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Assessment and associations with clinical factors

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Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

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BY
LOUISE KUHLMANN ASFERG

DISSERTATION SUBMITTED 2021

AALBORG UNIVERSITY
DENMARK

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Dissertation submitted January 2021

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PhD Series: Faculty of Medicine, Aalborg University

Department: Department of Clinical Medicine

ISSN (online): 2246-1302
ISBN (online): 978-87-7210-877-3

Published by:
Aalborg University Press
Kroghstræde 3
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Rosendahls, 2021

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Published papers

1. Faghih M, Phillips AE, **Kuhlmann LF**, et al. Pancreatic QST Differentiates Chronic Pancreatitis Patients into Distinct Pain Phenotypes Independent of Psychiatric Comorbidities. *Clin Gastroenterol Hepatol*. 2020.

2. Olesen S.S., **Kuhlmann L.**, Novovic S., Nojgaard C., Kalaitzakis E., Jensen NM et al. Association of multiple patient and disease characteristics with presence and type of pain in chronic pancreatitis. *J Gastroenterol Hepatol* 2020; 35: 326-333

3. Phillips AE., Faghih M., **Kuhlmann L.**, Larsen IM., Drewes AM., Singh VK. et al. A clinically feasible method for the assessment and characterization of pain in patients with chronic pancreatitis: Pain phenotyping in chronic pancreatitis. *Pancreatology* 2020; *20*(1): 25–34.

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5. **Kuhlmann L.**, Olesen SS., Olesen AE., Arendt-Nielsen L., & Drewes, AM. Mechanism-based pain management in chronic pancreatitis – is it time for a paradigm shift? *Expert Review of Clinical Pharmacology*, 2019; 12(3): 1–10.

6. **Kuhlmann L.,** Olesen SS., Grønlund D., Olesen AE., Phillips AE., Faghih M. et al. Patient and Disease Characteristics Associate with Sensory Testing Results in Chronic Pancreatitis. *Clinical Journal of Pain*. 2019; 35(9): 786–793.

7. **Kuhlmann L.**, Poulsen JL., Kohler M., Rasmussen HH., Vestergaard P., Drewes AM. et al. Osteoporosis in Chronic Pancreatitis Outpatients Associates with Several Risk Factors. *Journal of the Pancreas* 2018; 19(4): 183–189.

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10. **Kuhlmann, L.**, Joensson, IM., Froekjaer, JB., Krogh, K., & Farholt, S. A descriptive study of colorectal function in adults with Prader-Willi Syndrome: High prevalence of constipation. *BMC Gastroenterology*. 2014; 14: 63.

The thesis is based on the following papers

I. **Kuhlmann L.**, Olesen SS., Olesen AE., Arendt-Nielsen L., & Drewes, AM. Mechanism-based pain management in chronic pancreatitis – is it time for a paradigm shift? *Expert Review of Clinical Pharmacology*, 2019; 12(3): 1–10.

II. Olesen S.S., **Kuhlmann L.**, Novovic S., Nojgaard C., Kalaitzakis E., Jensen NM, Engjom T, Dimcevski G, Waage A, Haas SL, Vujasinovic M, Riauka R, Pukitis A, Ozola-Zālīte I, Okhlobystin A, Parhiala M, Laukkarinen J, Drewes AM; Scandinavian Baltic Pancreatic Club. Association of multiple patient and disease characteristics with presence and type of pain in chronic pancreatitis. *J Gastroenterol Hepatol* 2020; 35: 326-333

III. **Kuhlmann L.,** Olesen SS., Grønlund D., Olesen AE., Phillips AE., Faghih M. & Drewes AM. Patient and Disease Characteristics Associate with Sensory Testing Results in Chronic Pancreatitis. *Clinical Journal of Pain*. 2019; 35(9): 786–793.

IV. **Kuhlmann, L.,** Teo K., Olesen SS., Phillips AE., Faghih M., Windsor JA. & Drewes AM. Development of the Comprehensive Pain Assessment Tool Short Form (COMPAT-SF) for Chronic Pancreatitis: Validity and Reliability Testing. Submitted for publication in Gastroenterology

ABBREVIATIONS

BPI	Brief Pain Inventory
CFA	Confirmatory Factor Analysis
CNS	Central Nervous System
COMPAT	Comprehensive Pain Assessment Tool
CP	Chronic Pancreatitis
CPM	Conditioned Pain Modulation
EORTC-QLQ-C30	The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EPI	Exocrine Pancreatic Insufficiency
ICC	Intraclass Correlation Coefficient
IELTS	International English Language Testing System
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
NASQ	Nijmegen-Aalborg Sensory QST
OMERACT	Outcome Measures in Rheumatology
PANQOLI	Pancreatitis Quality of Life
ePDT	Electrical Pain Detection Threshold
pPDT	Pressure Pain Detection Threshold
PFC	Prefrontal Cortex
PGIC	Patient Global Impression of Change
ePTT	Electrical Pain Tolerance Threshold
pPTT	Pressure Pain Tolerance Threshold

QST	Quantitative Sensory Testing
RVM	Rostroventral Medulla
SBPC	Scandinavian Baltic Pancreatic Club
VAPAIN	Validation and Application of a patient-relevant core set of outcome domains to assess multimodal PAIN therapy
VAS	Visual Analog Scale

ENGLISH SUMMARY

Chronic pancreatitis (CP) is a fibro-inflammatory disease with progressive, irreversible damage to the glandular tissue, in time leading to endocrine and exocrine insufficiency. Many CP patients are affected by chronic abdominal pain. Assessment of pancreatic pain is typically based on non-validated questionnaires or questionnaires developed for other types of chronic pain. Research suggests that a detailed characterization of pain can lead to mechanism-based treatment algorithms, but thorough groundwork must be performed in order for the algorithm to be able to work sufficiently.

This thesis is a collection of a narrative review and three original manuscripts, based on four studies. It provides the basis for characterizing pancreatic pain in a detailed manner, focusing on pain mechanisms and risk factors for pancreatic pain.

The narrative review provides the background for estimating pain as objectively as possible and as detailed as possible. In manuscript 2, we assessed pain prevalence in a cohort of CP patients and detected associated risk factors for pancreatic pain. In manuscript 3, the sensory function in patients with CP was assessed through quantitative sensory testing. Manuscript 4 concerned the development of a validated, reliable, feasible short form of a pain questionnaire developed explicitly for CP patients.

The narrative review provides a theory of mechanism-based treatment algorithms as a more individual-oriented way of treating pain that could gain ground over the next decade.

In manuscript 2, we concluded that pancreatic pain was present in almost 60% of CP patients, and most had intermittent pain. Risk factors for pain included very heavy alcohol abuse, cigarette smoking, exocrine insufficiency, pancreatic duct changes, pseudocysts, and duodenal stenosis.

In manuscript 3, we showed that patients with painful CP had different pain processing than healthy volunteers and that specific defective pain mechanisms, especially conditioned pain modulation (CPM), were related to clinical pain intensity.

The final short form from manuscript 4 consisted of five pain dimensions, comprising six questions. Three types of validity were investigated, including content validity, construct validity, and criterion validity. The short form was hereafter shown to be reliable.

In conclusion, the studies have contributed with new knowledge about pancreatic pain and have developed an instrument to assess the pain in a valid and reliable way. This

can be used in research and clinical practice to improve care for patients with pancreatic pain.

DANSK RESUME

Kronisk pancreatitis (CP) er en fibro-inflammatorisk sygdom med progressiv, irreversibel skade på bugspytkirtelvævet. Med tiden kan det føre til endokrin og eksokrin insufficiens. Mange CP-patienter lider af kroniske mavesmerter. Smerterne fra bugspytkirtlen bliver typisk vurderet ud fra ikke-validerede spørgeskemaer eller spørgeskemaer som er udviklet til andre typer af kroniske smerter. Forskning tyder på, at en detaljeret karakterisering af smerte kan føre til mekanismebaserede behandlingsalgoritmer. For at en sådan behandlingsalgoritme kan fungere, så kræver det dog at forarbejdet med smertekarakteriseringen er grundigt gennemarbejdet.

Denne afhandling er en samling af et narrativt review og tre originale manuskripter, der er baseret på fire undersøgelser. Sammen danner grundlaget for karakterisering af smerter i bugspytkirtlen på en detaljeret måde med fokus på smertemekanismer og risikofaktorer for smerter.

Det narrative review gennemgår baggrunden for at estimere smerte så objektivt og detaljeret som muligt. I manuskript 2 undersøgte vi prævalensen af smerte i en gruppe CP-patienter samt mulige risikofaktorer for smerter ved CP. I manuskript 3 undersøgte vi den sensoriske funktion ved patienter med CP gennem kvantitativ sensorisk testning. Manuskript 4 omhandlede udviklingen af en valideret, pålidelig og gennemførlig kort udgave af smerte-spørgeskemaet COMPAT, der blev udviklet eksplicit til CP-patienter.

Den narrative gennemgang producerede en teori om mekanismebaserede behandlingsalgoritmer som en mere individ orienteret måde at behandle smerter på. Denne metode har potentiale til at kunne vinde indpas over de kommende år.

I manuskript 2 konkluderede vi, at bugspytkirtelsmerter var til stede hos næsten 60% af CP-patienterne, og de fleste havde intermitterende smerter. Risikofaktorer for smerte omfattede meget stort alkoholmisbrug, rygning, eksokrin insufficiens, ændringer i bugspytkirtel-udførselsgangenes anatomi, pseudocyster og duodenal stenose.

I manuskript 3 viste vi, at centrale smertemekanismer var ændret ved patienter med smertefuld CP sammenlignet med raske frivillige, og at specifikke defekte smertemekanismer, især betinget smertemodulation (CPM), var relateret til klinisk smerteintensitet.

Den endelige korte udgave af COMPAT spørgeskemaet fra manuskript 4 bestod af fem smertedimensioner, der indeholdt i alt seks spørgsmål. Tre typer validitet blev undersøgt, herunder i forhold til indhold, konstruktion og kriterier. Til sidst viste vi at den korte udgave af COMPAT var pålidelig.

Afslutningsvis har undersøgelserne bidraget med ny viden om smerter i bugspytkirtlen og har udviklet et instrument til at vurdere smerten på en valid og pålidelig måde. Dette kan bruges i forskning og klinisk praksis for at forbedre plejen af patienter med smertefuld CP.

ACKNOWLEDGEMENTS

I first became acquainted with Professor Asbjørn Mohr Drewes and the Mech-Sense research team in 2011. I was conducting my first research project at the Center for Rare Diseases in Aarhus and was invited to an event for close and distant collaborators at Professor Drewes' residence. I was fascinated by the comfortable yet highly dedicated atmosphere, and I was confident that I wanted to participate further in this research team. Luckily, Professor Drewes said yes when I approached him on the possibility for a Ph.D. study in the fall of 2015.

Firstly, I wish to thank Professor Drewes, my main supervisor, for his encouragement, constructive criticism, and inspiring good mood. It has been a pleasure learning from him through my studies. A special thanks to my co-supervisor, Søren Olesen, is also needed. He has always been ready to help me through big and small issues, inspired me with his tremendous statistical knowledge, and offered generous support when the going got tough. I would also like to thank my co-supervisor, Tine Hansen, for always being ready to spare some good advice and teaching me many things in advanced pain assessment, including EEG analysis, in collaboration with my co-worker Rasmus Nedergaard. I would also like to thank the Department of Gastroenterology and Hepatology at Aalborg University Hospital for providing the use of a laboratory, which was essential for the completion of my studies.

I would like to thank the medical department at the North Denmark Regional Hospital for providing me with the unique possibility of conducting my studies while remaining close to clinical practice. This possibility has allowed me to stay updated in my clinical capabilities during my studies, which is of great value for my future career. They have been incredibly cooperative while I was juggling clinical study planning, course activity, and work in night shifts.

I would also like to thank my colleagues at the Mech Sense research team. They have provided me with invaluable feedback and great social get-togethers throughout the years. I will miss you all.

This thesis included two clinical studies involving both patients and healthy volunteers. I would like to say a special thank you to all the participants for taking part in the studies, which could not have been performed without them.

Finally, I would like to thank my family, mostly my husband Alex, who has been very tolerant and understanding while I was working day and night, and he kept our family running. I could not have done this without him, and I am ever so grateful for the large amount of support he has sent my way.

Louise Kuhlmann Asferg, January 2021, Randers

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CHAPTER 1. INTRODUCTION

Pain is a frequent symptom in the primary and secondary health systems, and chronic pain affects up to 20% of the adult population[1,2]. Chronic pain has significant consequences on patients' quality of life as it affects physical and psychological health[3,4], daily activities[5], employment[6], and economic well-being, including employment[7].

Chronic pain is defined as pain outlasting standard healing time for the specific tissue; usually, this is considered when pain persists beyond 3-6 months[8,9]. Pain severity is not necessarily correlated with the amount of tissue damage, and symptoms can persevere long beyond the resolution of the damage[10]. Cognitive factors as, e.g., coping style[11], previous experiences with pain[12], emotional factors[13], education[11], and the pain-associated reactions of the patient's close acquaintances[10] can affect the patient's perceived pain severity.

Chronic pain has significant direct and indirect associated societal costs. These are exemplified by a chronic pain-associated estimated annual cost of $210 billion in the United States of America[10]. Pain treatment is an essential part of this equation's solution, as optimized pain treatment can, besides enhancing the quality of life in patients, lower chronic pain costs. The cost is lowered by minimizing admissions due to pain, reducing the need for disability payments, and diminished productivity[7,10].

Pain treatment remains challenging due to several factors. These factors include different condition-associated complications that can worsen chronic pain, the many pain associated risk factors, the diversity of possibly affected pain mechanisms, many different origins of pain, and pharmacological treatments with a broad spectrum of side effects[14].

To improve pain treatment, a step must be taken from treating pain patients as a homogenous group to targeting intervention according to 1) affected pain mechanisms[15], 2) pain qualities[16], and 3) cognitive factors such as e.g., coping style and psychological profiles[17–20]. In this context, pain characterization regarding risk factors, pain severity, pain quality, psychological handling, and neurophysiological examinations of pain mechanisms are essential.

Objectively estimating pain intensity is impossible due to the subjective nature of pain sensation[21]. The gold standard for assessing pain intensity is by patient self-report. Many different scales exist, such as the Visual Analogue Scale (VAS), the Numerical Rating Scale (NRS), and the Verbal Rating Scale (VRS)[21]. Their use introduces the risk of result bias due to pain distress and differences in the individual's conceptualization of pain[22]. Their main target is to monitor pain intensity changes, but they do not evaluate changes in other pain factors such as pain quality, medication,

pain characteristics, psychological aspects of pain, and pain coping[23,24]. Researchers have developed several pain questionnaires throughout the years to fill this gap, aiming to obtain a more comprehensive description of pain, including pain quality and concurrent symptoms[25–28].

Nonetheless, many pain questionnaires are only validated in specific patient groups, if validated at all. As pain can have different etiologies and characteristics, there is no such thing as one model to fit them all. Visceral pain is, e.g., differently characterized than somatic pain as it is not necessarily linked to actual or potential damage. It is typically a diffuse pain difficult to locate, is often associated with autonomic symptoms such as sweating, GI disturbances, nausea, and pallor, and it can be projected to remote locations[29]. Different chronic pain conditions can also present specific characteristics that differ from other types of pain and can complicate comparison. Therefore, questionnaires need to be either explicitly developed for or validated in the patient group and type of pain in question. In chronic pain, visceral characteristics can, however, become less evident, and central pain characteristics dominant. In these situations, guidelines such as the IMMPACT recommendations are sufficient to evaluate all etiologies of pain[30]. Study III and IV revolves around the development and validation of a pain questionnaire for pancreatic pain.

In addition to questionnaires and pain scales, neurophysiological examination with quantitative sensory testing (QST) is becoming an improved way of quantitatively assessing pain sensation. QST serves as an addition to pain questionnaires to evaluate the function of the sensory system[31]. The QST results could potentially guide the physicians to which pain mechanisms are likely affected. This knowledge enables the possibility of targeting these mechanisms in the choice of treatment[32]. Previous studies have shown that QST results have predicted treatment response in several pharmacological agents[33–37] or surgical interventions[38,39]. QST results have also been shown to associate with biopsychosocial mechanisms and can, therefore, be combined with questionnaires to provide a detailed description of different aspects of pain [31]. Study II is an example of a study aiming to characterize pancreatic pain for QST examinations.

If seeking to optimize non-pharmacological pain treatment, risk factor elimination is essential. In this context, knowledge of which modifiable risk factors are associated with maintaining chronic pain is important. Only a few studies of this kind exists, as most studies focus on risk factors for developing postsurgical pain, and often the results are non-modifiable[40–42]. Study I focuses on determining concurrent risk factors of pancreatic pain to enable risk-modifying treatment.

In this thesis, chronic pain in patients with CP has been the focus, as this is a classic example of organic, visceral pain, which presents a major challenge both in pain evaluation and treatment.

CHAPTER 2. BACKGROUND

2.1. CHRONIC PANCREATITIS

CP is a progressive fibro-inflammatory disease of the pancreatic gland[43]. It causes irreversible damage, including ductal dilation, pancreatic stones, calcification, and destruction of the glandular tissue. With time this can lead to exocrine and endocrine insufficiency. The most common reason for developing CP is long-term excessive alcohol intake, which accounts for around 50% of CP[44]. Other significant risk factors include smoking, nutritional factors, hereditary factors, efferent duct factors, immunological factors, and miscellaneous factors[45].

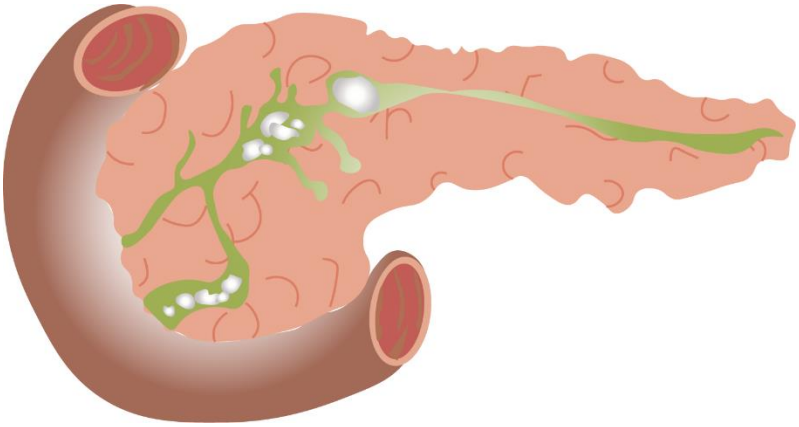

Figure 1: Chronic pancreatitis with fibrosis of the pancreatic tissue, calcifications, dilation of the pancreatic duct, pathological side branches, and pancreatic stones

The most common symptom in CP is chronic abdominal pain, affecting up to 60-70% of patients[46]. The pain is typically described as a continuous severe epigastric pain, radiating to the back[47]. Pain exacerbations or intervals with reduced pain can occur in a constant pain pattern. The pain pattern can also be characterized as intermittent pain with pain-free intervals in-between[48]. Pain patterns can be shifting over time, as patients with intermittent pain later in the course of the disease can experience constant pain and vice versa[48,49] The presence of constant pain is related to decreased quality of life[48,50].

The pathophysiology of pancreatic pain is multifactorial. In some patients, there are obvious causes of pain. These can either be intrapancreatic (e.g., pseudocysts, stenosis, or obstruction of the pancreatic duct) or extrapancreatic (peptic ulcers, duodenal stenosis, or stenosis of the bile duct due to pancreatic fibrosis and inflammation affecting the surrounding structures)[51]. Other times, there is no evident anatomical cause. In these patients, pain is probably caused by the interplay between several factors. Although disputed, some studies of CP patients with chronic pain have shown pancreatic tissue hypertension, which can cause a "compartment-like syndrome" in the pancreas, decreasing blood flow and inducing local ischemia[47]. Hyperstimulation of the pancreatic tissue with elevated CCK level might also be a cause for pain, as this can increase pressure in the pancreatic duct and independently activate nociceptive pathways in the CNS[47]. Several studies have also shown evidence of nerve alterations with increased nerve fiber diameter and neurogenic inflammation leading to peripheral sensitization and neuropathy[52]. Together with central sensitization, this probably plays a central role in the development and chronification of pancreatic pain. Central sensitization is an important part of pancreatic pain, as it has been shown that many CP patients with chronic pain show signs of generalized, widespread sensitization: These signs include increased areas of referred pain, decreased pain threshold to noxious stimulations, reorganizations of brain areas involved in pain processing, as well as the affection of central pain modulation mechanisms[47,53–57].

However, not all patients with CP develop chronic pain. Risk factors for developing CP are well-established, but there is a lack of studies examining risk factors for pancreatic pain[58,59]. The studies that exist show that pain is equally occurring in alcoholic and non-alcoholic CP, but, e.g., whether concurrent alcohol and tobacco use is associated with pain development after CP diagnosis has not been examined[60]. Recurrent acute pancreatitis might accelerate the nervous system's sensitization, and is this could be a risk factor for developing pancreatic pain[61].

This lack of knowledge limits the possibility of intervention. As a result, all patients with CP are now advised to abstain entirely from alcohol and tobacco, as these are well-established risk factors for CP, but evidence on whether these substances affect the course of pancreatic pain is less clear. Therefore, there is a need for a study such as study I to enhance focus on risk factors for pancreatic pain.

Pain has an enormous impact on the quality of life, which is significantly more impaired in CP than in other chronic diseases. Pain, as well as other quality-of-life altering complications, should therefore be an area of special attention when treating CP patients[62].

2.2. NORMAL PAIN PHYSIOLOGY

When evaluating QST measures as we did in study II, an understanding of normal pain physiology is essential. Pain is a protective mechanism that functions as a response to a damaging stimulus. The most common damaging stimulus evolves from the skin. The injury activates receptors at the peripheral nerves, and the signal is conducted through A- and C-fibres to the spinal cord, which transmits the information to the central nervous system (CNS)[63]. In the CNS, the information is processed to produce an appropriate response, such as retracting from the damaging stimulus. The receptors in the peripheral nerves can typically be activated by extreme temperatures (both hot and cold), mechanical stimulation, or toxins[64]. As a response to the activation of the receptor, a local action potential is generated. This action potential can be either up- or down-regulated due to other ligands and receptors in the peripheral nerve, using sodium channels to amplify the signal or potassium channels to inhibit the signal[63]. The difference between A fibers and C fibers concerns the nerve's diameter and the presence of myelin sheats. Therefore, the conduction speed of the two types of nerves is significantly different. A-fibers conduct at high velocities, are slowly adapting and responds throughout the duration of the stimulation. They typically produce a sharp and intense type of pain, while the C-fibres are more slowly conducting and results in a prolonged burning sensation[63,64].

The signal is transmitted through the dorsal root ganglion cells/trigeminal ganglion cells in the spinal nerve's dorsal root. Then it is forwarded through the spinothalamic tract via the thalamus to the cerebral cortex and various subcortical regions, and the medulla and brainstem through the spinoreticular and spinomesenchephalic tracts[65–67].

Visceral pain is differently transmitted than somatic pain, and the sensation of this type of pain is also quite different. Afferent spinal nerves innervate the viscera[68]. These are unmyelinated, thin nerves conducting at low velocities. Most of the visceral afferent nerves pass through para- and pre-vertebral ganglia to the spinal cord, where they terminate at several segmental levels. In the spinal cord, the fibers can converge with somatic fibers, which can explain referred pain to somatic structures, often present in visceral pain.

Additionally, the fibers project to the spinal cord with the same nerves as the sympathetic fibers, leading to local and central crosstalk[69]. This cross-talk can induce autonomic reflexes, tension of the muscles, and over time trophic alterations in somatic tissue[69]. Vagal nerves also play a role in the visceral pain nociception, normally as a part of central inhibitory pain modulation[69].

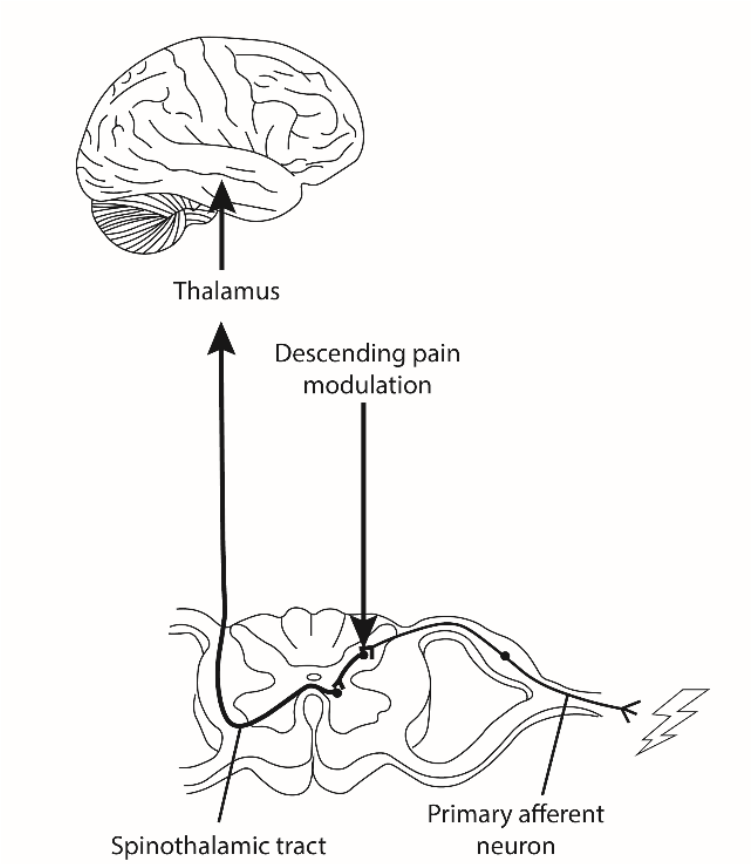

Figure 2: The nociceptive system

Nociception in the CNS is complex, with no single pathway being solely responsible for pain perception. Several aspects of pain are processed in the CNS, including somatotropic, emotional, intrinsic, and mechanical[63].

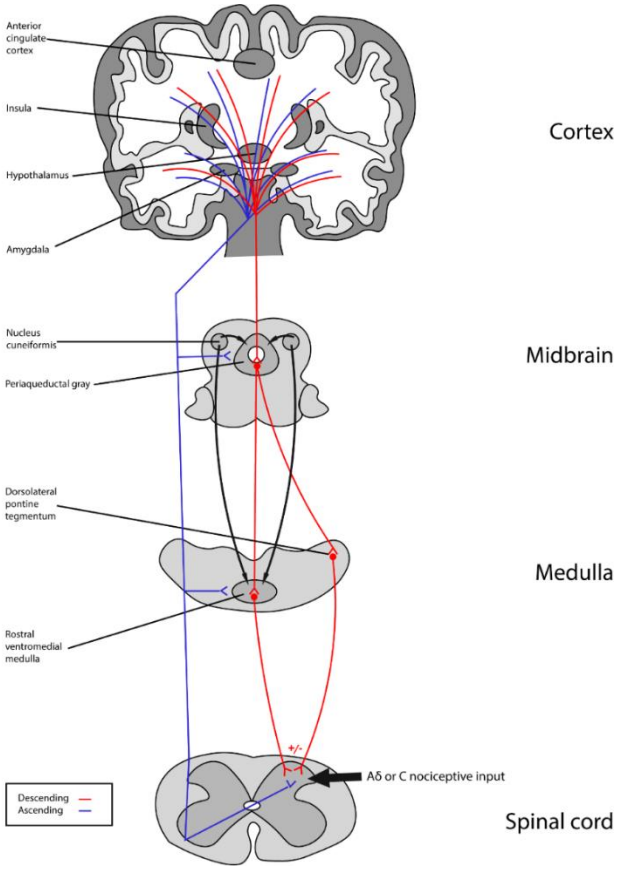

Figure 3: The descending pain modulatory systems. +/- indicates influences that are either pro- or anti-nociceptive, respectively

The brain can actively regulate sensory transmissions through the descending pain modulatory systems, and this enables us to regulate the information either by facilitation or inhibition depending on, e.g., stimulus intensity or context[66]. There is evidence of several brain regions' involvement in the descending modulation. These regions include the frontal lobe, anterior cingulate cortex, insula, amygdala, hypothalamus, periaqueductal gray, nucleus cuneiformis, and the rostral ventromedial medulla[66]. Through reciprocal connections, they mediate nociceptive inputs from various sites[66,70].

It has been suggested that the pain modulatory systems function as a filter. This filter allows the brain to focus on one noxious stimulus while other sensory stimuli affect different parts of the body[71]. The modulatory systems are relevant in a situation with

an immediate threat to life, where suppression of pain will increase the risk of surviving by enabling the body to either fight or flight[65].

The thalamus is also involved in nociception, as it is involved in converting the pain perception into a reasonable response guiding human behavior away from the damaging stimulus[72].

2.3. PAIN MECHANISMS

When pain becomes a chronic state, the nervous system might become sensitized. It affects local nerves, leading to peripheral sensitization, progressing to ipsilateral sensitization, segmental sensitization, extraterritorial sensitization, and finally, generalized, widespread central sensitization hypersensitivity is present in several somatic structures unrelated to the primarily affected area[73].

2.3.1. PERIPHERAL SENSITIZATION

Nociceptors are capable of adapting due to axon injury or exposure to inflammation. This adaption can lead to continuous signaling without noxious stimulation, causing chronic pain due to the nociceptor's sensitization by reducing the stimulation threshold, increasing responsiveness, and developing spontaneous discharges[67,74].

2.3.2. CENTRAL SENSITIZATION

Central sensitization is an enhancement in the function of the neurons and neurogenic circuits in the nociceptive pathways[75]. This enhancement is caused by changes in membrane excitability, inhibition, or synaptic efficacy due to the highly malleable nature of the nociceptive systems[75]. Due to the changes in synaptic efficacy, effects similar to peripheral sensitization changes occur, including increased spontaneous discharge, lower activation threshold, and an increased response to suprathreshold stimulations[75].

The patient becomes hyperalgesic with decreased pain threshold and increased response to a painful stimulus in both magnitude and duration[76]. In some patients, this progresses into tactile allodynia, where a normally non-painful stimulus elicits pain[77].

Central sensitization is characterized by, e.g., hypersensitivity, increased temporal summation, and defective descending pain modulation. Temporal summation is

defined as an increase in pain perception through repetitive painful stimulations[78]. It is an electrophysiological phenomenon where postsynaptic neurons respond to stimulations between 0.5 and 5 Hz by increasing discharge in the first 10-30 stimuli, and hereafter reaching a plateau[77]. In generalized, widespread sensitization, the temporal summation threshold frequency will typically be lowered, and the response enhanced[77].

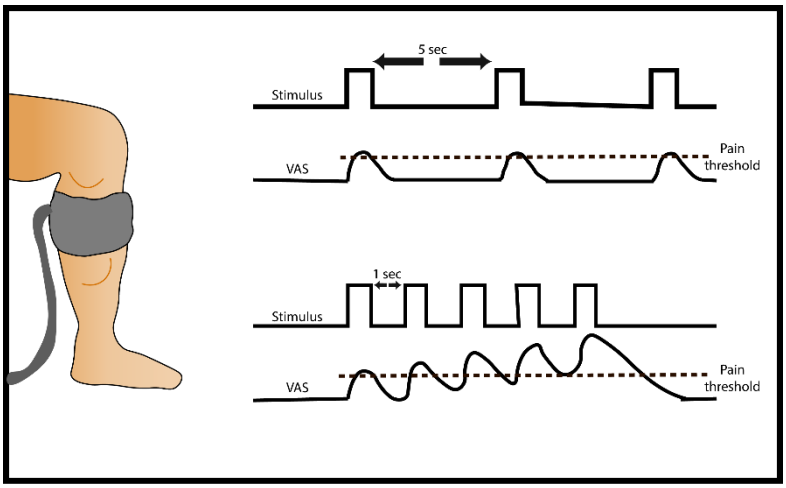

Figure 4: Temporal summation

2.3.3. DEFECTIVE DESCENDING PAIN MODULATION

In case of dual concurrent pain stimulation, under normal circumstances and in the absence of chronic pain conditions, the descending pain modulation will provide inhibition of nociceptive input from one of the pain stimuli, which is commonly described as 'pain-inhibits-pain,' 'counter-irritation,' 'diffuse noxious inhibitory,' or CPM[79,80]. The latter term will be used in the remainder of the thesis.

The amount of pain modulation in healthy adults differ significantly. The differences may be due to gender- and age-variation, and we performed a QST study examining these variations and proved that gender variation was significant, but age-variation was of limited effect size[56]. Other unknown factors can also affect the results[81,82]. While CPM capacity is a prognostic factor for, e.g., developing post-operative pain[39,80], the sex-variation is relevant to bear in mind if using it clinically.

While the modulatory systems can be essential for pain analgesia, descending pain modulation can also play a crucial role in developing and maintaining chronic pain. This opposing effect happens as an imbalance in the systems can facilitate nociception[70,83]. Several animal studies on neuropathic pain support this theory. They find evidence that descending facilitation of pain is increased in models of chronic neuropathic pain[84,85]. Evidence of dysfunction of descending pain modulation has also been found in several chronic pain types, including CP[35,86–88]. The effectiveness of pain inhibition has been shown to predict, e.g., the analgesic treatment response of duloxetine[35]. In other studies, no correlation has been found with the treatment response of pregabalin[33] or placebo[89].

2.3.4. COGNITIVE MODULATION

The pain modulatory systems also provide a pathway where negative emotions and stress can aggravate and extend the duration of pain[65]. Pain perception is vastly affected by psychological, cognitive, affective, and behavioral processes. Attention to pain has been extensively examined, as pain is perceived less intense during distractions, both auditory, visual, tactile, or cognitive[90,91]. As an example, a painful stimulus was conducted on healthy volunteers two times. The patients were asked to solve mentally challenging tasks during one of the stimulations, and the two results were then compared. The results were significantly lower pain ratings while being mentally distracted compared to the undistracted pain stimulation[91].

Emotional factors can also alter pain perception. A study found that pleasing stimulations positively affected emotional state in an experimental context, e.g., music and pleasant pictures reduced pain perception[90]. Negative emotions are associated with increased activity in the amygdala, the anterior insula, and the anterior cingulate cortex, which are essential parts of the pain modulatory system. It is, therefore, hypothesized that these emotions could facilitate nociception[65]. The precise cause of this effect is, however, not yet elucidated. The fact that chronic pain affects the mental state of mind also complicates the clarification.

Previous studies have found that fear of pain and other negative emotions can increase pain perception, but it is unclear whether the changed pain perception results from the increased fear of pain alone or perhaps an interplay with pain catastrophizing[92]. Studies on psychological aspects of pain should also be evaluated with caution, as it is difficult to distinguish the effects of changed emotional status from the impact caused by a change in attention towards pain.

2.4. PAIN ASSESSMENT

Pain assessment is notoriously tricky due to the subjective nature of pain and the complexity of pain perception. To truly measure the span of the experience of pain, several modalities will have to be combined. Psychometric tests such as questionnaires can evaluate both intensity, quality, and effect on daily-life, while quantitative sensory testing can provide a sensory profile of the patient[93,94]. Even in QST measures, the response is evaluated subjectively as pain intensity. Despite this, pain assessment is essential when evaluating treatment response, and a follow-up regimen must naturally include a minimum of one measure of pain assessment. Study III and IV were performed to develop a valid, reliable, and feasible questionnaire developed explicitly for pancreatic pain.

2.4.1. PAIN SCALES

Unidimensional pain scales are widely used in both medical departments and in research to assess pain intensity. Nevertheless, as the interpretation of pain intensity reflects on the individual's concept of pain, these ratings are highly subjective and can only be used to assess change in pain intensity, rather than being comparative[95].

2.4.2. PAIN QUESTIONNAIRES

The concept of pain differs from patient to patient, as many things are incorporated in the pain sensation. This is evident as many patients lack to define sensations such as tingling, numbness, and paresthesias as pain[23]. Pain sensation is equally affected by other pain-related symptoms, such as nausea, sleep disturbances, and fatigue, which may exaggerate the pain sensation[94]. Mood and degree of disability can also bias the pain assessment[23]. These facts sum up that psychometric instruments must be thorough and elaborative, but even so, interpreted with caution. To choose the most suitable tool for the specific situation, physicians must consider whether the questionnaire collects the necessary data without compromising the feasibility and simplicity needed to get reliable answers.

When using questionnaires to evaluate pain, it is essential that the questionnaire is reliable and validated. Like mechanical and electrical instruments, questionnaires are precision measurement instruments that need to be tested thoroughly to guarantee validity. Therefore, numerous trials precede validation, and even small changes can destroy the result.

Validation of a questionnaire can include four aspects. 1) Face validity, where a group of non-experts in methodologies assesses the questionnaire as to whether the test seems valid. 2) Content validity, a systematic evaluation of the questionnaire by a group of experts, assessing whether all essential parts of the subject are covered. 3) Construct validity, which can consist of two parts. Convergent validity assesses whether related questions correlate, and discriminant validity where un-related questions should show no or only minor associations. 4) Criterion validity, where the relationship to concurrent or future clinical outcomes are examined. These outcomes can either be clinical factors such as quality of life, opioid-use, hospitalizations, surgeries, or scores from related questionnaires[96].

Unfortunately, there is no validated pain questionnaire developed specifically for patients with CP, which stresses the need to develop such a questionnaire, as done in study III. The abdominal pain experienced in CP fits visceral pain characteristics as diffuse and poorly localized and involving autonomic and motor reactions such as nausea, sweating, and palpitations[97]. These features complicate comparison with, e.g., musculoskeletal pain, and a questionnaire developed for, at the least, visceral pain is essential to enlighten the pain characteristics fully. The Izbicki pain score[98], the Brief Pain Inventory (BPI)[99], and the McGill Pain Questionnaire[25] have frequently been used to evaluate pancreatic pain, although only the BPI is strictly validated in CP patients[100].

A new pain assessment questionnaire has recently been developed for chronic pancreatitis patients, the "COMprehensive Pain Assessment Tool (COMPAT) for chronic pancreatitis"[101]. This is a thorough and elaborate pain questionnaire covering all essential aspects of pain in CP, including pain pattern, pain intensity, pain provoking factors, pain-relieving factors, social and emotional factors, risk factors for pain, and pain treatment, both pharmaceutical and surgical. Its elaborate form makes it time-consuming to complete, making it less suitable for clinical practice and primary evaluation.

2.4.3. QUANTITATIVE SENSORY TESTING

QST is a method for quantifying a loss or gain of sensory function in the neural axis to increase our knowledge of the origin of dysfunction leading to chronic pain [31]. It can include various tests designed to examine the sensory function of pain perception from receptor to brain, including different afferents and central pathways[31]. Possible stimulation modalities include thermal, mechanical, chemical, electrical, and ischemic stimulations. Stimulation sites are typically cutaneous, but visceral stimulations have also been used[31,102]. As QST examination responses only are semi-objective, results are only valid if the patient is well-instructed and cooperative[103].

The use of QST in pain evaluation is increasing, and as the examinations are advancing, it is now possible to point out which pain mechanisms possibly are dysfunctional from the QST evaluations[102]. In recent years, this has led to QST gaining ground in predicting treatment response, and research in this area is increasing year by year[33,88,104,105].

Comprehensive QST batteries, including numerous examination modalities, have previously been used when examining pain sensitivity in chronic pain patients[106]. While these can function in the context of research, they are not suited for clinical practice, where time is limited, and examinations must be quick and efficient.

We have previously used visceral pain models to explore the pain system, but these are invasive and cumbersome to use[57,107–110]. As somatic and visceral fibers converge in the same segments of the spinal cord and share central mechanisms, quantitative sensory testing of the skin can be used to determine the functioning of the visceral nociceptive system indirectly. A combination of pinprick, mechanical and thermal stimuli can unravel whether the pain is localized to the pancreatic dermatome where it is considered reversible or spread to several spinal segments and the brain, causing widespread sensitization. It can also be determined whether there is abnormal activation of specific pain mechanisms reflecting chronification. These are a) central integration to repeated stimuli and b) efficacy of descending pain inhibition from the brainstem to the spinal cord, gating the afferent barrage from pancreatic nerves. Together with an assessment of the pain experience and psychological comorbidity, such QST has the potential to be a powerful instrument to determine the pain phenotype and guide treatment, but more evidence is needed before it can be used in clinical practice. In study II we tested a feasible, bedside QST paradigm designed to evaluate pancreatic pain efficiently.

2.4.3.1 Peripheral and generalized widespread sensitization

Optimally, the sensitization of the central nervous system is assessed using electrophysiological recordings from central neurons. However, this is not a viable measure in humans, and sensory evaluation of the nervous system's nociceptive excitability is a decent surrogate marker[111]. The pain detection threshold and pain tolerance threshold can provide information in this assessment by comparing it with normative data[56]. Typically, thresholds are examined in several locations throughout the body to examine differences and distinguish between peripheral sensitization and central sensitization. If lower thresholds are present locally, it can be caused by peripheral sensitization due to tissue injury with a resulting outlet of inflammatory mediators that activates signaling cascades in the sensory neuron[112]. Thresholds can also be lowered in several locations, independent of proximity to present injury/disease, indicating central sensitization[111]. Evaluation of several sites,

including sites unrelated to the anatomically affected area, is therefore essential. Figure 5 shows different evaluation sites used in study II, which gives the possibility to evaluate peripheral and generalized widespread sensitization in CP patients.

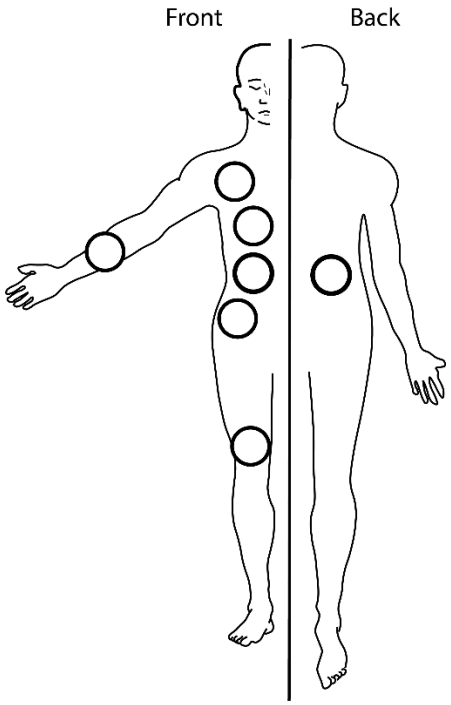

Figure 5: Evaluation sites that allow the evaluation of the presence of peripheral and widespread sensitization

2.4.3.2 Wind-up ratio

The wind-up ratio is the proportion of increased pain intensity caused by a series of repetitive, rhythmical, painful stimulations compared to a single stimulus. An increased wind-up ratio is caused by temporal summation. The wind-up ratio can be assessed by using, e.g., mechanical, thermal, or electric stimuli[111,113]. The patient is asked to rate one stimulus in pain intensity, and afterward, a series of at least five stimuli are applied. The patient is asked to rate the series intensity as a whole, and a ratio between the two intensities is calculated[114].

2.4.3.3 CPM

CPM estimates the change in pain perception after a conditioning stimulus. A wide variety of conditioning stimuli have been used, but the two most commonly used are cold water or ischemia[115]. The pain detection threshold or pain tolerance threshold to a given stimulus is assessed before and after the conditioning stimulus, and the values are compared. The threshold is typically significantly higher after the conditioning stimulus than before. Patients with deficient CPM capacity will often not be able to raise the threshold, and in some, it will be lowered despite the conditioning stimulus. CPM capacity is deficient in various chronic pain conditions, including CP[54,116–118], and recent studies suggest that different analgetic treatments can affect the pain modulation[35,86,119,120]. In a study by Bouwense et al., pregabalin was shown to increase conditioned pain modulation in a group of responders where nearly half had widespread hyperalgesia[119].

CHAPTER 3. HYPOTHESIS AND AIMS

The objective of this Ph.D. was to optimize methods of evaluating and quantifying pain in patients with CP. Thus, it was hypothesized that chronic pancreatic pain could be thoroughly assessed by evaluating the following disease-specific factors: 1) pain risk elements, 2) quantitative sensory testing (QST), and 3) pain questionnaires.

The thesis is based on a peer-reviewed narrative literature review, two published original papers, and a paper submitted for publication. The three original papers were based on four studies:

Study I is a cross-sectional study that assesses chronic pain prevalence in patients with CP and associated pain risk factors.

Study II is a cross-sectional study investigating QST results in patients with painful CP and comparing these with clinical features.

Study III is a cross-sectional study focused on developing a short form of the pre-existing COMPAT-questionnaire, which is made explicitly for patients with painful CP.

Study IV is a prospective study designed to evaluate the reliability and validity of the COMPAT-SF questionnaire.

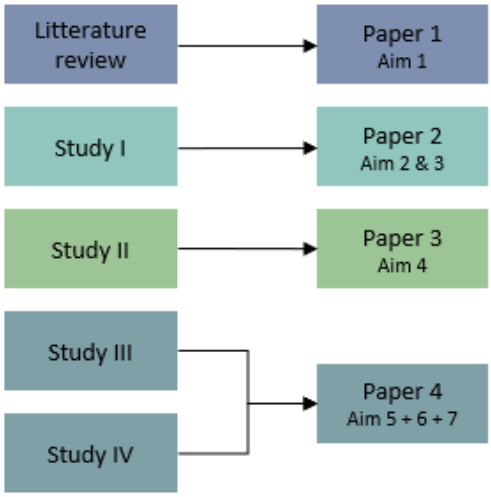

Figure 6: Overview of the Ph.D. studies, papers, and aims

3.1. AIMS

1. To review the literature to develop a mechanism-based treatment algorithm
2. To determine the prevalence of pain in a multicenter cohort of Scandinavian-Baltic patients with CP
3. To determine associations between disease characteristics and presence and pattern (intermittent vs. constant) of pancreatic pain
4. To show that a simple, bedside QST regime can be used to characterize differences in pain sensitivity between CP patients and healthy volunteers and investigate associations between pain sensitivity and clinical characteristics
5. To use the newly developed chronic pancreatitis specific questionnaire (COMPAT) to form a feasible screening instrument (SF-COMPAT)
6. To validate the developed COMPAT-SF on content and construct, as well as criterion validity
7. To test the SF-COMPAT for reliability in two patient cohorts with chronic constant and unstable pain.

CHAPTER 4. METHODS

Data for this thesis was collected from four studies. All studies comply with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines.

4.1. STUDY I

Study I was a cross-sectional study based on data from the Scandinavian Baltic Pancreatic Club (SBPC) database[46]. The SBPC database is an open, continuously recruiting prospective multicenter registration of patients with CP. The database was started in February 2016 and is continuously recruiting[46]. The data were obtained by the 1st of January 2019 and included 1384 CP patients from 11 centers in seven countries in the Scandinavian-Baltic-Russian region[121].

Patients characterized as having definitive or probable CP, according to the M-ANNHEIM classification system[45], were included in the study. The only exclusion criterion was a history of pancreatic cancer.

Information in the database was obtained from patient interviews and a review of the patient's medical records, including biochemistry. The treating physician identified etiological risk factors based on the M-ANNHEIM classification system, where more than one etiology can be assigned to the individual patient. No threshold for risk factors was applied[45].

Data derived from the database included

- Gender and age
- Duration of CP
- Etiological risk factors for CP
- Presence of diabetes and exocrine pancreatic insufficiency (EPI)
- Pain pattern
- Imaging abnormalities, including pancreatic calcifications, pseudocysts, and common bile duct or duodenal stenosis
- Current alcohol consumption
- Current smoking pattern

Pain pattern was characterized as either no pain, intermittent pain, constant pain, or constant pain with acute exacerbations[100]. The primary analysis compared patients with no pain against patients with pain to uncover potential associations between risk

factors and the presence of pain. The secondary analysis compared associated risk factors for intermittent or constant pain, where constant pain and constant pain with acute exacerbations were pooled into the latter. The focus was on the current pain pattern, regardless of previous classifications, to uncover the association between current risk factors and the presence of pain/present pain pattern. The importance of defining pain pattern is evident from earlier studies, as it has a significant effect on rates of disability, hospitalization, use of analgesic medications, and quality of life[48].

Patients current alcohol consumption was measured as alcohol units ingested per week, and patients were divided into five groups[122]:

1. Abstainers (no alcohol use)
2. Light drinkers (≤ three units per week)
3. Moderate drinkers (four to seven units per week for women and four to 14 units per week for men)
4. Heavy drinkers (eight to 34 units per week for women and 15 to 34 units per week for men)
5. Very heavy drinkers (≥ 35 units per week)

Smoking habits were registered as the number of cigarettes smoked per day, and the patients were divided into four groups[123]:

1. Non-smokers (past or never)
2. Light smokers (< 10 cigarettes per day)
3. Moderate smokers (10-20 cigarettes per day)
4. Heavy smokers (> 20 cigarettes per day)

The demographical information and clinical features were compared between patients with and without pain. Multivariable model development and analysis was performed to detect independent associations between clinical factors and the presence of pain and pain patterns[124]. In the primary analysis, logistic regression with backward selection was performed, including removing variables one after another depending on the significance level. As diabetes was considered clinically relevant, it was forced back into the model[124]. As marked pancreatic duct pathology and pancreatic calcifications expressed a linear relationship, pancreatic calcifications were omitted from the model. A nested log-likelihood test was performed to examine the interaction between smoking and alcohol intake, comparing models including the single variables and a model including the interaction between the two[125].

4.2. STUDY II

Study II was a cross-sectional study aiming to characterize CP patients' sensory profiles based on QST results, including data from a previous study conducted in Denmark and the Netherlands[126].

The study included 91 CP patients and 28 healthy controls. Patients' inclusion criteria included a diagnosis of CP by a Lüneburg score ≥ 4 and abdominal pancreatic pain, either intermittent or constant[127,128]. The control group's inclusion criteria included no major chronic diseases, absence of chronic pain, and no regular use of any analgesics.

A detailed medical history was recorded for all patients, including pain localization and characterization, comorbidities, alcohol and tobacco use, and medications. All patients completed a pain questionnaire and a quality of life questionnaire (BPI[129] and The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)[130]) and kept a daily pain diary one week before the examination.

In this study, a simple, bedside-suitable QST sequence developed in collaboration between Denmark and the Netherlands (the Nijmegen-Aalborg Sensory QST (NASQ) paradigm[131]) was applied. Only the most often affected pain mechanisms were examined. The specialized equipment needed has also been kept to a bare minimum, and the sequence consisted of only three examination modalities.

The QST sequence was performed on all patients and healthy volunteers by one of three trained QST investigators.

4.2.1. STATIC QST ASSESSMENT

The static QST assessment in study II consisted of two stimulation modalities, pressure stimulation and electrical stimulation. Five different stimulation sites on the patient's right side were examined, including:

1. Below the clavicular midline (C5 dermatome)
2. The abdominal, pancreatic area above the umbilicus (abdominal Th10 dermatome)
3. Dorsal pancreatic area, just lateral of the spine (dorsal Th10 dermatome)
4. The anterior, superior, iliac spine (L1 dermatome)
5. Quadriceps muscle 5 cm proximal to the patella (L4 dermatome)

Pressure stimulation thresholds were obtained using a pressure algometer with a 1.0 cm^2 probe (Somedic AB, Stockholm, Sweden). Pressure pain detection threshold (pPDT) and pressure pain tolerance threshold (pPTT) were measured[33,132].

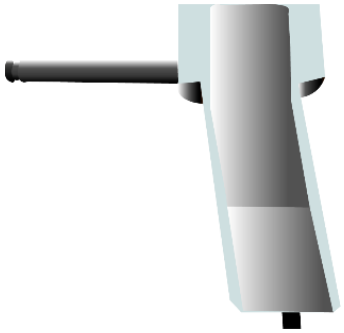

Figure 7: Pressure algometer

The electric constant skin stimulation thresholds in study II (Digistim; Biometer A/S, Copenhagen, Denmark) were measured using tetanic stimulation at 100 Hz, using two electrodes placed 3 cm apart. The equivalents of the two pressure thresholds were determined (electrical pain detection threshold (ePDT) and electrical pain tolerance threshold (ePTT))[55,126].

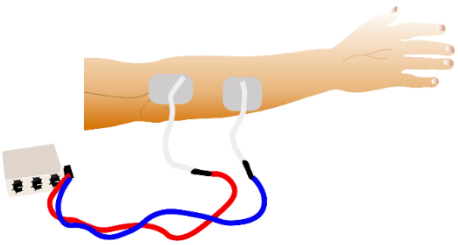

Figure 8: Electrical skin stimulation

4.2.2. DYNAMIC QST ASSESSMENT

In study II, CPM capacity was quantified by the cold pressor test, where the conditioning stimulus was cold water (2.0°C ± 0.3°C, continuously stirred), and the test stimulation was pressure stimulation with a pressure algometer on the L4 dermatome, 5 cm above the patella. During the conditioning stimulus, the patient's dominant hand was immersed in the cold water for two minutes[133].

Figure 9: Cold pressor test

If the pain became unbearable before the two minutes were over and distraction was insufficient to enable the continuation of the stimulation, the participants could remove the hand from the water ahead of time. Pressure stimulation estimating pPTT was applied before and immediately after the conditioning stimulus on the quadriceps muscle 5 cm proximal to the patella on the non-dominant side.

The CPM capacity was established as the absolute and relative changes in pPTT before and after the conditioning stimulus.

Demographics, clinical information, and CPM parameters of CP patients and controls were compared using the student’s t-test, fishers exact test, and 1-way analysis of variance with Bonferroni corrections. Electrical and pressure thresholds were log-transformed before using a mixed-effects model to compare the groups.

Subgroup analysis of clinical parameters and associated QST parameters were performed using univariate and multivariate regression analysis.

4.3. STUDY III AND IV

Study III was a cross-sectional study. It was designed to develop a short form of the COMPAT questionnaire, a pain questionnaire created explicitly for patients with CP and acute recurrent pancreatitis. It included patients from a center in New Zealand and a center in Denmark. Inclusion criteria included painful CP diagnosed by a Mayo score ≥ 4[134]. Exclusion criteria included under 18 years of age, severe comorbidities, acute pancreatitis, autoimmune pancreatitis, and CP secondary to malignancy.

Patients filled out the full version of the COMPAT questionnaire[101], including 23 main questions and 180 secondary questions. The questionnaire was developed in English but translated to Danish for the Danish patients. The translation was back-translated to English by a native Danish speaker with in-depth knowledge of the English language, demonstrated by an International English Language Testing (IELTS) score of 8.5, corresponding to a native English speaker. Any inconsistencies were discussed with the original authors to ensure no decline in the nuance of the language. Part of the original McGill questionnaire was incorporated in the COMPAT questionnaire, and the translation of this part was based on a previously validated translation[135].

Study IV was designed to test the reliability and validity of the COMPAT-SF questionnaire. The study was conducted at three centers in Aalborg, Denmark, Pittsburgh, USA, and Baltimore, USA. Inclusion and exclusion criteria were the same as in study III. Inclusion of patients from Aalborg and Pittsburgh was focused on patients with a stable pain status. Stable pain status was defined as no surgical or endoscopic interventions, and no major pain medication changes six months before inclusion. All eligible patients, regardless of fluctuating pain, could be included from the center in Baltimore. This difference was designed to exemplify whether fluctuating pain levels could influence the reliability and enhance knowledge of CP reliability studies' difficulties. The sample size was determined to detect a possibly significant correlation between the two answers of the COMPAT-SF questionnaires. Alpha was set at 0.05, beta at 0.2, intraclass correlation coefficient (ICC) below 0.60 was considered not relevant, and from a hypothesized ICC of 0.80, the sample size was calculated to be a minimum of 40 participants.

Seventy-six patients were included for the reliability study, 51 were from the stable pain status group, and the subject to item ratio was thereby 8.5. To validate the COMPAT-SF questionnaire, all patients completed the COMPAT-SF questionnaire, the Izbicki pain scale[98], and the BPI pain questionnaire[129] at baseline. After 2-6 weeks, patients completed a second COMPAT-SF. Forty-one patients from the stable pain status group and 25 patients from the unstable pain status group fulfilled the trial and completed both COMPAT-SF questionnaires. Reliability was examined by comparing the first and second completion of the COMPAT-SF questionnaire.

For an overview of the course of the two studies, please see figure 10.

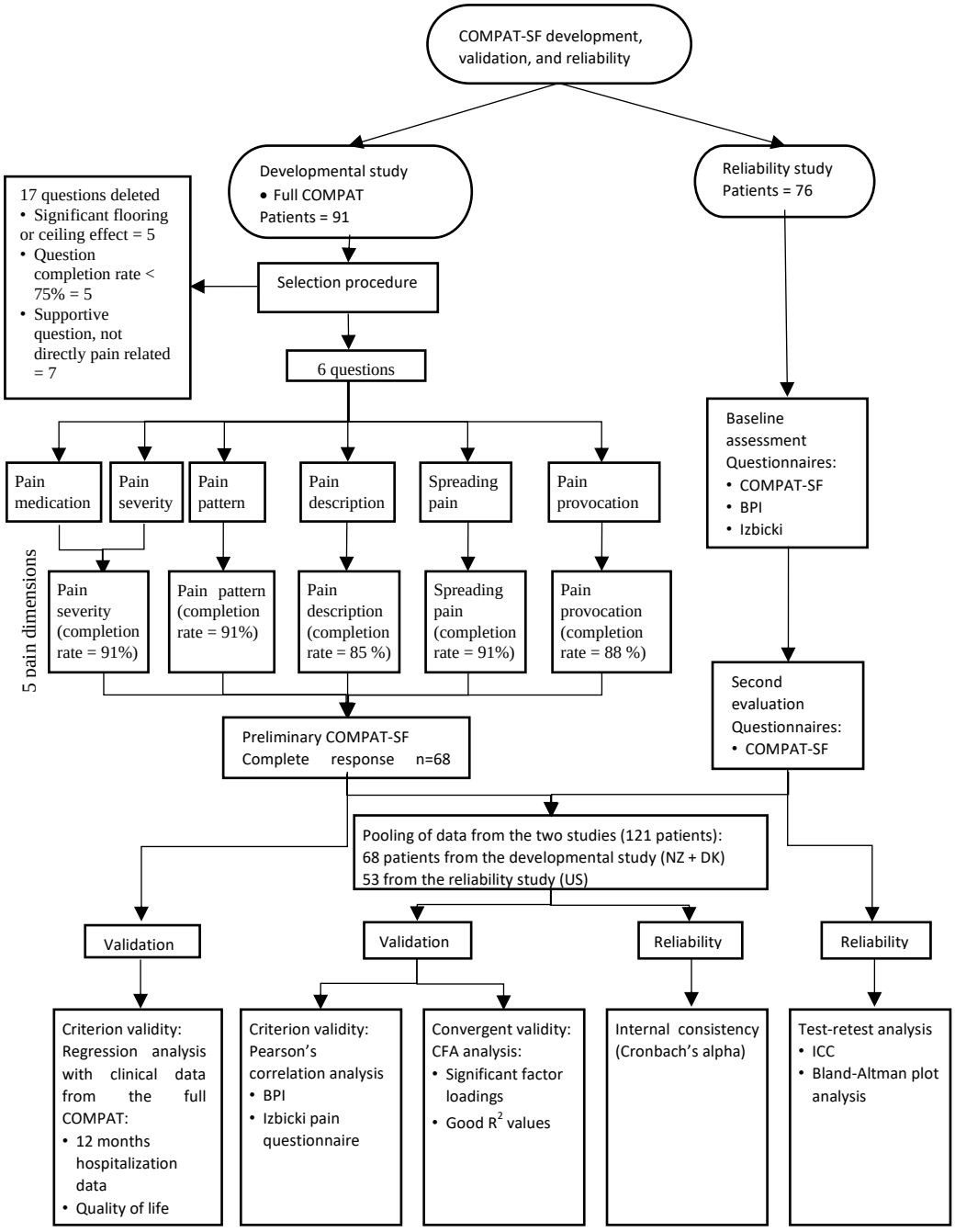

Figure 10: Development, validation, and reliability testing of the short form

4.3.1. DEVELOPMENT

Questions to include in the COMPAT-SF were chosen based on the content of the 91 patients' questionnaire answers.

To allow for statistical calculations, answers were interpolated if a limited number of secondary questions were left blank (<20%). Interpolation was performed by carefully finding patients who had answered correspondingly in the other secondary questions and choosing a relevant response from their questionnaire fulfillments. If a main question was left entirely unfilled, no interpolation was performed to limit the answers' uncertainty.

Four questions were designed to be answered by subgroups of patients according to their pain pattern (question 10 – 13). The pain intensity secondary questions from these questions were merged into one pain intensity question to enhance the item response rate and simplify the questionnaire.

The distribution of answers in the remaining questions was inspected, and items with pronounced flooring or ceiling effect above 20% were excluded. This was done to minimize the risk of type I errors[136,137].

Then all unclear or irrelevant questions were omitted. A question was deemed irrelevant or unclear based on the completion rate, where below 80% was considered the cut-off value[138].

At last, all supportive and not directly pain-related questions were excluded. These were dropped to limit the number of questions in the short form. Although it is advised that factors such as sleep, sexual function, quality of life, and psychological aspects of pain are evaluated in chronic pain patients, these are more universal aspects of pain, and questionnaires developed for chronic pain conditions in general can easily be used.

If multiple questions from the same pain dimension remained, their scores were merged into one mean pain dimension score. All pain dimension scores were normalized on a 0-100 scale and weighted according to clinical relevance.

4.3.2. VALIDATION

After the COMPAT-SF questionnaire content was chosen, validity was assessed in three ways.

Content validity was assessed by an expert panel consisting of the original COMPAT questionnaire's developmental team and specialists in pancreatic pain by ensuring that all essential pain dimensions from the original COMPAT questionnaire were included[139].

Construct validity was ensured by performing confirmatory factor analysis (CFA) on the included pain dimensions[140].

Criterion validity was assessed in two ways: 1) by comparing the COMPAT-SF scores with hospitalization days during the past year and the Pancreatitis Quality of Life Instrument (PANQOLI) score[141] from the full COMPAT questionnaire, using negative binomial regression and linear regression. 2) By correlating the COMPAT-SF total score against the BPI scores and the Izbicki pain questionnaire using Pearson's correlation coefficient[96].

4.3.3. RELIABILITY

Reliability was assessed by comparing the answers from the first and the second COMPAT-SF from the reliability study using the ICC and Bland-Altman plots. Internal consistency was examined by calculating Cronbach's alpha, as the questionnaire is developed to be unidimensional[96].

CHAPTER 5. KEY RESULTS

5.1. AIM I

Aim: To review the literature to develop a mechanism-based treatment algorithm (paper I).

Key results:

- No single analgesic is the best match for every patient
- QST and psychological evaluation could provide a platform for individualized and multimodal pain management
- A proposed treatment algorithm is provided, although the overall concept is not yet validated; see figure 11

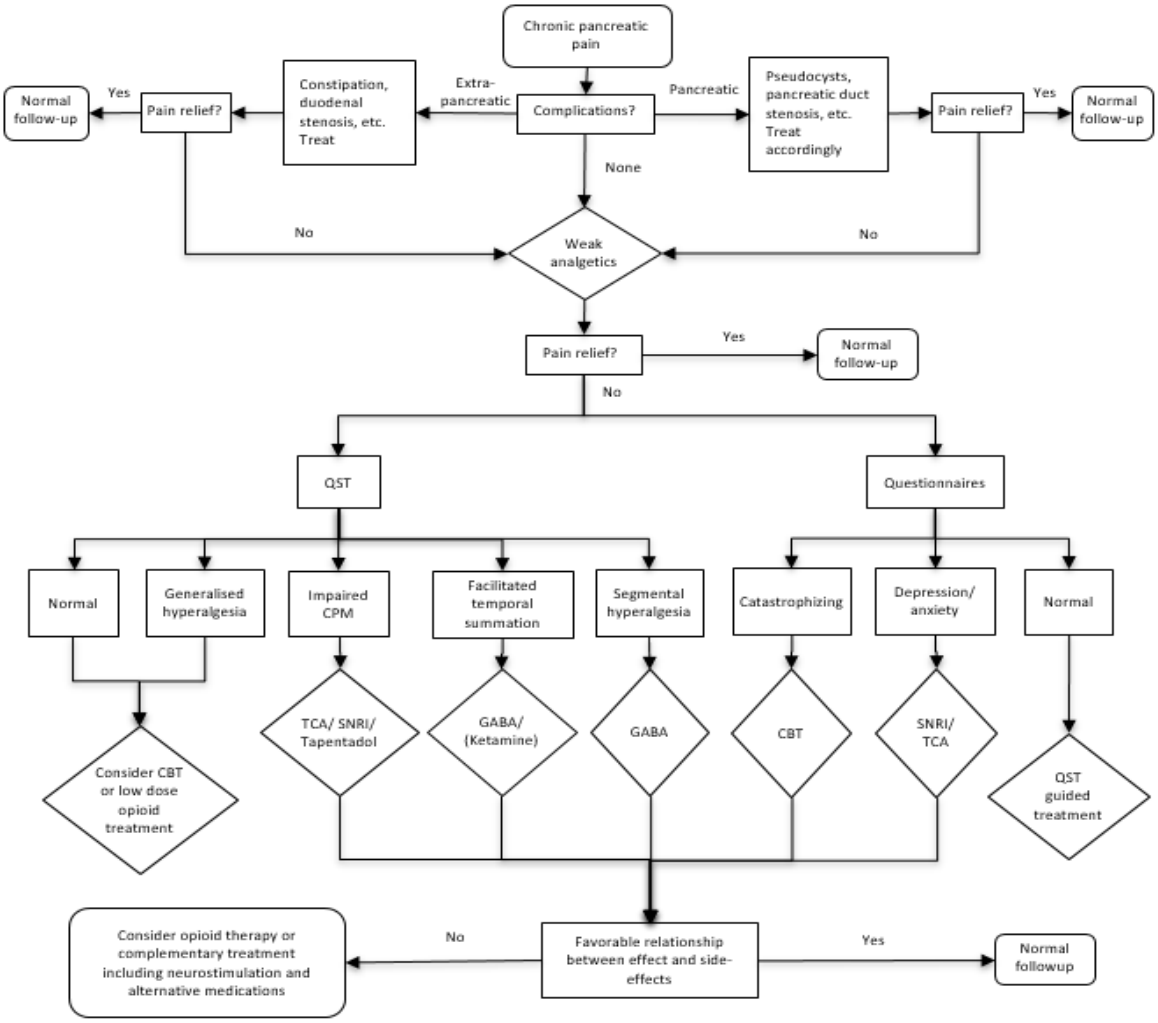

Figure 11: The flowchart exemplifies a mechanism-based treatment algorithm that can be used to guide pain management in CP patients. Abbreviations: GABA = gabapentinoids, QST = Quantitative Sensory Testing, SNRI = Serotonin and Norepinephrine Reuptake Inhibitor, TCA = Tricyclic Antidepressants, CBT = Cognitive Behavioral Therapy.

5.2. AIM II

Aim: To determine the prevalence of pain in a multicenter cohort of Scandinavian-Baltic patients with CP (paper II).

Key results:

- Nearly 60% of patients reported pain, of whom 71% reported intermittent pain, 19% constant pain with acute exacerbations, and 10% constant pain.

5.3. AIM III

Aim: To determine associations between disease characteristics and presence and pattern (intermittent vs. constant) of pancreatic pain (paper II).

Key results:

- Pain associated disease characteristics confirmed by multivariate analysis included:
  - Very heavy alcohol abuse (> 5 units of alcohol per day)
  - An increasing number of cigarettes smoked per day increased the risk of painful CP
  - Exocrine insufficiency
  - Moderate pancreatic duct changes
  - Pseudocysts
  - Duodenal stenosis
- Associations between pain pattern and disease characteristics confirmed by multivariate analysis included
  - Smoking habits, as moderate and heavy smokers were more likely to report constant pain
  - Active alcohol consumers were more likely to report intermittent pain
  - Moderate to marked ductal changes in the pancreas trended towards associating with constant pain
  - EPI trended towards association with constant pain

5.4. AIM IV

Aim: To show that a simple, bedside QST regime can be used to characterize differences in pain sensitivity between CP patients and healthy volunteers and investigate associations between pain sensitivity and clinical characteristics (paper III).

Key results:

- CP patients were hypersensitive to pressure stimulation at the dorsal pancreatic dermatome, the abdominal pancreatic dermatome, and the L4-control dermatome compared to healthy controls
- Likewise, CP patients were hypersensitive to electrical stimulation at the dorsal pancreatic dermatome and the L4 dermatome
- The cold pressor test showed that the tolerated duration was lower in CP patients than in healthy controls.
- CPM: The patients had lower pPTT before and after the cold pressor test, and the change between the two was significant. There was no correlation between the duration of the cold pressor test and the CPM response.
- Clinical pain intensity was significantly associated with low CPM response
- Pain interference score on the BPI questionnaire was associated with average pressure pain thresholds (mean of all stimulation sites thresholds), indicating generalized hyperalgesia.

5.5. AIM V

Aim: To use the newly developed chronic pancreatitis specific questionnaire (COMPAT) to form a feasible screening instrument (SF-COMPAT) (paper IV)

Key results:

- The developed COMPAT-SF questionnaire is comprised of five pain dimensions containing six questions. The total COMPAT score includes all of the dimensions scores, weighted based on clinical relevance, and normalized on a 0-100 scale.

5.6. AIM VI

Aim: To validate the developed COMPAT-SF on content and construct, as well as criterion validity (paper IV)

Key results

Validation:

- Content validity: All experts in the focus group agreed that the questionnaire contained the most relevant aspects of the full COMPAT questionnaire and would be suited to use as a brief questionnaire for research, in clinical, or as a screening tool for further investigation using the full COMPAT questionnaire.
- Construct validity: CFA found highly significant factor loadings for all five factors (pain dimensions), ranging from 0.44-0.78 ($p<0.001$). The four strongest factors all had R^2 values above 0.3 and an overall factor R^2 value of 0.81.
- Criterion validity: The COMPAT-SF total score correlated significantly with the Izbicki Pain Scale and the BPI ($p<0.0001$). The highest correlation coefficient was with the Izbicki Pain Scale (0.78 vs. 0.61, respectively).
- Criterion validity: The COMPAT-SF total score and three of the subscores (pain pattern, pain severity, and pain provocation) were significantly correlated to 12 months hospitalization rates ($p<0.05$). The COMPAT-SF total score and all subscores were significantly correlated with quality of life ($p<0.05$).

5.7. AIM VII

Aim: To test the SF-COMPAT for reliability in two patient cohorts with chronic constant and unstable pain (paper IV)

Key results

Reliability:

- Reliability in the COMPAT-SF was good, with an ICC of 0.89 in the stable pain group. However, the limits of agreement were above average but acceptable. The ICC in the unstable pain group was only moderate (0.61) with very high insecurities of approximately ±30%.
- The Cronbach‘s alpha of the COMPAT-SF questionnaire was good at 0.77 with a confidence interval of 0.7 – 0.82, indicating good internal consistency.

CHAPTER 6. DISCUSSION

The Ph.D. thesis had seven objectives:

1. To review the literature to develop a mechanism-based treatment algorithm
2. To determine the prevalence of pain in a multicenter cohort of Scandinavian-Baltic patients with CP
3. To determine associations between disease characteristics and presence and pattern (intermittent vs. constant) of pancreatic pain
4. To show that a simple, bedside QST regime can be used to characterize differences in pain sensitivity between CP patients and healthy volunteers and investigate associations between pain sensitivity and clinical characteristics
5. To use the newly developed chronic pancreatitis specific questionnaire (COMPAT) to form a feasible screening instrument (SF-COMPAT)
6. To validate the developed COMPAT-SF on content and construct, as well as criterion validity
7. To test the SF-COMPAT for reliability in two patient cohorts with chronic constant and unstable pain.

The discussion is divided into two parts, first concerning methodological considerations in pain assessment of CP patients, hereafter a discussion on clinical implications and future perspectives of performing a comprehensive pain assessment, including several layers to establish as precise an estimation of pain intensity, quality, and life interference as possible.

6.1. METHODOLOGICAL CONSIDERATIONS

6.1.1. DIAGNOSTIC CRITERIA

The thesis is based on four different studies performed in collaboration with several teams from around the world. This background has resulted in structural differences, for instance, concerning different ways of diagnosing CP. Study I was based on data from the SBPC database, a database formed from a collaboration between several sites in the Scandinavian and Baltic regions. For this database, the steering group had agreed upon using the M-ANNHEIM diagnostic criteria. Study II was a study based on patients from Aalborg, Denmark, and Nijmegen, The Netherlands. Data collection was started as a part of a different study in which the Lüneburg criteria were used as a diagnostic inclusion criterion. Afterward, further data collection was conducted, naturally maintaining the primary inclusion criteria. Studies III and IV were performed in collaboration with teams in New Zealand and the United States of

America. As the diagnostic criteria used in these two countries are the Mayo criteria, it was natural to adopt these criteria to the inclusion criteria.

The usage of three different diagnostic methods could raise doubt about whether the patients in the four studies are comparable. The Lüneburg criteria and the Mayo criteria are generally quite similar, but the Lüneburg criteria also account for indirect pancreatic function tests and findings on ultrasonic and diagnostic procedures. The M-ANNHEIM diagnostic criteria are mainly focused on the presence of either calcifications or marked ductal alterations and persistent exocrine insufficiency as definite diagnostic criteria for CP[142]. These criteria are generally present in all the different diagnostic methods for definitive CP. Therefore, the diagnostic criteria used will probably not affect the result, as all patients included in the studies had definite CP.

6.1.2. DATABASE STUDIES

The design of study I was based on data from a continuously recruiting database. The database design provides a basis for gathering a large amount of data. The amount of data is essential when conducting outcomes analyses, as large datasets enable the use of multivariate analysis that can be used on complex datasets with several potential factors of significance.

Examining large datasets typically produce estimates with smaller confidence intervals, making the results more reliable and form the basis for hypothesis development[143]. Database design can also present challenges, as the data input often is less than perfect, which leaves room for biases as to which patients have incomplete registration. The causes for the incomplete data entry are almost impossible to detect post hoc. Variation in data quality can also be a problem concerning the consistency of coding, which is difficult to bypass when the database collaborates between different centers. When examining a disease like CP, multicenter collaborations are essential, as the disease is not a frequently occurring disease, limiting the availability of patients. Therefore other centers can help in establishing a large patient cohort for the database. To avoid coding inconsistencies in the SBPC database, a steering group is in charge of establishing standard ground rules that are followed universally at all sites. These ground rules have been established through frequent contact and meetings in the steering group.

To ensure comparability in the collected data, all included centers in the SBPC database are secondary or tertiary referral centers with a particular interest in CP[46].

In study I, the prevalence of pain was assessed and grouped into chronic and intermittent pain. This listing showed significant differences from an American

database study (NAPS2) on CP patients[48], where a larger percentage of patients experienced pain, and the group of patients with constant pain far exceeded the group with intermittent pain. This difference could relate to different pain assessment methods, ethnic differences, differences in disease stage, and differences in alcohol and tobacco consumption, as described in the article. The way pain is registered in the database could also be of interest when assessing the difference's cause. In the SBPC database, patients treated with analgesics and reported no pain were registered as being pain-free. While this is a factual truth, the cause for analgesic treatment prescription is not explored, and this could hide a large group of patients with chronic pain that is well-treated with analgesic agents.

Database studies are favorable, as the data is collected continuously without any inconvenience to the participant. The patient's behavior is typically not affected by the awareness of being studied, as the process is continuously and typically following an outpatient follow-up regime[144]. However, it does not leave room for an extended gathering of information, e.g., if additional health information is required, it is often not accessible due to the anonymization of data, which poses a limitation.

6.1.3. QST STUDIES

Objective assessment of pain is desirable yet hardly obtainable due to the subjective nature of pain sensation. According to Melzack et al., perceived pain comprises several dimensions, including sensory, affective, and evaluative[25]. To separate the sensory dimension from the other dimensions is likely impossible, and pain intensity estimation comes with accepting subjective influence.

QST paradigms have evolved significantly over time. Earlier batteries included complex visceral stimulations and several different stimulation types. This provided detailed information but was also quite time-consuming and not possible to include in the clinic[107,145]. Therefore, a simplified paradigm, the NASQ paradigm, was developed, which is the paradigm used in study II. This paradigm only involved somatic stimulations, making it better tolerated by patients, and included an evaluation of CPM and pain thresholds by pressure and electrical stimulations[131]. Table 1 provides a review of previously performed QST studies in CP patients.

Studies	QST stimulations	References
Treatment studies		
Pregabalin	Somatic pressure stimulation, somatic electrical stimulations, cold-pressor test, visceral electrical stimulation	[33,83, 117,145]
Ketamine	Somatic pressure stimulation	[147]
Opioids	Pinch stimulation, somatic heat stimulation, transcutaneous electrical stimulation, somatic pressure stimulation, somatic electrical stimulation, visceral mechanical stimulation, visceral electrical stimulation, and visceral thermal stimulation	[148]
Pancreatic duct decompression/pancreatic resection	Electrical stimulation, cold-pressor test	[149]
Thorascopic splanchnic denervation	Somatic pressure stimulation, somatic electrical stimulation	[150,151]
Electrical accentuation of vagal tone	Somatic pressure stimulation, cold-pressor test	[152]
Examination of pain processing		
Organization and connectivity of brain networks	Contact heat-evoked potentials, electrical stimulation of the oeosophagus, stomach, and duodenum	[53,153,154]
Comparison of pain responses with healthy volunteers	Pinch stimulation, heat stimulation, transcutaneous electrical stimulation, somatic pressure stimulation, somatic electrical stimulation, repetitive pinprick stimulation, cold-pressor test, visceral mechanical stimulation, visceral electrical stimulation, and visceral thermal stimulation	[76,107, 115,131, 144,155]
Examining QST phenotypes of CP patients	Somatic pressure stimulation, repetitive pinprick stimulations, cold-pressor test	[156]
Association between sympathetic activity and hyperalgesia	Somatic pressure stimulation	[157]
Reliability of QST measurements in CP patients		
Reliability of static and dynamic stimulations	Somatic pressure stimulation, somatic electrical stimulation, cold-pressor test	[132]

Table 1. A review of previously performed QST studies in CP patients.

Unfortunately, an examination of temporal summation was not included in the NASQ paradigm. After 71 patients had been completed, an examination of temporal summation was included in the protocol. As an effect of the late addition, the final

data was too incomplete to include this part in the analysis. This is a disadvantage when using data from several studies; not all registrations will be complete, which will weaken the ability to examine all subjects of interest. However, the advantages of extracting as much knowledge from data already collected as possible outweigh the disadvantages, as it minimizes patient discomfort and enhances the outcome gained from the time patients use when participating in clinical studies.

In our study by Phillips et al.[56], an algorithm for phenotyping central pain processing based on normative criteria for a P-QST paradigm was proposed. The P-QST paradigm was designed to simplify the NASQ paradigm further, aiming to create a paradigm that provides the information needed from an as simple as possible bedside examination. This algorithm included 1) CPM capacity, 2) cold pressor endurance time, 3) the sum of pPDT, and 4) temporal summation of the forearm and abdomen as markers of generalized, widespread sensitization and 5) a pPDT index (an index between the mean value of the pancreatic dermatome (ventral and back) and the mean value of the three other examination sites) and 6) temporal summation of the abdomen as markers of segmental sensitization[56]. This paradigm can be the basis for the diagnosis of sensitization and can prove valuable in future treatment response studies and treatment algorithms. In another study, we showed that this paradigm could differentiate CP patients into distinct phenotypes that were not confounded by psychiatric comorbidity[156].

For future studies, a test for temporal summation should be included from the beginning to showcase a complete pain processing concept.

The reproducibility of QST can also pose a limitation. In CPM paradigms, reproducibility has been an issue in previous studies, especially when examining chronic pain patients[114,132,158]. These problems can be caused by several things, including fluctuating pain levels and generalized hyperalgesia[132]. Furthermore, the CPM paradigm consists of both pre- and post-conditioning stimulation thresholds, and these are subject to their own variability, as described by Olesen et al.[132]. In some studies, CPM capacity has been shown to predict treatment response[35,86], and other studies have shown that specific treatments can change the CPM capacity significantly[119,120]. Likewise, many different pain conditions have been shown to have deficient pain modulation[54,118,159] and taken together with the link to treatment response, it is a mechanism that needs to be examined when evaluating pain processing, despite the reproducibility issues. Different CPM regimens have proven to have better reproducibility, and the CPM paradigm can be optimized to improve reproducibility. Studies have shown that tourniquet cuff as the conditioning stimulus and pressure pain threshold as the test stimulus (preferable computer-controlled) has the highest reproducibility[160,161]. However, the reproducibility is often merely examined by estimating the ICC, and although this is the classical evaluation method, it is probably getting outdated, as more recent research focuses on Bland Altman plot analysis as a more reliable measure of reproducibility[162].

6.1.4. QUESTIONNAIRE DEVELOPMENT

Comparison of clinical trials typically limited the use of heterogeneous outcome measures, affecting the quality of meta-analyses. The OMERACT (Outcome Measures in Rheumatology) is an international initiative developed to improve the outcome measures in rheumatology by developing "core domains" to include in pain assessment[163]. The OMERACT initiative emphasizes the importance of validity (truth), reliability (discrimination), and feasibility as basic features essential for all outcome measures. Afterward, projects such as the "Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials" (IMMPACT)[30] and "Validation and Application of a patient-relevant core set of outcome domains to assess multimodal PAIN therapy" (VAPAIN)[164] followed. The IMMPACT recommendations were developed by a group representing academia, governmental agencies, and pharmaceutical agencies and defined six core domains that should be applied to pain assessment in clinical studies regardless of etiology. The domains included pain assessment, physical functioning, emotional functioning, global improvement evaluation, symptoms and adverse effects if treatments are involved, and patient disposition[30]. The VAPAIN consensus statement was developed by a multi-professional panel, including patient representatives, pain physicians, physiotherapists, psychologists, and researchers. It resulted in 8 core domains, including pain intensity, pain frequency, physical activity, emotional wellbeing, satisfaction with social roles and activities, productivity, health-related quality of life, and patient's perception of treatment goal achievement[164]. The use of any of these recommendations will increase pain evaluation's homogeneity and improve clinical studies' comparability.

As no pain questionnaire has been developed explicitly for CP and validated sufficiently in the patient group, many different questionnaires have been used in clinical studies. This makes the pain evaluation heterogeneous and complicates the comparability of the studies. Table 1 sums up the different pain assessment tools used in CP.

Pain assessment tools	No. of studies	No. of RCT's	References
One-dimensional			
Visual Analogue Scale (VAS)	53	21	[165]
Numerical Rating Scale (NRS)	9	2	[166]
Pain improvement groups	5	1	[167]
Pain intensity groups	16	7	[168]
Pain pattern	12	2	[169]
Frequency of pain attacks	10	4	[170]
Post-prandial pain	5	3	[171]
Two-dimensional			
(No. of days with pain) x (median pain VAS)	1	1	[172]
(Daily pain duration) x (median pain VAS)	1	1	[173]
(Degree of frequency) x (median pain VAS)	1	0	[174]
(Pain frequency) x (pain severity)	1	0	[175]
(No. of hours of pain) x (median pain VAS)	1	1	[176]
Multi-dimensional			
McGill Pain Questionnaire	5	3	[166]
PainDetect Questionnaire	1	1	[126]
Pain score (based on scores of intensity, frequency, and pain consequences)	1	0	[177]
Impact of pain			
Quality of life scales	19	5	[178–180]
Brief Pain Inventory (BPI)	2	1	[126]
Pain Coping and Cognition List (PCCL) Questionnaire	1	0	[178]
Pain Disability Index (PDI)	2	1	[181]

Table 2. Pain assessment tools used in clinical studies in CP patients. References indicate the first time the tool was used in an intervention study[94].

Study III and IV concerned developing a short form of the COMPAT questionnaire and testing for validity and reliability. The COMPAT questionnaire was primarily developed in New Zealand in English[101], and therefore a translation of the study had to be established to collect data from patients from Aalborg. Translations introduce the risk of misinterpretations and changes in the meaning of the wording[182]. Although many Danish citizens speak English decently, details can be lost when it is not the participants' mother tongue. This study's patient group often consists of socially vulnerable persons with less educational level than the general population's average

educational level[183]. These problems could also lead to misinterpretations and result in incomplete answers or answers of inferior quality. The questionnaire's interpretation was performed meticulously with contact with the original authors, if in doubt, to enhance the interpretation's quality. A native Danish speaker performed a back-translation, which is a limitation, as it would be optimal to have a native English speaking translator doing the translation. However, as our translator had an IELTS score of 8.5, which simulates that of a person with very good knowledge of the English language, it was deemed sufficient and did not significantly lower the translation quality. No significant differences were found between the translation and the original questionnaire, and it was evaluated that the language did not lose linguistics in the translation. The Danish patient group's answers were also compared with those of the New Zealandic patient group (see appendix A), and the only significant difference between the two groups concerned the rating of the word tender in the McGill-questionnaire part of the COMPAT-SF. This difference is probably cultural, as the McGill questionnaire translation previously has been validated.

Developing short forms of questionnaires is a task that needs to be evaluated thoroughly. It needs to capture the essence of the original questionnaire without losing too much depth. Usually, the short form items are chosen based on item response theory, item-total correlations, or factor analysis[184]. Nevertheless, many of these methods were not usable in the COMPAT questionnaire due to 1) a complex structure involving parts that only subgroups should answer and 2) the original questionnaire's comprehensiveness. The results are, however, controlled by confirmatory factor analysis, which endorsed the remaining items. As the original COMPAT questionnaire is not yet validated, the COMPAT-SF questionnaire was treated as a separate questionnaire that could withstand validation against other frequently used pain questionnaires. This validation gives the questionnaire independent value but does not prove that the results can compare to the original questionnaire results, and this must be done in future studies, preferably when a scoring system for the original questionnaire has been established.

The validation process included three out of four commonly used validation methods. Face validation evaluates whether the questionnaire seems to capture the subject in focus and is done by non-experts in methodologies. This type of validation was omitted in the present study, as its value has been disputed[96]. Instead, the questionnaire was validated on content, construct, and criterion.

6.2. CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

This thesis is focused on the characterization of pain and pain-related risk factors in patients with CP. It gives us an exhaustive knowledge of how the patients experience pancreatic pain and how pain mechanisms are affected by chronic pain.

As there now is a pain questionnaire explicitly developed for CP patients and validated against previously used questionnaires, as well as clinical factors such as quality of life and hospitalization burden, this could be incorporated into the monitoring of CP, and specific attention could be directed to those who scores above average and might be insufficiently treated. The long evaluation period in the COMPAT-SF questionnaire can complicate the use in clinical research. In treatment studies, the evaluated time-span can pose a bias to detect treatment effect during shorter treatment regimens. This must be addressed by considering a change to the evaluated period to accommodate the individual study.

The characterization of risk factors for pain in CP can prove valuable when assessing which interventions could help manage CP, including non-pharmacological interventions. Smoking and alcohol cessation has been known to be substantial risk factors for developing CP[48,185]. However, study I shows that the current abuse is also essential for the present pain profile and intensity, and this could be used as an educational tool when introducing the importance of abstaining from alcohol and tobacco to the individual patient.

QST examinations can prove valuable when assessing pancreatic pain. It can indicate which patients could benefit from invasive treatment such as surgery or endoscopy and which would be more inclined to respond to medical treatment[105]. The Mech Sense research group is currently working on a study implicating QST results in predicting response to endoscopic treatment. It is hypothesized that patients with signs of central sensitization have significant changes in their central nervous system and would, on that behalf, not benefit from local treatment. If this proves to be the point, it would be able to spare patients from enduring endoscopies that do not improve their pain status and limit those for patients where the chance of clinical improvement is probable.

If surgery is deemed inefficacious, the QST results can potentially also be used to choose medical treatment and predict treatment response. This thesis opens to the possibility of creating and validating treatment algorithms, such as the one proposed in paper I. The thesis lays the basis for such an algorithm as it is impossible to build an algorithm without the tools necessary to form an in-depth characterization of pain. It should also include assessing the psycho-social aspects of pain, such as depression, catastrophizing thoughts, sleep, and sexual function[186]. The COMPAT-SF is an essential tool in estimating pain intensity and pain characteristics that affect patients' quality of life. However, several vital aspects of pain have not been included in this questionnaire, such as anxiety, depression, sleep disturbances, and sexual disturbances. These are universal aspects similar in all chronic pain conditions and can be assessed through previously validated questionnaires.

Further studies on QST-based prediction of treatment response could improve an algorithm's outcome, and the algorithm must be kept up to date as new research emerges.

If a treatment algorithm is proved effective, it opens the door to scaling the knowledge beyond CP onto the general chronic pain patient. QST guided treatment in patients with central sensitization could be easily transferable, as the mechanisms causing central sensitization are likely, not disease-specific but generally the same despite the origin of pain[73]. This is currently being examined in the validation of the full COMPAT questionnaire, where answers from patients with other types of chronic pain are compared with answers from CP patients, and preliminary data indicate that those who show signs of being centrally sensitized are comparable between the two groups, whereas the others are not.

However, to use an algorithm developed for CP patients for other chronic pain patients, characterization must be adjusted to fit the individual pain condition, focusing on disease-specific complications, questionnaires validated for the patient group in question, and segmental QST measurements targeted on affected dermatomes.

This could lay the groundwork for changing pain treatment in chronic pain patients. However, it calls for validation of the algorithm, which is a difficult study to perform, as randomization can only be done at center-level, due to knowledge of the algorithm possibly could bias the choice of analgesic treatment in the standard-care group if the same doctors were involved in both arms of the trial.

CHAPTER 7. CONCLUSION

This Ph.D. thesis aimed to identify clinical risk factors of pain in patients with CP and characterize pancreatic pain thoroughly and comprehensively through QST and a pain questionnaire. Based on the six objectives, we concluded that pancreatic pain is a frequent symptom in CP and is challenging to manage, as many factors need to be considered in the choice of treatment. Concurrent, modifiable risk factors for pancreatic pain include smoking, very heavy alcohol abuse, pseudocysts, and duodenal stenosis. A trend towards constant pain was shown in moderate to marked pancreatic duct changes.

The remaining aims focused on pain characterization as a primary step towards individualization of pain management. We concluded that pathophysiological pain processing mechanisms in patients with CP could be characterized using QST. The QST examinations in study II showed significant differences between patients and healthy controls, and some of the differences were associated with clinical pain intensity and interference scores, underlining the clinical importance of defective pain processing.

Furthermore, a brief pain assessment questionnaire was developed explicitly for patients with CP, and it proved to be both valid and reliable. These two measures (QST and the COMPAT-SF questionnaire) comprise a reasonable basis for pancreatic pain characterization. They can be combined with additional assessment tools, including depression and anxiety scales, sleep evaluation, pain catastrophizing scales, and quality of life questionnaires, depending on the study.

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APPENDICES

Appendix A. COMPAT-SF results

This table compares the answers of the COMPAT-SF questionnaire from Danish and New Zealandic patients, respectively. The comparison is performed as student t-tests, Mann-Whitney U test, or Chi-square test as appropriate. Due to multiple comparisons, the results are Bonferroni corrected with a significance value of 0.5/42 = 0.0012. Significant values are marked in bold.

		Denmark	**New Zealand**	**p-value**
Pattern	A	34%	43%	0.0110
	B	16%	5%	
	C	29%	50	
	D	21%	2%	
Pain intensity	Average	5.3	5.7	0.3912
	Worst	7.9	7.6	0.6284
	Least	4.1	3.3	0.5163
Opioid use		39%	36%	0.8080
Provoking factors	Any food	2	2	1.0000
	Fatty food	2.2	2.5	0.3049
	Fluids	1.2	1.3	0.5850
	Alcohol	2.5	3.0	0.2247
	Stress	1.5	2.0	0.1296
	Cigarettes	1.7	2.8	0.0274
	Exercise	1.5	1.7	0.6085
	Socialising	1.4	1.2	0.6167
	Weather changes	1.0	0.9	0.9088
	Light touch on skin	1.1	1.0	0.7797
	Cold/heat on skin	0.9	1.0	0.8793
	Pressure on skin	1.4	1.3	0.8248
Widespread pain	Head	1.8	1.2	0.1046

	Joint	2.3	1.7	0.2748
	Limbs	2.3	1.6	0.1876
	Back/neck	2.7	2.2	0.3122
	Abdominal/pelvic	1.7	1.5	0.7019
	Muscle	1.2	1.2	0.9372
	Chest	1.1	0.8	0.5855
McGill	Throbbing	2.1	3.4	0.0809
	Shooting	3.9	4.1	0.8447
	Stabbing	2.7	4.8	0.0204
	Sharp	5.5	5.8	0.7184
	Cramping	3.1	4.2	0.1970
	Gnawing	2.8	3.8	0.2634
	Hot-burning	2.4	3.2	0.3312
	Aching	1.9	4.3	0.0041
	Heavy	5.9	4.1	0.0619
	Tender	1.8	4.3	**0.0005**
	Splitting	0.7	2.7	0.0030
	Tiring-exhausting	4.2	5.8	0.0764
	Sickening	4.2	5.4	0.1725
	Fearful	5.7	3.6	0.0241
	Punishing-cruel	3.4	3.7	0.7386

ISSN (online): 2246-1302
ISBN (online): 978-87-7210-877-3

AALBORG UNIVERSITY PRESS