af MRE- og T1 -kortlægning, på trods af et normalt bugspytkirtelvolumen. Dette tyder på, at begge nye teknikker kan være mere specifikke for de tidlige vævsforandringer ved KP end tab af kirtelvolumen.

Samlet set giver artiklerne I og II en bedre forståelse af sygdomsprogressionen ved KP, hvorimod artiklerne III & IV foreslår nye MR-biomarkører til brug ved diagnosticering af de tidligere stadier af KP-sygdommen. Denne viden bidrager til at forbedre forståelsen af den komplekse KP-sygdom og peger i retning af en paradigmeforandring i diagnosen tidlig KP.

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Emily Steinkohl
Aalborg, October 14, 2021

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# Chapter 1

# Introduction

Chronic pancreatitis (CP) is a progressive fibro-inflammatory syndrome characterized by irreversible functional and morphological changes of the pancreatic gland. The disease process causes pancreatic duct abnormalities, loss of parenchymal parenchyma, and fibrosis. Patients typically present with chronic visceral pain and symptoms of pancreatic exocrine and endocrine dysfunction, risk of secondary pancreatic cancer, and other complications [1–3]. In most patients, CP is associated with a significantly reduced quality of life (QOL), high health resource utilization, and excess mortality [4, 5].

Common imaging findings of CP include pancreatic atrophy, duct distortion and strictures, intraductal and parenchymal calcifications [2, 6]. Nevertheless, not all components have to be present in an individual patient. Therefore, the presence of CP is often confirmed relatively late in the process, years after, e.g. the detection of abnormal duct imaging or pancreatic calcifications.

Since no effective and curative treatments of established CP exist, there has been an increased focus on early diagnosis and intervention [7]. Unfortunately, the diagnosis of early CP has remained elusive and challenging, as the current diagnostic methods mainly detect CP when there are severe morphological changes [8].

The need for establishing new non-invasive biomarkers for diagnosis of early CP has been highlighted recently [7], and a new mechanistic definition of CP was proposed to diagnose earlier stages of CP, based on underlying pathogenesis and biomarker evidence of disease activity and stage [2, 9]. Nonetheless, to date, there are no specific, reliable, and validated biomarkers for the early diagnosis or prognosis of CP [10].

Reliable, imaging-based measures of CP should detect morphological changes of the pancreas early in the process to help to identify and slow down the progression of CP at an early stage by the initiation of interventions and appropriate therapies [2, 11]. Moreover, biomarkers of early CP (which may potentially reversible) would provide the possibility to test antifibrotic and/or anti-inflammatory treatments [12–15].

Magnetic resonance imaging (MRI) is a non-invasive technique that could provide reliable CP biomarkers, as it, with the recent developments, allows

comprehensive quantification of pancreatic parenchymal- and ductal-related changes. Conventional T1- and T2- weighted imaging provides information on anatomic features of the pancreas parenchyma, magnetic resonance cholangiopancreatography (MRCP) allows visualization of the ductal system. In addition, novel techniques such as diffusion-weighted imaging (DWI), T1 mapping, and magnetic resonance elastography (MRE) have shown to be valid for the assessment of pancreatic fibrosis [16–19]. Furthermore, MRI allows the quantification of pancreatic fat content using Dixon imaging [20].

Altogether, the mentioned MRI techniques might serve as new non-invasive imaging biomarkers that could reflect early changes of CP and different stages of CP. However, testing in longitudinal studies is essential to understand and validate such relevant imaging parameters. Moreover, novel techniques like T1 mapping and MRE have to be tested and evaluated. Characterization of the morphological changes in CP using multiple MRI modalities may significantly improve our understanding of CP progression.

# Chapter 2

# Background

## 2.1 Chronic pancreatitis: epidemiology, etiology, and pathophysiology

The incidence of CP increases with age and is about 10 per 100.000 inhabitants per year in the Western world [21–23]. The prevalence of the disease is rising, and a Danish nationwide population-based study reported a five-fold increased mortality and an 8 years lower life expectancy compared to the background population [21]. The most common etiological factors of CP in the Western world are excessive long-term alcohol consumption and smoking [23]. Moreover, there seems to be an additive effect of the above mentioned factors. Other etiological risk factors are hereditary, nutritional, immunological, efferent duct, and miscellaneous factors [24]. The number of idiopathic cases is estimated at about 20 %; however, it is likely decreasing due to the improved understanding of the pathophysiology of CP.

Various pathophysiological mechanisms have been proposed to explain the pathogenesis and progression of CP. Pathological processes in CP involve, among others, the activation of pancreatic stellate cells, macrophages, and cytokines, which likely leads to acinar cell injury, inflammation, and fibrosis [25–27]. However, the mechanisms involved in the pathophysiology of CP remain a topic of ongoing research, as they are very are complex not fully understood yet.

A significant proportion of patients with CP have a history of AP (acute pancreatitis) or RAP (recurrent acute pancreatitis). AP is characterized by reversible pancreatic inflammation, and CP is widely acknowledged as the product of repeated attacks of acute and chronic inflammation of the pancreas [28,29].

A widely acknowledged approach to explain the pathogenesis/ development of CP is the sentinel AP event (SAPE) hypothesis model, which is based on a two-hit hypothesis [30]. In a setting with pre-existing risk factors for AP (genetic, metabolic, and environmental), a first (sentinel) episode of AP (considered as the first hit) activates the immune system. The first hit can either result in complete recovery or progression towards CP. The progression

towards CP can be triggered by several factors and mechanisms that modulate the immune system (considered the second hit), including alcohol consumption and tobacco use, or mechanisms like oxidative stress or repeated episodes of acute inflammation [28].

Approximately 20 % of patients with AP have a recurrence and 36 % of RAP patients develop CP, with a higher risk of disease progression among males, alcoholics, and smokers [28]. This supports that acute pancreatitis (AP) and CP are not distinct entities but represent a disease continuum via recurrent acute pancreatitis (RAP) to early and end-stage CP [28, 29] (see Fig. 2.1). This is the background for the proposal of a new mechanistic definition of CP made by Whitcomb and colleagues [2], as summarized in Fig. 2.1.

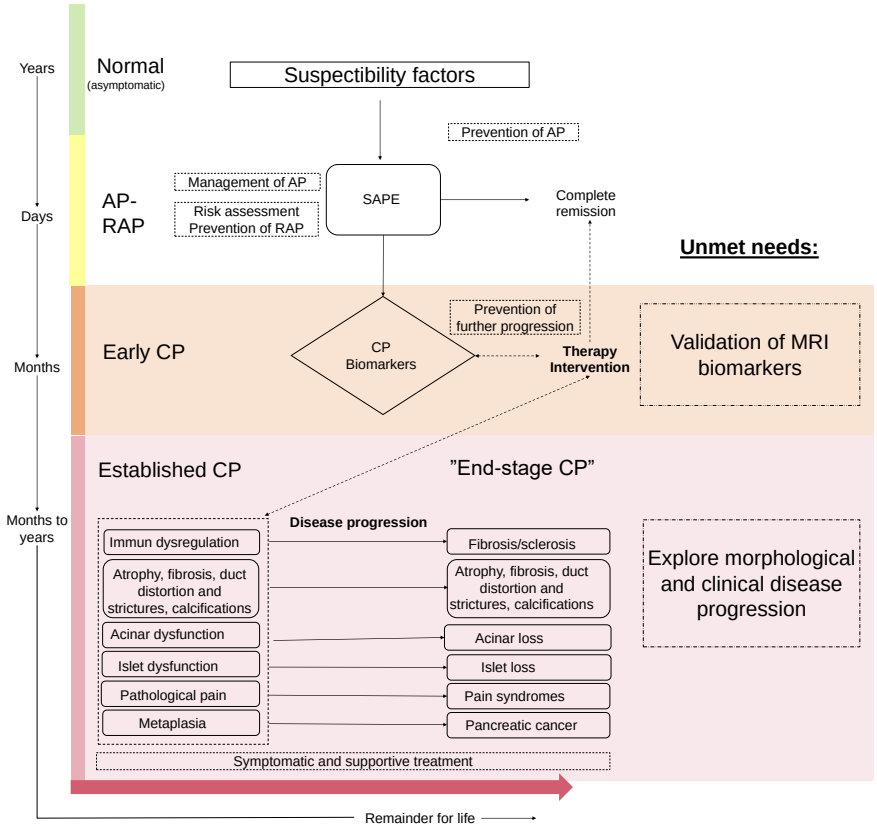


**Fig. 2.1:** Schematic overview of development and progression of CP [2]. Abbreviations: AP, acute pancreatitis; RAP, recurrent acute pancreatitis; SAPE, sentinel acute pancreatitis event; CP, chronic pancreatitis.

## 2.2 Diagnosing and staging of chronic pancreatitis

Diagnosing CP remains challenging in many cases. The following section focuses on the diagnosis and staging of CP. Today several different classification systems for CP exist, focusing either on the clinical or the morphological appearance of the disease or using a combination of both. Due to the high number of classification systems and their several modifications, only a few relevant to this Ph.D. thesis will be addressed.

Overall, most diagnostic criteria used for CP focus on the more advanced disease stages, like parenchymal calcifications, ductal pathology, or pancreatic function loss, as references. However, despite patients with severe CP can be diagnosed and staged sufficiently, these criteria do not meet the needs to identify patients with early and milder stages of CP.

Plenty of existing diagnostic systems, such as the Cambridge classification and the Lüneburg Clinic Diagnostic Criteria, are accepted tools for diagnosing CP. These major classification systems focus mainly on the ductal features of CP, like duct dilatation and dilated side branches, being predominantly based on imaging [31,32], demonstrating that imaging is fundamental to the CP diagnosis. Other globally accepted classification systems, like the M-ANNHEIM classification, focus more on the clinical aspects of the disease, including the presence of pancreatic exocrine and/or endocrine insufficiency and the presence of complications. The M-ANNHEIM system integrates CP's clinical-stage, severity, and clinical findings and is the only system providing a severity index [24].

There is no single universally accepted test for diagnosing and staging of CP, especially in its early stages [9]. Even if no radiological, clinical or endoscopic diagnostic method can definitively diagnose all stages of CP, there is a wide range of diagnostic tools trying to do so. However, in clinical practice, the diagnosis and staging of CP are often based on a combination of clinical information, imaging findings, and testing of exocrine pancreatic function [8].

### 2.2.1 Clinical symptoms

Although CP diagnosis may be suspected when typical clinical symptoms are present, these symptoms are usually not suited to confirm a diagnosis fully, as common symptoms like abdominal pain, weight loss, steatorrhea, and malnutrition are vague and not specific to CP. Moreover, the clinical presentation of the disease can vary from being completely silent to acute abdomen.

The most presenting symptom in CP patients is abdominal pain, often epigastric and radiating to the back. However, intensity, duration, and pain pattern are quite variable, but as the disease progresses, the pain attacks

usually become more frequent, and pain-free intervals decrease [33,34]. The degree of abdominal pain in CP does not always correlate with the severity of morphological changes of the gland [17,35].

Other less frequent initial clinical manifestations that can be related to complications of CP like pancreatic pseudocysts may presenting with pain or swollen abdomen, biliary obstruction may presenting with jaundice, cholangitis, or attacks of indigestion and obstruction of the splenic vein, by an edematous pancreatic tail can cause portal hypertension, gastric varices, and gastrointestinal bleeding [36].

### 2.2.2 Pancreatic function testing

The dysfunction and loss of islet cells of the pancreas can lead to pancreatic endocrine insufficiency. This form of diabetes can be defined as type 3c diabetes [37]. The measurements of fasting glucose and glycated hemoglobin A1c (HbA1c) are valid for screening type 3c diabetes [37].

Exocrine pancreatic insufficiency (EPI) is defined as decreased pancreatic secretion of digestive enzymes and bicarbonates and often occurs late in the disease due to the large functional reserve capacity of the pancreas of 90 - 95 % [38]. A diagnosis of EPI supports the CP diagnosis and can be helpful in the staging of the disease [39]. Collection of pancreatic juice by a duodenal tube after intravenous administration of the gastrointestinal hormone secretin or cholecystokinin makes it possible to measure volume, bicarbonate, and enzyme levels (e.g., lipase and trypsin) in the pancreatic juice. It is considered the gold standard for measuring pancreatic exocrine function [40].

Still, these tests are invasive, time-consuming, uncomfortable for the patient, expensive, and rarely available outside of specialist centers [41]. Indirect tests include measurement for fecal elastase, fecal fat, and serum trypsinogen. In general, indirect tests have moderate sensitivity and specificity for diagnosing advanced CP, but sensitivity and specificity are less for early disease. Studies have demonstrated that FE-1 with a cut-off value of 200 µg/g is correlated with pancreatic duct changes shown by both endoscopic retrograde cholangiopancreatography (ERCP) and MRCP [42,43].

### 2.2.3 Histological findings

Histological findings are highly accurate and specific, including parenchymal fibrosis, fat infiltration, atrophy, ductal changes, and intraductal calcifications [44]. Even though pancreatic biopsy is the most precise diagnostic method, the acquisition of pancreatic tissue is difficult due to the retroperitoneal location of the pancreas and the inhomogeneous location/distribution of parenchymal changes in CP. Moreover, there is the risk of severe complications, like bleeding, acute pancreatitis, or sepsis [45]. Therefore, histology

is rarely assessed, and in most cases, other modalities are used.

### 2.2.4 Endoscopic retrograde cholangiopancreatography

ERCP is a sensitive diagnostic method for CP and allows the detection of caliber changes of the pancreatic duct and irregularities of side branches. The Cambridge criteria were developed in 1984 and enabled to classify CP, based on the number of ductal abnormalities found at ERCP [46]. Subtle variations of early CP are usually detectable. Furthermore, endoscopic treatment provides therapeutic options like dilatation, stone extraction, and pancreatic duct stenting. Another advantage of ERCP is the possibility of collecting pancreatic juice [42]. However, ERCP is an invasive procedure that is uncomfortable for the patient, time-consuming, expensive, and has potential severe complications, including post-ERCP pancreatitis [47]. Most importantly, a normal ERCP finding cannot exclude very early CP since ERCP does not evaluate the pancreatic parenchyma.

Nonetheless, with the availability of other non-invasive imaging modalities, ERCP should not be used as the first tool to diagnose CP. Cross-sectional imaging (computed tomography (CT) or MRI/MRCP) and high-frequency endoscopic ultrasound (EUS) have replaced ERCP as a routine diagnostic tool, and the principles of the Cambridge classification have been modified to CT or MRCP [32, 48].

### 2.2.5 Ultrasound

EUS is a widely available, cheap imaging modality to assess morphological changes of the pancreas. It is widely used to diagnose and evaluate the severity of CP in the early stages of the disease [49]. However, EUS is an invasive method that is uncomfortable for the patient. Furthermore, recent studies showed a suboptimal correlation between functional and morphological tests in the early stages of CP [50, 51]. Transabdominal ultrasound is non-invasive but limited to the deeper location of the pancreas, so its sensitivity and accuracy are way lower than EUS [52].

### 2.2.6 Computed tomography

CT is a widely used availability and a reliable non-invasive method of quantifying pancreatic morphology and is suggested as first-line imaging for patients with clinical suspicion of CP [53]. Typical CT findings in patients with CP are atrophy, ductal dilatation, and pancreatic calcifications. Moreover, it may be used to assess CP-related complications, like pseudocysts and duodenal and biliary stenosis and acute inflammation [53], or to rule out possible

differential diagnoses [54]. However, early changes of CP may often not be reliably detectable by CT [55].

### 2.2.7 Magnetic resonance imaging

MRI is a non-invasive diagnostic imaging method without ionizing radiation or other known adverse side effects. The measured MRI signal derives from the 1H protons in the body and whether they are intracellular or extracellular located. Since its beginning in clinical use in 1980, the advances in MRI led to increased use of pancreatic MRI [56]. MRI is more sensitive than CT and it is increasingly used as the first choice of imaging modality or as a supplement to previous CT when CP is suspected [57].

MRCP allows visualization of pancreatic parenchyma and abnormalities of the ductal system of the pancreas. When secretin is administered, it improves the visualization of ductal abnormalities of the main pancreatic duct and side branches [58]. In addition, MRCP also allows the detection of complications of CP, such as pseudocysts, biliary strictures, or pseudocysts, and allows quantitative assessment of exocrine secretion capacity [56]. MRCP allows similar visualization of the pancreas as ERCP, but is non-invasive and therefore associated with fewer complications [37, 59].

## 2.3 Advanced pancreatic MRI

The technical developments in MRI allow the evaluation of pancreatic anatomy using conventional T1- and T2-weighted images. Furthermore, the assessment of the complex ductal- and parenchymal-related changes associated with CP is possible, including estimation of the degree of fibrosis and fat infiltration [20].

Hence, pancreatic MRI can now provide even more detailed information on pancreatic parenchyma by using advanced MRI techniques like DWI, Dixon imaging, T1 mapping, and MRE [60–63]. This chapter focuses on the techniques used in this Ph.D. thesis.

### 2.3.1 Diffusion-weighted imaging

DWI is a well-validated MRI technique. It is based on the random thermally induced diffusion of water molecules ($^1H$-protons) in the body in the biological setup known as Brownian motion [64]. A restriction of $^1H$ protons diffusion/movements results in high signal intensity (SI) on the DWI series and a low signal on the quantified apparent diffusion coefficient (ADC) maps [60]. In contrast, the unhampered diffusion of $^1H$-protons occurs higher ADC values [64]. Recently, intravoxel incoherent motion imaging (DWI with multiple

b-values and estimation of diffusion and perfusion fractions) is available and has shown promise for the evaluation of pancreatic parenchyma in CP [63].

Several studies investigated the use of DWI for assessing pancreatic fibrosis [16–18] and reported that pancreatic fibrosis caused restricted diffusion and thereby lower ADC values compared to healthy subjects. Still, no significant difference in ADC values was seen when comparing mild and severe stages of CP [18,65].

### 2.3.2 Dixon imaging

The Dixon method is a chemical shift MRI technique that allows the quantification of water and fat content in tissues by separating the fat and water signals. It was first described in 1984 [66] and used the fact that water and fat molecules process at different rates and so, over time, will alternate between being in-phase and out-phase. In the early 2000's better and faster algorithms were developed, allowing valid assessment of fat content in abdominal organs, using 2-point and 3-point techniques [66]. Recently, multipoint techniques (multi-echo acquisition) were used to assess a quantitative proton density fraction (PDFF) [67].

Previous studies reported a higher degree of fat in CP patients than in the healthy pancreas and a moderate correlation to the fat content as assessed by histopathological evaluation [20,68]. As pancreatic fibrosis is often accompanied by large areas of fat, Dixon imaging, with quantification of fat content, is has the potential being a biomarker of pancreatic fat content [69].

### 2.3.3 T1 relaxation mapping

T1 relaxation mapping is a technique allowing the calculation of the T1 relaxation time of a particular tissue by displaying it voxel-vice on a parametric map, where it can be quantified [70]. T1 mapping has been successfully used to evaluate myocardial fibrosis and is currently available for abdominal evaluation [61,71,72]. T1 is the longitudinal (spin-lattice) relaxation time of tissue after it was disturbed from its equilibrium state (e.g. by applying an radiofrequency pulse to invert magnetization) [73]. T1 reflects intracellular and extracellular compartments changes and can be affected by collagen, protein, water (edema), lipids, and iron content [70]. The longitudinal magnetization recovery after inversion is, approximated in many instances by an exponential function. T1 values can then be computed pixel-wise from a signal intensity versus time curve fitting model [70,73].

Previous studies have reported that the T1 relaxation time of the pancreas is increased in CP patients compared to a healthy pancreas [19,61,74].

### 2.3.4 Magnetic resonance elastography

MRE is a phase-contrast MRI technique assessing the mechanical properties of soft tissue stiffness [75–80]. With MRE, the examined organ of interest is cyclically compressed and relieved by acoustic (or pressure) waves transmitted automatically from a wave generator. The acoustic waves cause small displacements in the tissue. These displacements are called "shear waves" and occur horizontally [81, 82]. If applied continuously, the waves' speed propagation is reflected in the wavelength, dependent on the tissue. The wavelength becomes longer with increased tissue stiffness, as pressure waves travel faster in hard tissue [83].

Synchronous MRE uses motion-encoding magnetic field gradients to obtain raw phase images, showing the micron-level displacements resulting from the applied shear waves. The displacement images are processed by mathematical image analysis techniques to produce tissue stiffness maps (elastograms). These elastograms show the differences in elasticity and provide the possibility to obtain quantitative measurements of the tissue stiffness. The tissue stiffness is reported in kilopascals and several pathological processes, like fibrosis, inflammation, and edema, go along with changes in tissue stiffness [82, 84].

MRE has successfully been used in various organs, including the liver, brain, and heart [77–80, 85–88]. Moreover, as described in our recent systematic review on pancreatic MRE, an increasing number of studies successfully used MRE to differentiate healthy from pathological tissue of the pancreas, both with or without fibrosis [84]. Previous studies demonstrated elevated stiffness levels for CP patients [61, 89]. Moreover, MRE had a high sensitivity for diagnosing even mild CP [61]. Furthermore in a recent study by Liu et al a correlation of the MRE-derived stiffness with the histologically assessed fibrosis grade was shown [19].

# Chapter 3

# Hypothesis and Aims

The overall objective of this Ph.D. thesis was to provide a deeper understanding of the pathophysiology behind the development and progression of CP using non-invasive pancreatic MRI. Hence, with the use of repeated pancreatic MRI and application of new non-invasive MRI imaging methods in CP patients, this Ph.D. thesis explores the potential of pancreatic MRI to diagnose CP at earlier stages with the ultimate goal to provide clinicians the opportunity for therapeutic intervention to slow the progression of CP.

The thesis is based on three published peer-reviewed original papers and a paper submitted for publication. The four original papers were based on two studies, see Fig. 3.1.

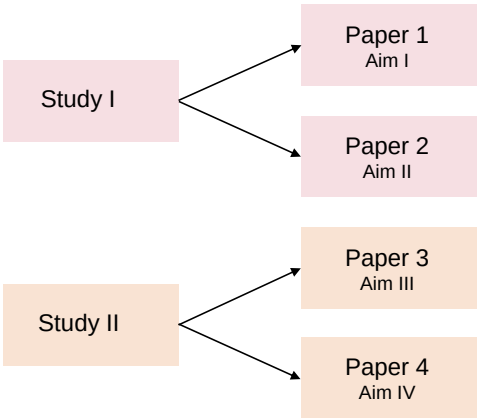


**Fig. 3.1:** Overview of the Ph.D. studies, papers, and aims.

Study I was a longitudinal study investigating the development of structural pancreatic changes (using conventional MRI with T2-weighted imaging, MRCP, DWI, and Dixon imaging) in CP patients over four years and their relationship to risk factors and clinical parameters.

Study II was a cross-sectional study investigating new MRI imaging techniques (including T1 mapping, MRE, and Dixon imaging) in CP patients as

compared to healthy controls (HCs).

## 3.1 Aims

1. To assess and explore the morphological changes in CP patients over four years and explore their association with each other.
    - The hypothesis was that CP patients developed increased pancreatic atrophy, fibrosis, fat infiltration, and ductal pathology after four years, and furthermore that these observed changes were associated with each other.
2. To explore the relationship between the morphological progression of the pancreas and the clinical progression of the disease in CP patients over four years.
    - The hypothesis was that the changes in parenchymal and ductal-related parameters during the four years were associated with the clinical status and outcomes of the patients.
3. To obtain pancreatic parenchymal MRI findings including pancreatic volume, T1 relaxation time, MRE-derived pancreatic stiffness, and PDFF in patients with CP and healthy controls and determine their diagnostic performance for diagnosing different stages of CP.
    - The hypothesis was that new MRI techniques MRE and T1 relaxation time mapping would have a high diagnostic performance in detecting mild CP that was higher than that of gland volume and PDFF.
4. To investigate the association of MRE-derived stiffness and T1 relaxation times and explore their relationship to pancreatic gland volume and pancreatic functions in CP patients and healthy controls.
    - The hypothesis was that MRE-derived stiffness and T1 relaxation times were internally associated and potential suited biomarkers for the degree of fibrosis in patients with CP with relevant relation to the state of pancreatic functions.

# Chapter 4

# Materials and Methods

## 4.1 Materials

Data for this thesis was collected from two MRI studies. The studies complied with the Declaration of Helsinki and were approved by the local Ethics Committees (N-20130040 & N-20130059 (study I) and Journal-no.: H-18017705 (study II)). Informed consent was obtained from both patients, and healthy controls after both oral and written information were given.

### 4.1.1 Study I

Study I was conducted at the Department of Radiology at the Aalborg University Hospital. Pancreatic MRI was performed in 25 patients with CP on two occasions: at baseline (December 2013 to January 2015) and after four years using the same 1.5 T MRI scanner. At baseline, patients were recruited from our outpatient clinic as part of a cross-sectional study assessing pancreatic MRI in patients with CP [90]. The diagnostic criteria for CP were based on the Lüneburg criteria, defined as a score of $\geq 4$ [91].

Only patients with a pancreatic gland size of $\geq 20$ ml were included for rescanning to provide enough pancreatic parenchyma to perform the parenchymal measurements. Additional exclusion criteria were the inability to undergo follow-up MRI, major illnesses such as cancer, and major pancreatic surgery. At baseline and follow-up visits, the following clinical information was obtained as described in section 4.8. Data on QOL and pain and pain interference were collected from questionnaires filled out of the patients on their annual clinical exams closest to the individual MRI date on both occasions.

### 4.1.2 Study II

Study II was conducted at the Centre for Pancreatic diseases, Department of Gastroenterology & Hepatology, and the Department of Radiology, Aalborg University Hospital, Denmark. The study was and was part of a larger

prospective multicenter study [92]. According to the M-ANNHEIM diagnostic criteria, 49 patients with CP and 35 HCs were included in study II. Patients were classified according to the Cambridge classification system (grade 0-4) adopted for the use of MRI/MRCP and/or a history of recurring acute pancreatitis [92]. The group distribution was as follows: mild CP group (n=19; Cambridge grade 2 or less (no main duct changes) or recurring acute pancreatitis) and moderate/severe CP group (n=30; Cambridge grade 3 and 4 (main duct changes)). Patients with acute exacerbation of pancreatitis were excluded.

All HCs had no history of pancreas- or gastrointestinal-related diseases. From January to December 2020, pancreatic 3 T MRI was performed in all subjects. Information on disease duration, etiology, and information on exocrine and endocrine function, was obtained by patient interviews and reviews of their medical records. Blood samples were collected at the same date for their individual MRI scanning. Also, additional data on QOL and pain were collected from questionnaires on the same day.

## 4.2 Methods

Study I and II were performed at the same hospital but using two different MRI scanners (Signa and General Electric Healthcare) with different field strengths (1.5 T and 3 T) for acquiring the data. The methods, including the MRI protocols, are described in the following section, and Fig. 4.1 shows an overview of the methods used in the two studies.

### 4.2.1 MRI protocol study I

MRI on all subjects was performed at baseline and after four years using the same 1.5 T MRI scanner (Signa HDxt, General Electric Healthcare, Milwaukee, Wisconsin, USA) in a supine position and an 8-channel body coil. The imaging protocol is provided in Table 4.1.

### 4.2.2 MRI protocol study II

For study II, pancreatic MRI was performed in all subjects using a 3 T MRI scanner (Signa Premier, General Electric Healthcare, Milwaukee, Wisconsin, USA) and a flexible 30-channel body coil (AIR™) in a supine position. All subjects were instructed to fast for at least three hours prior to their MRI.

In addition to the routine pancreatic MRI sequences, T1 mapping and MRE were performed in the same session. The complete imaging protocol for study II is provided in Table 4.2.

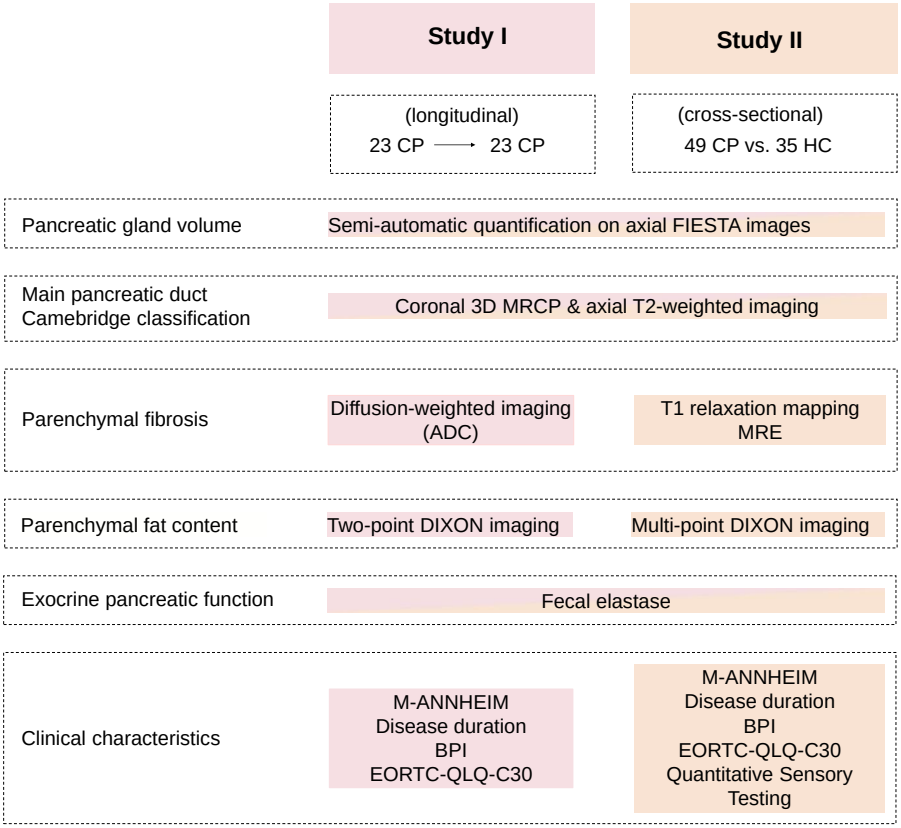


**Fig. 4.1:** Overview of techniques used in study I and study II. Abbreviations: 3D MRCP: 3-dimensional magnetic cholangiopancreatography; MRE, magnetic resonance elastography; M-ANNHEIM: M-ANNHEIM clinical staging of chronic pancreatitis.

**Table 4.1:** MRI protocol for study I. DWI was performed with multiple b-values 0, 50, 400, and 800 $sec/mm^2$. Abbreviations: TR/TE: repetition time/echo time; FOV: field of view; FIESTA: fast imaging employed steady-state acquisition; SSFSE FS: Single-shot fast spin-echo fat-saturated: 3D MRCP: 3-dimensional magnetic resonance cholangiopancreatography; LAVA-flex: liver acquisition with volume acceleration flex; DWI: diffusion-weighted imaging; BH: Breath-hold; FB RTr: Free-breathing with respiratory triggering.

| Imaging Sequence | Plane | TR/TE (ms) | Slice thickness (mm) | Matrix | FOV (cm) | Acquisition |
|---|---|---|---|---|---|---|
| Balanced steady-state gradient echo sequence (FIESTA) | oblique (axial) | 3.5/1.5 | 4.0 | 256x192 | 44 | BH |
| T2 SSFSE FS | oblique (axial) | 900/90 | 5.0 | 320x224 | 44 | BH |
| 3D-MRCP | coronal | 3500/630 | 2.6 | 320x256 | 44 | FB RTr |
| T2 SS | coronal | 3000/90 | 2.5 | 320x192 | 44 | FB RTr |
| Two-point-Dixon sequence (Lava-Flex) | oblique (axial) | 7/4 | 2.6 | 320x192 | 44 | BH |
| DWI | oblique (axial) | 4000/70 | 6.0 | 160x192 | 44 | FB |
| T2SSFSE | coronal | 2500/120 | 10.0 | 256x224 | 44 | BH |

**Table 4.2:** MRI protocol for study II. Abbreviations: TR/TE: repetition time/echo time; FOV: field of view; FIESTA: fast imaging employed steady-state acquisition; SSFSE FS: Single-shot fast spin-echo fat-saturated: 3D MRCP: 3-dimensional magnetic resonance cholangiopancreatography; BH: Breath-hold; FB RTr: Free-breathing with respiratory triggering.

| Imaging Sequence | Plane | TR/TE (ms) | Slice thickness (mm) | Matrix | FOV (cm) | Acquisition |
|---|---|---|---|---|---|---|
| Balanced steady-state gradient echo sequence (FIESTA) | oblique (axial) | 3.5/Minimum | 3.0 | 256x192 | 42 | BH |
| T2 SSFSE FS | oblique (axial) | variable/90 | 3.0 | 256x320 | 44 | FB RTr |
| 3D-MRCP | coronal | variable/900 | 2.6 | 320x320 | 34 | FB RTr |
| 3D-IDEAL IQ (multi-point Dixon sequence) | oblique (axial) | 5.9/Min Full | 2.0 | 160x160 | 44 | BH |
| 2D- modified Look-Locker inversion recovery (MOLLI) | oblique (axial) | 2.8/1.2 | 6.0 | 148x160 | 36 | BH, pulse triggered |
| SSFSE (Pancreas) | oblique (axial) | 2000/90 | 7.0 | 256x320 | 42 | BH |
| Gradient echo EPI pulse sequence (MR Touch) | oblique (axial) | 1000/ Min Full | 7.0 | 64x64 | 42 | BH |

## 4.3 Assessment of pancreatic size

### 4.3.1 Pancreatic gland volume

For both studies, the pancreatic gland volume was measured on axial FIESTA images in a customized semi-automatic Matlab application (MathWorks, Natick, Massachusetts, USA). On each slice, the pancreas contour was manually segmented. The gland volume was then automatically calculated by adding all segmented areas and multiplying them with slice thickness. The main pancreatic duct (MPD) and cystic lesions were excluded, aided by anatomical information from other image series, as described previously [20, 93] (see Fig. 4.2).

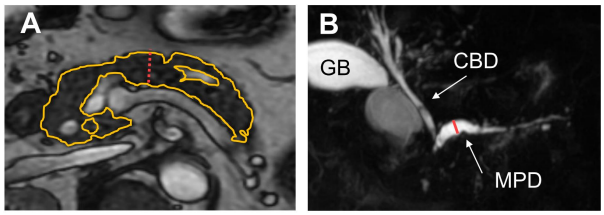


**Fig. 4.2:** Measurements of the pancreatic gland volume and anterior-posterior diameter of the pancreatic body (A) and main pancreatic duct (B) in a patient with chronic pancreatitis. Abbreviation: MPD, main pancreatic duct; CBD, common bile duct; GB, gallbladder

### 4.3.2 Anterior-posterior diameter

In study I, the anterior-posterior diameter was measured on axial FIESTA images at standardized positions for quantification of parenchymal thickness. The measurements were performed perpendicular to the pancreatic axis in the pancreatic head, body, and tail according to recent guidelines of cross-sectional imaging in CP [94] (see Fig. 4.2).

## 4.4 Main pancreatic duct and Cambridge classification

Both studies measured the largest anterior-posterior diameter of the MPD in the head, body, and tail of the pancreas, see Fig. 4.2. In addition, the presence of pathological side branches of the MPD, pseudocysts (diameter $>5$ mm), ductal obstruction, and intraductal filling defects were assessed, according to the international imaging guidelines for CP [53], on 3-dimensional

MRCP and T2-weighted images using the commercially available PACS system EazyViz (v. 7.6.7-270, Karos Health A/ S, Valby, Denmark). This information was used to characterize the CP patients according to the modified Cambridge classification used for CT/MRI [32,48].

## 4.5 Assessment of fibrosis

### 4.5.1 Apparent diffusion coefficient (study I)

For study I, ADC maps of the pancreas were generated from the DWI series, using commercially available software (AW server 2.0, General Electric, Milwaukee, Wisconsin, USA). ADC maps were based on three b-values (50, 400 and 800 sec/mm$^2$). Regions of interest (ROIs) were drawn and positioned in the pancreatic head, body, and tail to automatically calculate pancreatic ADC values (see Fig. 4.3 A).

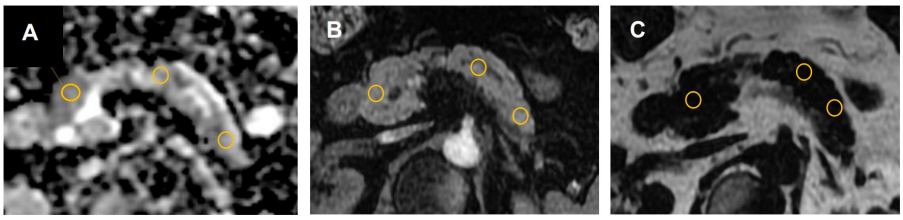


**Fig. 4.3:** Placement of regions of interest (yellow circles) for study I for measurements of apparent diffusion coefficient (A), fat signal fraction on water-only (B) and fat-only (C).

### 4.5.2 T1 relaxation mapping (study II)

For assessment of T1 relaxation time, T1 maps were generated using the MOLLI-sequence. Measurements were performed on the T1 maps directly on the MRI scanner workstation (Signa Premier, General Electric Healthcare, Milwaukee, Wisconsin, USA) in the pancreatic head, body, and tail, see Fig. 4.4 A+B.

### 4.5.3 Magnetic resonance elastography (study II)

For MRE, mechanical waves were generated by an active pneumatic driver system (General Electric Healthcare, Milwaukee, Wisconsin, USA), located outside the scanner, at a frequency of 40 Hz. The mechanical waves were delivered via a plastic tube into the body and pancreas through a passive rigid round driver (diameter 19 cm) (General Electric Healthcare, Milwaukee,

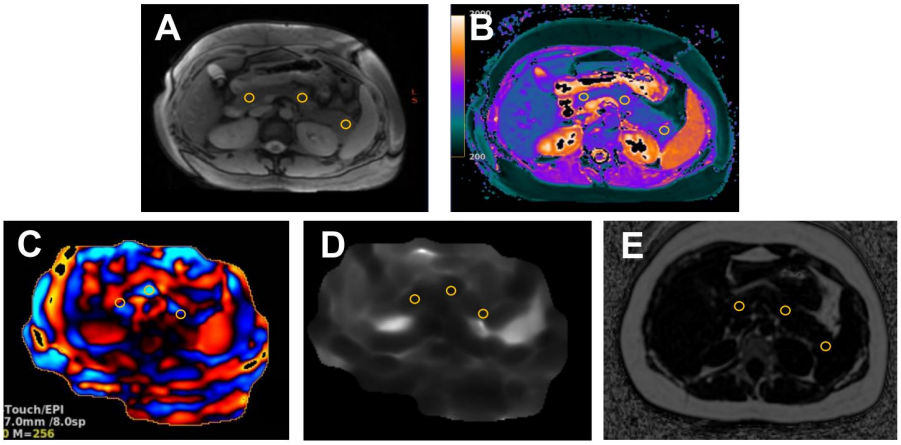


**Fig. 4.4:** Imaging approach for study 2. Assessment of T1 relaxation time using the MOLLI-sequence (A) and T1 relxation maps (B). Pancreatic wave image (C) in color showing traversing shear waves through abdomen and grey scale stiffness map (D) for pancreatic stiffness evaluation. Assessment of pancreatic fat fraction on multi-point Dixon proton density fat fraction maps (E).

Wisconsin, USA), located in the epigastric region at the level of the xiphisternum. The passive driver was fastened on the stomach with an elastic belt, see Fig. 4.5.

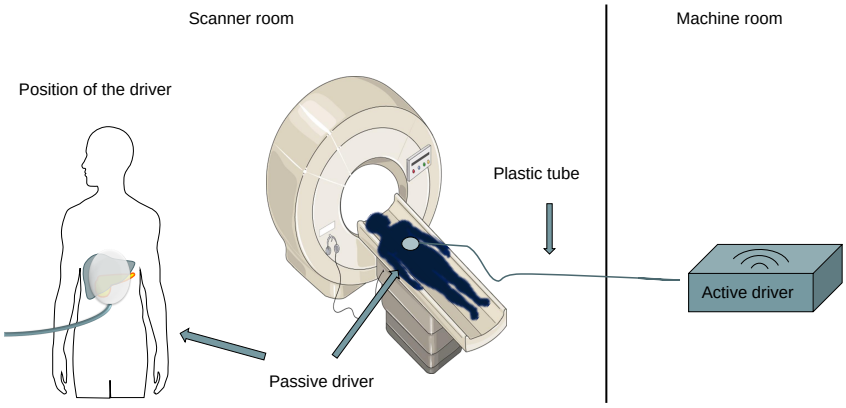


**Fig. 4.5:** Schematic diagram of MRE setup used in study II.

Wave images were automatically processed using a direct inversion algorithm installed on the MRI scanner workstation, and pancreatic stiffness maps (elastograms) were automatically generated and transferred to our PACS system EazyViz. The measurements of pancreatic stiffness were performed using commercially available software (AW server 3.2, General

Electric, Milwaukee, Wisconsin, USA) by drawing ROIs in the pancreatic head, body, and tail on the corresponding stiffness maps guided by T2-weighted images with the same slice thickness and field of view [95], see Fig. 4.4 C+D.

## 4.6 Assessment of fat content

### 4.6.1 Two-point Dixon imaging (study I)

For the fat signal fraction (FSF) analysis, ROIs were placed on the fat-only and water-only images of the LAVA-flex (Dixon) sequence using PACS system EazyViz. ROIs were placed in the pancreatic head, body, and tail in the same position as DWI analyses, as described in section 4.5.1 and shown in Fig. 4.3 B+C. The mean SI in the ROIs was used to calculate FSF using the formula:

$$FSF = \frac{SI_{fat-only}}{SI_{water-only} + SI_{fat-only}}$$

### 4.6.2 Proton density fat fraction (study II)

The PDFF was directly measured on the fat fraction images of the IDEAL IQ sequence generated on the MRI scanner workstation and transmitted to our PACS (see Fig. 4.4 E).

## 4.7 Pancreatic exocrine and endocrine function

For both studies, pancreatic acinar cell function was described by obtaining fecal elastase values using a commercially available fecal elastase test kit (Pancreatic Elastase ELISA, BIOSERV diagnostics GmbH, Rostock, Germany). Fecal elastase concentration was determined by a photometric double-sandwich enzyme-linked immunosorbent assay (Pancreatic Elastase ELISA, BIOSERV diagnostics GmbH, Rostock, Germany). A fecal elastase concentration below 200 mg/g was defined as exocrine pancreatic insufficiency [42].

Pancreatic islet cell function was evaluated by obtaining glycated hemoglobin A1c (HbA1c) and glucose-lowering therapy.

## 4.8 Clinical characteristics in chronic pancreatitis

For both studies, clinical data was obtained from patient interviews and a review of the patients' medical records, including biochemistry samples. For

both studies, the following clinical parameters were obtained in all subjects:

1. Etiology of CP
2. Duration of CP (from the initial diagnosis until the baseline and follow-up MRI scan)
3. Presence of endocrine insufficiency
4. Presence of exocrine insufficiency
5. Body mass index

For study II, patients were classified according to modified M-ANNHEIM clinical staging system as 0: asymptomatic chronic pancreatitis; I: symptomatic stage without pancreatic insufficiency; II: stage of partial pancreatic insufficiency; III: stage of painful complete pancreatic insufficiency; IV: stage of secondary painless disease (burnout) [24].

## 4.9 Disease burden in chronic pancreatitis

For both studies, disease burden was characterized by the patient-reported outcomes: QOL and pain scores. To evaluate QOL, the European organization for research and treatment of cancer quality of life questionnaire was used. The questionnaire has been validated for use in patients with CP [96]. Pain scores were assessed using the modified Brief Pain Inventory short form [97].

## 4.10 Statistical analysis

Different statistical analyses were used for studies I and II, depending on their aim and data structure. The statistical analyses for the two studies are reported in detail in papers I-IV. In general, differences between two continuous or categorical variables were analyzed using t-test or two-sample Wilcoxon-rank-sum test. A one-way analysis of variance was used for comparing more than two groups, followed by group-wise comparisons using Bonferroni corrected posthoc tests. The potential confounding of age, gender, and height on the MRI parameters was explored using linear regression models. Diagnostic performance was obtained using receiver operating characteristic (ROC) curve analysis and reported as the area under the curve (AUC), sensitivities, specificities, accuracy, and positive and negative likelihood ratios. Pearson or Spearman correlation tests were used to perform correlation analyses, as appropriate. A P-value less than 0.05 was considered statistically significant. The software package STATA version 15.1 (StataCorp LP, College Station, Texas, USA) was used.

# Chapter 5

# Key Results

The key results to answer the four aims are presented in this chapter. Detailed results are reported in the papers. An overview of the main results is illustrated in Fig. 5.1.

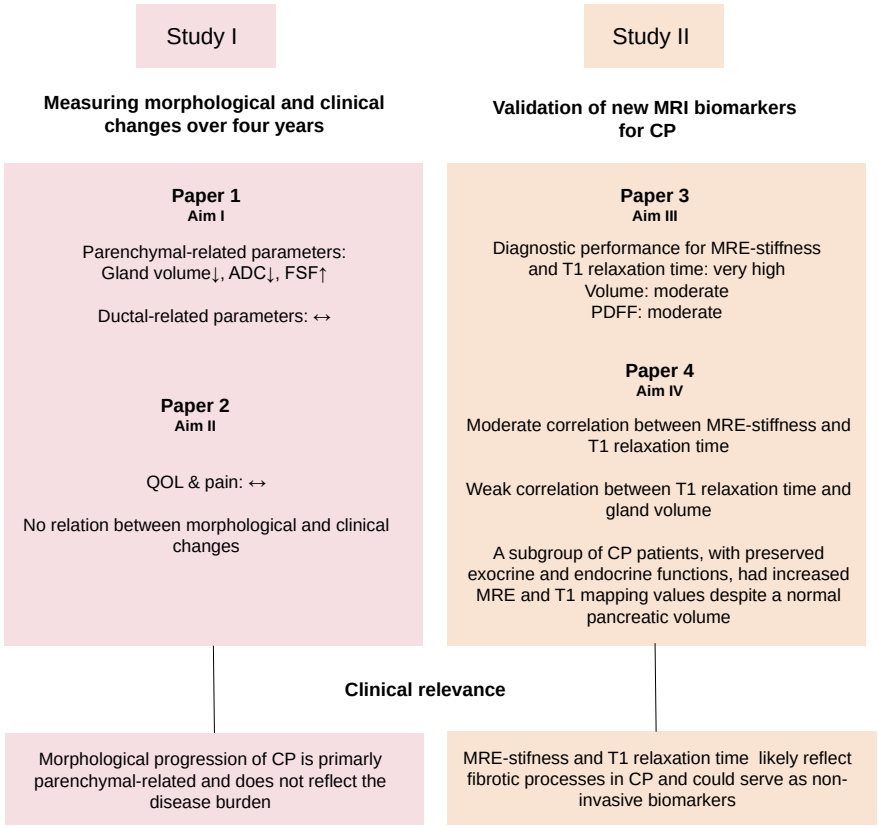


**Fig. 5.1:** Overview of the main results from Paper I-IV. Abbreviations: CP, chronic pancreatitis; MRI, magnetic resonance imaging; ADC, apparent diffusions coefficient; FSF, fat signal fraction; QOL, quality of life; MRE, magnetic resonance elastography; PDFF, proton density fat fraction.

## 5.1 Aim I

Aim: To assess and explore the morphological changes in CP patients over four years and explore their associations with each other. (Paper I)

**Key results:**

- Over four years, the pancreatic gland volume decreased significantly (P<0.001).
- Patients developed reduced ADC values, meaning a higher degree of fibrosis (P<0.001).
- Patients developed increased FSF, meaning a higher degree of fat infiltration (P<0.001).
- Patients developed higher Cambridge classification scores (P=0.033), but no significant change of the MPD diameter (P>0.05)
- There were no clear and systematic associations were found between the progressions of the different MRI parameters.

*Interpretation: Morphological progression in chronic pancreatitis seems to be more parenchymal-related than related to ductal changes, which seem more variable. Therefore, parenchymal MRI parameters could represent suitable biomarkers for disease progression, whereas ductal-related MRI parameters are likely not of use for monitoring disease progression in CP.*

## 5.2 Aim II

Aim: To explore the relationship between morphological progression of the pancreas (over four years) and the clinical progression of the disease. (Paper II)

**Key results:**

- Patient-reported outcomes of QOL and pain did not change significantly over four years (all P>0.05).
- The 4-year changes in QOL and pain were not significantly related to the progression of the morphological changes (all P>0.05).
- The progression of pancreatic atrophy and the changes in fecal elastase concentration over four years were associated (R=0.61; P<0.001).

*Interpretation: The changes of gland morphology might be a sensitive tool for monitoring morphological disease progression of the pancreatic gland but do not directly reflect patient-reported disease burden and progression of symptoms in CP patients, except from a confirmation of the association between the loss of pancreatic parenchyma and exocrine function loss.*

## 5.3 Aim III

Aim: To obtain pancreatic parenchymal MRI findings (gland volume, T1 relaxation time, MRE-derived stiffness, and PDFF) in patients with CP and HCs and determine their diagnostic performance for diagnosing different stages of CP. (Paper III)

**Key results:**

- T1 mapping and MRE had high diagnostic performances for differentiating the mild CP group from the HCs (ROC-AUCs: 0.94 and 0.93, respectively) and for diagnosing the presence of any grade of CP from the HCs (ROC-AUCs of 0.98 and 0.97, respectively).
- Pancreatic volume and PDFF showed a moderate diagnostic performance for diagnosing mild CP (ROC-AUCs of 0.66 and 0.58, respectively). For diagnosing the presence of any CP, pancreatic volume and PDFF had ROC-AUCs of 0.89 and 0.68, respectively.

*Interpretation: T1 mapping and MRE had high performance in detecting mild CP, outperforming gland volume and PDFF. T1 relaxation time and MRE-derived stiffness might reflect the early parenchymal changes in CP and have the potential to serve as future imaging-based biomarkers for CP to detect especially early/mild stages of CP.*

## 5.4 Aim IV

Aim: To investigate the association between MRE-derived stiffness and T1 relaxation times, and explore their relationship to pancreatic gland volume and pancreatic functions in a group of CP patients and HCs. (Paper IV)

**Key results:**

- MRE-derived pancreatic stiffness and pancreatic T1 relaxation times were positively correlated in the CP group ($R^2=0.42$, $P<0.001$) and in the control group ($R^2=0.14$, $P=0.028$).

- MRE-derived pancreatic stiffness and gland volume were not significantly correlated in the CP group (R2=0.007; P=0.065) or the HC group (R2=0.010; P=0.57).
- T1 relaxation time was related to gland volume (R2=0.19; P=0.002) in the CP group but not in the HC group (R2=0.11; P=0.056).
- Patients without loss of exo- and endocrine functions exhibited increased MRE-derived stiffness and T1 relaxation time with only a minor decrease in gland volume compared to HCs. With the gradual loss of one and two exo- and endocrine functions, a further increase in MRE-derived stiffness and T1 relaxation time was observed together with a marked reduction in gland volume.

*Interpretation: The positive association between pancreatic MRE-derived stiffness and T1 relaxation times suggests that these two modalities likely reflect aspects of fibrotic processes in CP and might be considered non-invasive biomarkers for quantifying early pancreatic fibrosis in CP patients. Both techniques were only weakly associated with gland volume suggesting that the gland volume might not be suited as a diagnostic tool for early changes in CP, as atrophy probably occurs later in the disease process. A subgroup of CP patients, characterized by preserved exo- and endocrine functions, had fibrosis as assessed by MRE and T1 mapping values despite a normal pancreatic volume, suggesting that both techniques might be more specific for the early parenchymal changes CP than the loss of gland volume.*

# Chapter 6

# Discussion

Advanced and multimodal MRI techniques were used to assess morphological pancreatic changes in CP patients and to explore their potential in detecting early/mild disease and monitoring disease progression. The discussion is divided into two parts, first concerning methodological considerations in pancreatic MRI, hereafter discussing clinical implications and future perspectives.

## 6.1 Methodological considerations

### 6.1.1 Pancreatic gland volume

Evaluation of pancreatic gland size has been performed since 1980, as pancreatic atrophy of the pancreatic is a well-known feature of CP [20,69]. Traditionally the anterior-posterior-diameters were measured, however with further developments in software applications, the more precise volumetric measurements of pancreatic size were more often used. However, the volumetric segmentation of the pancreatic gland is a time-consuming procedure, which cannot be integrated into clinical practice.

Moreover, the problem with volume measurements is the missing standardized definition of pancreatic atrophy. Several studies have shown the considerable variation in the size of the normal pancreas [98–102], making an objective definition of a normal range for pancreas volume difficult. A recent study suggested that pancreatic atrophy is not a specific factor of CP and is influenced by several factors like age, gender, height, and ethnicity [100,103].

Several previous studies demonstrated lower pancreatic gland volumes in patients with chronic pancreatitis compared to healthy volunteers [20,69], and we confirmed this in both of our studies. Additionally, in our prospective study I, we found pancreatic atrophy to be a progressive finding in patients with established CP, indicating that the degree of pancreas atrophy could be a suitable parameter for monitoring morphological progression in CP. The lack of atrophy definition seems less problematic when evaluating the individual progression of pancreatic atrophy in a single patient.

But, when comparing the measurement of pancreatic volume, as a diagnostic tool for detection of mild CP, with the new MRI techniques (T1 mapping and MRE) in study II, pancreatic volume was clearly outperformed. More than that, we observed a subgroup of CP patients with preserved exo- and endocrine functions, having elevated measurement with the new techniques, despite a pancreatic volume within the considered normal range. This suggests that volume loss could be a relatively late phenomenon in CP development that appears after initiation of the fibrosis process, related to loss of exocrine/acinar elements, and influenced by several cofactors (especially age, gender, and body composition) [100, 103].

Correspondingly, Frøkjær et al. found no association of pancreatic fibrosis obtained by diffusion-weighted imaging and the atrophy-related parameters [17]. Hence, even if the pancreatic volume might be a suitable marker for CP's morphological disease progression, it is likely not suited as a biomarker for detecting of early changes in CP.

### 6.1.2 Main pancreatic duct and Cambridge classification

The Cambridge classification initially developed for ERCP in 1984 and then adapted to CT/MRI, has since then served as a reference standard in diagnosing and staging CP, meaning that mainly ductal abnormalities laid the foundation for the diagnosis of the established disease [46]. But as ductal changes in CP are likely following fibrotic changes, they may not be suited for solely diagnosing early stages of CP. Recent guidelines also highlighted this, emphasizing the need to incorporate both ductal and parenchymal imaging biomarkers and future imaging scoring systems [48, 53].

Moreover, in our study I, the ductal parameters had no pronounced progression over time, implying that progression of ductal features is not suited to measure disease progression and stage patients with CP. In comparison to that, the parenchymal-related parameters (degree of atrophy, fibrosis, fat content) seem to be more valid biomarkers for CP disease progression. This indicates that traditional ductal-based diagnosis and staging systems should likely be revised if more information on mild stages and gradual progression of CP is wanted.

Still, the ductal changes in CP are widely used to characterize the disease, and the diagnosis of CP is often made based on duct dilatation or other ductal pathology seen on imaging. However, the ductal-related parameters such as dilated side-ducts, ductal irregularity, and caliber variation have been shown to have a low inter-reader agreement [94], making it different to compare and evaluate especially subtle changes of the ductal system. Despite that, several studies reported significant variation of MPD size according to age, gender, and localization in the pancreas (head, body, or tail) [104]. Moreover, MPD diameter showed considerable variation between and within CP patients [20],

which also is in line with our findings.

Altogether, ductal features in CP are likely insensitive biomarkers of the more detailed and gradual progression of CP once the disease is established, as the ductal changes in CP likely follow the fibrotic changes.

### 6.1.3 Pancreatic fibrosis

Fibrosis of the pancreas is a histological feature in CP. Recent studies, using animal models, have proposed that CP develops through activation of pancreatic stellate cells, producing collagen and forming parenchymal fibrosis [26, 27, 105]. This results in permanent loss of the normal pancreatic parenchyma, deformation of the ductal system, and severe destruction of the pancreatic acinar and islet cells, resulting in exocrine and endocrine insufficiency [106]. Our findings support these assumptions, pointing at the increase of fibrosis and not the resulting atrophy and ductal changes as the driving force in the CP progression, especially in the early/mild phases of the disease.

In line with several studies, in study I, CP patients had restricted diffusion of the pancreas with reduced ADC values [16, 107, 108] and developed significantly lower ADC values at the follow-up, which means progression with an even higher degree of fibrosis. However, ADC measurements have a very high variation, relatively long acquisition time, and are not directly comparable across different MRI scanners and/or using different field strengths. Therefore, other fibrosis-targeting MRI techniques, like T1 mapping and MRE, could provide promising possibilities for faster, robust, and more generalizable noninvasive fibrosis assessment in CP.

T1 relaxation time is tissue-specific and comparable across different MRI scanners using the same field strength. MRE-derived pancreatic stiffness is a mechanical property and is therefore independent of the magnetic field strength. Both techniques could be integrated into a standard MRI examination to provide rapid, reliable, and comprehensive imaging. Both methods are based on different methodical principles, and they are likely to represent different co-existing aspects of the physiological fibrosis process. The implementation of the two techniques in pancreatic imaging is relatively new and has only been investigated in few studies.

In study II, both techniques showed excellent diagnostic performances, outperforming gland size and fat content assessment in the detection of CP. The highest T1 relaxation times and MRE-derived stiffness values were found in the moderate/severe group compared to the mild CP group and the healthy controls. The stepwise increase of these values likely reflects the previously described continuous progressive fibroinflammatory process from early to established to end-stage CP [2]. The lengthened T1 relaxation time and higher MRE-derived stiffness values seen in the CP can probably be ex-

plained by pancreatic fibrosis and extracellular matrix remodeling. This is supported by a recent study by Liu et al. showing that both T1 mapping and MRE parameters were strongly correlated with the degree of histologically obtained pancreas fibrosis [19]. Moreover, it was shown that a combination of T1 mapping and MRE-derived stiffness was the best approach to grade pancreatic fibrosis [19].

More than that, in study II we interestingly observed a subgroup of CP patients with preserved exo- and endocrine pancreas functions that had fibrosis as assessed by MRE and T1 mapping values despite a normal pancreatic volume. This suggests that both techniques might be more specific for the early parenchymal changes in CP than pancreatic atrophy. Our findings support the current understanding and mechanistic approach of the CP disease, where the development and progression of CP start with fibrosis and progresses with gland atrophy and gradual loss of exo- and endocrine functions.

As both techniques are based on different methodological principles, they are likely representing different co-existing aspects of the physiological fibrosis process. However, both methods provide valuable information on pancreatic tissue and might help to evaluate treatment response and safely monitor chronic pancreatic disorders. Ultimately, MRI combined with T1 mapping and/or MRE could avoid pancreatic biopsies in some cases. More than that, they have several advances compared with histopathological evaluation since it has a higher reproducibility and less sampling variability due to the uneven distribution of pancreatic fibrosis or a small local lesion.

### 6.1.4 Pancreatic fat content

Fat infiltration and replacement of pancreatic tissue with fat is a common finding in CP but often overseen by radiologists. Moreover, the role of pancreatic fat infiltration in CP is not fully understood. However, the importance of pancreatic fat content for the development of diabetes has been previously highlighted, as increased fatty acids can cause $\beta$ cell dysfunction [109, 110]. Recent studies have shown that patients with CP tended to have higher pancreatic fat contents compared to HCs [69, 111], though was the degree of fat infiltration not associated with the severity of CP.

However, fat infiltration changes in chronic pancreatitis are variable and inhomogeneously distributed, making it challenging to define an objective and standardized reference for normal and abnormal fat content and interpret the findings.

In most studies, the quantification of pancreatic fat using MRI was shown to be reliable and valid, and more accurate than CT and ultrasound [112,113]. Moreover, Yoon et al. have shown that the pancreatic fat content assessed using MRI was moderately correlated histopathological assessed fat content [68].

In our study I, the degree of fat content in patients increased significantly over the four years, indicating that this might help monitor disease progression. However, when using multi-point Dixon imaging with PDFF in study II, the assessment of pancreatic fat content showed only moderate diagnostic performance in detecting mild CP. The fat distribution in our cohort was very variable in all groups, including the healthy participants, also demonstrating that the intra-, inter-, and extralobular fat distribution changes in CP and their significance are not understood yet. Overall, our results suggest that the assessment of fat content is not suited to diagnose early changes in CP.

### 6.1.5 Study limitations

There are study limitations in both study I and study II.

For study I, the sample size was relatively small, and there was a considerable dropout rate of 48% for the 4-year follow-up. Reasons for the dropouts are described in paper I. Since nearly half of the patients were not available for re-scanning, this may potentially have affected the MRI results, as these patients could have been those with the more pronounced progression of the ductal features, resulting in selection bias. Further, no HCs were enrolled in this study, so "normal age-related" morphological progression in healthy subjects was not observed, making it challenging to validate if the observed progression is due to the disease or partly due to normal aging and other factors. Moreover, in study I, pain symptoms were only assessed through clinical questionnaires. Future studies should therefore include quantitative sensory testing to better assess the underlying changes in the sensory system. However, this is why in study II in addition to the assessment of pain via questionnaires, a yearly quantitative sensory testing assessment was performed and will be used in further future analyses (not included in this thesis).

Study II was a cross-sectional study; hence, it was impossible to finally determine the true potential of the new MRI techniques for describing CP-related progression of morphological pancreatic abnormalities. However, as study II was part of a prospective follow-up study, patients will be re-investigated after 2 and 4 years, which will allow assessment of progression, including association to clinical disease characteristics. Also, in study II, no analyses of the association of the MRI parameters with risk factors were not performed; however, this is planned as a part of the prospective follow-up study. The new potential MRI biomarkers for quantifying pancreatic fibrosis were not validated against the "gold standard" of histopathological samples in patients with CP. Finally, other promising techniques based on DWI, like intravoxel incoherent motion imaging, were not included and could also be investigated in future studies.

Both study I and study II share some common limitations. A major lim-

itation is that in both studies, only one observer performed all the measurements. However, it was possible to discuss all relevant cases and reaching a consensus decision with an experienced radiologist in pancreatic imaging. Still, the reproducibility of the measurements is questionable. More than that, the observer was biased as involved in the patients' inclusion and handling, which potentially could have influenced the measurements. Hence larger inter-observer studies are needed in order to facilitate incorporation into clinical routines.

Moreover, only single-ROI measurements were performed in both studies, with the risk of missing local changes and heterogeneous distribution of the parenchymal pathology. However, studies with the segmentation of the whole pancreas and parenchymal texture analysis (see below) are needed and already planned at our center. Furthermore, no histological validation of pancreatic fibrosis was made. However, histological examinations are not feasible in the clinical routine and are not suited to measure disease progression due to its related risks.

## 6.2 Clinical and future perspectives

As outlined above, the non-invasive MRI-based assessments of pancreatic fibrosis and partly fat infiltration are promising parenchymal biomarker candidates for identifying morphological pancreatic changes in CP, especially when considering the mild/early stages of the disease. More than that, as an important future perspective, assessment of parenchymal fibrosis could be of great use to monitor response to potential anti-fibrotic treatments. Still, more research is needed to understand their role in monitoring the natural progression of CP.

Moreover, to successfully implement new potential CP biomarkers in clinical decision-making, a broader consensus of the clinical definition of especially early CP is indeed needed. The definition of early CP often varies across studies and between the different available diagnostic modalities and is mostly based on the investigators' judgment more than the guidelines of professional societies. Traditionally, the previous definitions and grading of CP are based on a "gold standard" from methods such as ERCP, MRCP and EUS, (e.g., Cambridge and Rosemont classification), which fundamentally makes it difficult to develop and validate new and better methods for characterizing CP.

With the following mechanistic definition of CP made by Whitcomb and colleagues: "chronic pancreatitis is a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental, and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress" advances into a more common direction

of a standardized and broadly accepted CP definitions were done [2]. This mechanistic definition is generally accepted among pancreatologists, and currently represents the most agreed-upon strategy for defining and exploring mild/early stages of CP. This definition could enable early CP diagnosis based on a combination of etiological risk factors and validated CP biomarkers (including the potential imaging biomarkers MRE-stiffness and T1 relaxation time as presented in this thesis).

To more definitively validate new potential imaging biomarkers for early CP, it is essential to prospectively collect imaging data from a group of patients with suspected CP, without clear evidence using traditional imaging methods, and follow the cohort over several years, using the same imaging methods.

The first step in fulfilling this strategy was done in this PhD-project by assessing the above-mentioned new imaging parameters in patients with established CP, patients with subtle changes, and patients without any obvious changes on traditional imaging. However, to further evaluate the used methods as biomarkers for CP, follow-up data has to be collected and assessed to identify subjects who progressed into CP. This approach could support the new mechanistic definition of the disease and help identify populations of "at-risk"-patients in which a certain CP-biomarker could be especially valuable.

As next steps in fulfilling the strategy, the patients included in this Ph.D. project (along with other well-characterized patients) are already included as a part of a large prospective study [92] where they prospectively will be followed with serial assessment of imaging, clinical, functional, and biochemical parameters to evaluate the fibroinflammatory process associated with CP development and further implement the investigated techniques as non-invasive biomarkers for early CP.

Regarding MRI-related future perspectives, several other promising techniques assessing parenchymal changes in CP could be investigated. More advanced diffusion-weighted imaging, like intravoxel incoherent motion imaging (with the assessment of perfusion and diffusion components of DWI with multiple b-values), but also magnetic resonance fingerprinting and magnetization transfer imaging have shown potential in pancreatic imaging and could be further investigated [114–116]. Also, magnetic resonance spectroscopy allows the evaluation of pancreatic metabolites and could provide information on morphology and functionality in one session but has so far not been successfully applied in pancreatic imaging due to technical limitations.

Seen in light of the recent developments in computer techniques and artificial intelligence, a rapid and automated assessment and analysis of the imaging data could be of great potential use. Automatic pancreatic segmentation and machine learning based on radiomics features and texture analysis

could help to give more detailed information about pancreatic tissue composition and especially heterogenicity, which could be very relevant for characterizing CP. These more advanced approaches are currently under evaluation in our research group. Finally, the potential use of multiparametric imaging with the combination of data from different MRI techniques has been highlighted.

# Chapter 7

# Conclusion

This Ph.D. thesis had an overall objective, divided into four aims.

In summary, it was demonstrated that CP patients, after a 4-year follow-up period, developed an increased degree of pancreatic atrophy, fibrosis, and fat infiltration, whereas the ductal changes were insignificant. The degree of progression of these imaging parameters was mainly unrelated with each other. The parenchymal MRI parameters showed a pronounced and significant long-term progression (aim I) and showed potential as biomarkers for disease progression in CP, whereas the ductal-related parameters could not be used. A potential link of these morphological changes of the pancreas to the disease burden in CP patients could not be confirmed. Both QOL and pain symptoms were not related to atrophy, fibrosis, fat content, or ductal changes of the pancreas (aim II).

The new MRI techniques, T1 mapping and MRE, showed great potential for noninvasive quantification of pancreatic fibrosis, even though histological fibrosis was not assessed. They had a high diagnostic performance in detecting different stages of CP; whereas, the performance of proton density fat fraction and gland size assessment was only moderate (aim III). These results align with the assumption that the fibrosis-related parameters are suited to detect early changes in CP and, therefore, could be of great use as noninvasive biomarkers for CP. The value of these techniques as potential biomarkers was further demonstrated when observing the relationship of T1 mapping and MRE and their relation to gland size and pancreatic function. A stepwise increase of the fibrosis-related parameters was observed when categorizing the CP patients regarding their pancreatic function level, even in patients with a normal pancreatic volume, suggesting that T1 mapping and MRE could be more specific for the early parenchymal changes of CP than the loss of gland volume (aim IV).

Overall, this Ph.D. thesis documents and supports that parenchymal MRI parameters provide valuable information on the disease features that can be used as relevant noninvasive biomarkers in diagnosing and staging patients with CP. Especially fibrosis-related parameters have shown great potential to identify early changes in CP.

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