MECHANISTIC PAIN PROFILING OF PATIENTS WITH OSTEOARTHRITIS

CURRENT KNOWLEDGE AND FUTURE DIRECTIONS

DOCTORAL THESIS (DR.MED.)

KRISTIAN KJÆR PETERSEN
This thesis is dedicated to my close collaborator, mentor, and friend dr.med., Ph.D. Ole Simonsen, who retired as orthopedic surgeon and excellent researcher in the summer of 2020. This work and the work of so many other young researcher in Aalborg would not have been possible without Ole Simonsen as a source of inspiration, motivation, and continued support. The pain field and the general research environment around musculoskeletal pain conditions in Aalborg are forever in depth to Ole Simonsen’s work and commitment.
KRISTIAN KJÆR PETERSEN (KKP)

KKP is trained as a biomedical engineer, received his M.Sc. degree in 2011 and his Ph.D. degree under the supervision of Prof. Lars Arendt-Nielsen in 2014 from Aalborg University, Denmark.

KKP's long-term mission is to develop the concept: "Personalized Mechanistic Pain Medicine" to provide the correct treatment for the right patient. Specific focuses are on 1) development of pain assessment tools and models, 2) validation and reliability of these models and tools and 3) understanding underlying features of pain mechanisms and predicting pain outcomes after treatment.

Through extensive work with Prof. Thomas Graven-Nielsen, Prof. Lars Arendt-Nielsen, and industrial partners, KKP has developed the cuff algometer, which is being used in studies around the world.

KKP has published more than 70 peer-reviewed papers with focus on pain mechanistic profiling and understanding the underlying mechanisms for chronic pain. In the period 2017-2020, he was ranked as the 3rd most publishing author and the 2nd most cited authors in the world within the topic of: "Central sensitization in patients with knee osteoarthritis" according to Scopus SciVal.

KKP has years of experience on leading national and international research projects (approx. 35% of papers are published with international partners), has hosted and given lectures at the World Congresses on Pain (IASP) and the Congresses of the European Pain Federation (EFIC), and was appointed as an "Aalborg University Talent" by the Executive Directors at Aalborg University in 2017.
The Osteoarthritis Research International (OARSI) provides clinical guidelines for the treatment of pain in osteoarthritis, and some of the most utilized treatments are Non-Steroidal Anti-Inflammatory Drug (NSAID) plus paracetamol and total joint arthroplasty. Most patients will benefit from these treatments, but some patients are less responsive or showing unwanted side effects, and selecting the right patients for the most optimal treatment would further highlight the opportunities of personalized pain medicine. Quantitative sensory testing (QST) of patients with OA includes measures of widespread pressure hyperalgesia (assessed by pressure pain thresholds, PPTs), temporal summation of pain (TSP), and conditioned pain modulation (CPM). The current dissertation has focused on how assessment of central pain pathways using QST prior to treatment can predict pain and pain reduction after treatment.

The studies presented here found associations between preoperative widespread hyperalgesia (paper 2), facilitated TSP (papers 1, 3, and 4), and impaired CPM (paper 5) and chronic postoperative pain in patients with painful osteoarthritis after total joint arthroplasty. In addition, pre-treatment facilitated TSP was associated with limited analgesic response to 4 weeks of COX-2 inhibitors (paper 6) and 3-weeks of NSAIDs plus paracetamol (paper 7). Finally, impaired CPM was associated with limited analgesic response of 3 weeks of NSAIDs plus paracetamol (paper 8).

A systematic review on all studies related to QST, chronic postoperative pain, and responses to pharmacological interventions is included in this dissertation (paper 9), which highlights that pressure pain stimuli, TSP, and CPM were the most frequently assessed QST modalities, and TSP (50%) and CPM (approx. 44%) were most frequently associated with chronic postoperative pain or response to pharmacological treatments.

Conclusively, these studies (papers 1-8) demonstrate that patients with a pro-nociceptive sensory profile might respond poorly to the standard OA pain treatment as recommended by OARSI, and the systematic review (paper 9) might indicate that this information is useful in other painful disorders than osteoarthritis.
DANSK RESUME


Denne afhandling indeholder et systematisk review over alle studier, som anvender QST og undersøger kroniske postoperative smerter eller analgessisk respons til længerevarende farmakologiske behandlinger (artikel 9), hvori det findes, at PPT, TSP og CPM er meget ofte brugte målemetoder, og TSP (50%) og CPM (ca. 44%) målt før behandlingsstart ofte er associeret til kroniske postoperative smerter eller analgessisk respons af farmakologiske behandlinger. Denne afhandling konkluderer, at smerteoverfølsome patienter med slidgigt er fundet associeret med dårligere behandlingsrespons til standard slidgigtsbehandling, som er anbefalet af OARSI (artikel 1-8). Det systematisk review kan indikere, at disse fund ikke kun er gældende for patienter med slidgigt, men vil kunne anvendes for andre smertefulde patientgrupper (artikel 9).
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Lars Arendt-Nielsen has been my mentor for the last years. We have discussed research but more importantly, we have discussed strategies for research, how I could position myself in the research arena and how to advance a scientific area. Lars is not only my mentor but also a friend and his continued support and trust in my work has been fundamental for my career. I have my deepest respect for my co-authors, who have been vital for the many projects presented in this. I am grateful for the strong interdisciplinary collaboration between Center for Sensory-Motor Interaction (SMI), Center for Neuroplasticity and Pain (CNAP) and the Department of Orthopedic Surgery, Aalborg University Hospital. Ole Simonsen and Mogens Berg have been my clinical supervisors within osteoarthritis and their continued motivation, experience and dedication to drive this field forward have been essential for this work. Director and Professor Thomas Graven-Nielsen is head of CNAP and the group for Pain and Motor System Plasticity and have often challenged my views, which is greatly appreciated and have made the work stronger. Professor Anne Estrup Olesen and I have worked together on several project and Anne introduced me to the (somewhat tedious) world of Good Clinical Practice (GCP), which has been fundamental for my research career. Masashi Izumi came to Denmark when I was a young PhD student and together we conducted some interesting studies, learned from each other and had a lot of fun. Dennis Boye Larsen joined me as a postdoc in 2018 with a mindset to work hard and push forward and together we completed an immense amount of projects, manuscripts and reviews within a very short time (watch out for Dennis in the future!!). Thank you to my co-biomedical engineer Line Lindhardt Egsgaard who conducted the many projects at CCBR and who provided me with written support for this dissertation despite just given birth (much respect and love from Aalborg). Carsten Dahl Mørch was my teacher during my bachelor education, my opponent at my PhD defense and I am now proud to call him my collaborator. I visited Robert R Edwards in Boston in 2015 to understand the impact of pain catastrophizing on pain and later Rob have provided me with help for funding applications, international visits and new project ideas – thank you Rob (I think the next beer is on me). I joined Professor Brigitte Scammell at University of Nottingham in 2016 and together with Lars Arendt-Nielsen and Thomas Graven-Nielsen, we have conducted a lot of studies on patients with osteoarthritis and Brigitte was fundamental for my Talent Management Programme – thank you to Brigitte and the team (Tom Kurien, William Cottam, Sarina Jennifer Iwabuchi and Dorothee Auer) at the Academic Orthopaedics, University of Nottingham. Professor Audun Stubhaug, University of Oslo provided me with much needed support for my research and critical revisions of my funding applications and manuscripts. Professor Andre Wolff, University Medical Center Groningen reached out to us in 2017 and in 2018 I drove through a blizzard in Germany to reach the Netherlands and to set up a new collaboration – the team (Hans Timmerman and Ingrid Schuttert) at University Medical Center Groningen are dedicate hard working people who needs acknowledgement and I look forward to continue our collaboration in the future. In 2013, I witnessed that Professor Olive Wilder-Smith defended his doctoral dissertation at Aalborg University and from that moment I knew that I would commit my life to research on pain mechanisms – I am very humbled that I was allowed to publish a paper with Professor Wilder-Smith before his retirement. To my friend, collaborator and side-kick at countless international bars Associate Professor Henrik Bjarke...
Mechanistic Pain Profiling of Patients with Osteoarthritis

Vægter, University of Southern Denmark: I think that you were the right kind of company for a visit to a Michelin starred restaurant in Florence.

Projects of the magnitude as presented in this dissertation are not possible without technical personal and I have been fortunate to work with the best! Susanne Nielsen Lundis was head the SMI secretary for years and now runs the Research Administrative Team at the Department of Health Science and Technology. Susanne holds the world record for reading most of my work, since she has tirelessly reviewed and proof-read manuscripts, funding applications and statements for the last 10 years. In addition, Susanne has tremendous knowledge on leader-
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Section Leader for the Medical Laboratory Technologists Tina Beith Christensen was my first project coordinator when I initiated my studies at the Regional Hospital in Frederikshavn in 2011. Tina is an incredible leader and she managed to organize staff, patients, surgical plan and pain testing in an impressive manner, which ensured the completion of a lot project within a short duration of time. I still refer to Tina as my best project coordinator to date!

I have worked together with Poul Pedersen (formally at Cortex Technology) for nearly a dec-
- ade and together we have optimized the cuff algometer from an idea to a device, which is now implemented in more than 20 international research projects. Poul has tirelessly implemented and adjusted the machines, so that it fit the needs for many of the studies included in this dissertation. The work presented here would never have been possible without Poul Pedersen.

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Thank you to my family Naja, Viktor and Gunilla for allowing me to pursue my dream and for providing me with the much needed support for conducting this work.
PREFACE: THE CONCEPTUAL FRAME FOR THIS DISSERTATION

The aim of this thesis is to explore a basis for "Personalized Mechanistic Pain Profiling" using quantitative sensory testing with the vision of generating new knowledge to further developing the concept of personalized management of painful osteoarthritis in a validated evidence-based and safe manner.

The hypothesis was that patients with osteoarthritis and a higher level of pain sensitivity might be characterized as a group of patients with more complex pain, and therefore these patients might respond less positively to standard osteoarthritic treatment such as total joint arthroplasty and NSAIDs plus paracetamol.

This dissertation consists of work demonstrating how quantitative sensory testing might act as a predictive "biomarker" for standard pain treatment (pharmacological and surgical interventions) of patients with osteoarthritis. To further pursue the vision, studies must be able to demonstrate that e.g., modulating specific mechanisms or specific preoperative pain profiles can improve the patients' outcomes or that certain patients can be selected for more appropriate pain care. The current dissertation will not provide the complete evidence for the fulfilment of the goal to describe the concept for implementation of personalized, mechanistic pain management of painful osteoarthritis, but highlight novel findings to additionally update the discussion on the further progress of the field of personalized pain management.

Kristian Kjær Petersen
18 December 2020, Aalborg
LIST OF PAPERS

This dissertation is partly based on the following 9 peer-reviewed papers:


1. Setting the Scene: Chronic Pain as a Major Clinic Problem

Chronic pain is estimated to affect approx. 20% of the world's population [33, 69, 83] with low back and neck pain being the most prevalent diseases [227], and generally musculoskeletal disorders are representing 2/3 of all cases of chronic pain.

In the US, the economic consequence of chronic pain, including treatments and low worker productivity, is estimated to be between $560 and $635 billion per year [66]. Surprisingly, the economic burden of chronic pain is higher in the US than other commonly well-known clinical problems such as diabetes, heart diseases, and cancer [66].

1.1 Defining Chronic Pain and Cut-off Points for the Treatment of Pain

Acute pain is an essential protective mechanism, which main purpose is to alert the brain about injury and thereby preventing further damage. On the other hand, chronic pain has been defined as being pain, which persists past the normal time of healing [31]. It is important to realize, however, that some injuries do require healing and regrowth before the organism is fully functional [138]. For research purposes, the IASP Task Force on Taxonomy suggested that chronic non-malignant pain should be defined as pain for more than six months, and chronic pain after surgery is defined as pain persisting more than three months after surgery [138].

It is important to evaluate clinical relevant cut-off points when studying the treatment of chronic pain. As an example, it is commonly debated if the clinical cut-off value for an effective pain pharmaceutical treatment is either a 30% or 50% reduction in pain intensities. Another example could be that the common goal of pain treatment is to reduce the pain to a mild intensity level (e.g., less than 30 mm on a 100 mm visual analogue scale, VAS), and therefore, effective treatments could be categorized if the patient is reporting less than 30 mm on the VAS by the end of the treatment. Finally, more complicated clinical cut-off points have been established, which rely on a combination of e.g., reduction in pain, improvement in function, and improvement in quality of life [171]. Due to this ongoing debate, a range of different cut-off points for the evaluation of pain treatments are being used, and the work carried out in this dissertation is no exception. Multiple cut-off points have been utilized in this work to explore if measures of pain sensitive can predict poor response to the standard pain treatments.

In most pain trials, pain has been selected as the primary outcome parameter. Often trials do not reach the outcome as sometimes the selected pain parameter may not be significantly affected, but the patients' function and quality of life has been improved suggesting clinical studies in particular on musculoskeletal pain should include measures for function and quality of life.

1.2 The Development of Chronic Pain

Currently, it is unknown why some patients develop chronic pain, and one reason for this could be that chronic pain is an umbrella term for multiple different conditions. The IASP Task Force...
for Classification of Pain Diseases (ICD-11 development of pain codes) divides chronic pain into seven different disorders [222]: 1) chronic primary pain, 2) chronic cancer pain, 3) chronic posttraumatic and postsurgical pain, 4) chronic neuropathic pain, 5) chronic headache and orofacial pain, 6) chronic visceral pain, and 7) chronic musculoskeletal pain.

The studies discussed in this dissertation will focus on the chronic musculoskeletal pain condition: “osteoarthritis”, and therefore, the results from these studies may not necessarily be transferable to six other chronic pain disorders. When suited, the author will describe links to other disorders to inform the reader of the similarities and to broaden the perspective of the findings presented here.

The focus of this work has been to describe and provide emerging evidence for the predictive value of central pain mechanisms for standard pain treatment of patients with osteoarthritis (OA).
2. OSTEOARTHRITIS IS A MAJOR CLINICAL WORLD-WIDE ISSUE

OA is characterized by cartilage degeneration, joint stiffness, and pain. Cartilage degeneration is traditionally assessed using x-ray, and the radiological assessment of OA is often found using the Kellgren & Lawrence scale [101]. The global burden of disease studies estimate the world age-standardized prevalence of OA to be 3,754 per 100,000 capita with North America (prevalence of 5,924 per 100,000 capita), North Africa and the Middle East (prevalence of 4,610 per 100,000 capita), and Australia (prevalence of 4,595 per 100,000 capita) demonstrating the highest regional prevalence and expected to increase in future [198]. The prevalence of OA increases with age [25], and people in Europe, the United States, and other developed countries tend to live longer [28,61], which could explain part of the reason for the increasing prevalence of OA.

Obesity is one of the world leading health care issues [216], and models predict that global level of obesity will continue to rise although many health care systems aim to prevent this [97]. Obesity is linked with development and fast progression of OA in weight- and non-weight-bearing joints [185], and it is assumed that this increase in global obesity will affect the prevalence of OA in future.

Projection studies expect a rise in the prevalence of total joint replacement surgeries [3,116]. Kurtz et al. 2007 [116] predicted a six fold increase in total knee arthroplasties from 2005 to 2030 in the US. A more recent study from Australia concludes that “Australia faces an unsustainable joint replacement burden by 2030, with significant healthcare budget and health workforce implications” [3], which emphasizes that OA is as a major clinical issue in the modern world.

2.1 PAIN IN THE OSTEOARTHRITIC JOINT

As OA is characterized as a cartilage degenerative disease, it would be natural to assume that cartilage degeneration is directly associated with pain, but studies finds no or limited association between the radiological assessment of cartilage degeneration and pain in OA [47,60,85]. This suggests that other factors than cartilage generation are important for OA pain [15]. Multiple factors have been found associated with OA pain, and in general, these can be divided into factors directly associated with OA affected joint or other factors. An overview of potential factors associated with OA pain is found in figure 1 [13,16,68,117,162].
2.2 OSTEOARTHRITIS AS A LOCALIZED JOINT PROBLEM

Nociceptors (pain receptors) produce action potentials when activated, which travel through the nerve system to the brain where it is categorized as pain. The synovium membrane, the Hoffa's fat pad, and the subchondral bone are highly innervated by nociceptors whereas under normal conditions, cartilage is minimally innervated, which could explain the lack of association between cartilage degeneration and pain in OA. In addition, nociceptors are found in muscles, tendons, and ligaments surrounding the joint, and these can all give rise to pain. Treatments such as inter-articular injections target a potential inflammation within the joint, and this is successful when used sparingly, but not advised to be used often due to further risk of cartilage degeneration. Similar total joint arthroplasty is considered a treatment targeting OA as a localized problem, and this is very effective since up to 80% of patients are satisfied with the procedure.

2.3 OSTEOARTHRITIS AS A WIDESPREAD PAIN PROBLEM

Referred pain to the knee joint is often observed in patients with hip OA, and referred pain does often follow a segmental spread. Experimental pain models can produce referred muscle pain areas where the development of referred muscle pain area is delayed compared with the local painful muscle stimuli, and the referred muscle pain area decreases as the local painful muscle stimuli are reduced. Therefore, the manifestation of referred pain...
2. Osteoarthritis is a Major Clinical Worldwide Issue

Muscle pain areas has been suggested to be a result of central segmental pain mechanisms [75], and these are often facilitated in patients with OA [15], which could be one of the reasons for the widespread pain often observed in OA. Studies have shown that widespread pressure hyperalgesia decreases in patients with hip [113] and knee [81] OA undergoing TJA indicating that referred pain sensitization areas can be normalized if OA is the primary source of pain. Patients with chronic postoperative pain following TJA seem to have a worsening of widespread pressure hyperalgesia [206,207], which might indicate that this specific subgroup of patients does not only have a localized painful joint problem, but it is also complex. Widespread pressure hyperalgesia is widely reported in patients with severe OA compared with healthy subjects [11,15], and widespread pressure hyperalgesia seems to be associated with increased clinical pain ratings [9,12].

2.4 OSTEOARTHRITIS AS A MULTI-COMORBIDITY DISEASE

It is fair to conclude that OA pain is more than just cartilage degeneration [47,60,85], and that OA pain is affected by multiple factors. Currently, more than 25,000 papers exist in relation to OA and pain, and the numbers are increasing (see figure 2). This tremendous attention to the field makes it impossible to review all of the factors associated with OA pain. Therefore, some of the more common factors influencing OA pain will be reviewed in the following.

Figure 2: Number of papers published (y-axis) since 1950 on osteoarthritis and pain

2.4.1 OBESITY

Obesity is a risk factor for early onset of OA and has been associated with fast progression of OA although this is currently being debated [46,48,148]. Interestingly, obese patients are more likely to develop OA in both weight bearing (e.g., hip or knee OA) and non-weight bearing joints [185] suggesting that other factors than mechanical load are associated...
2.4.2 CHRONIC LOW-GRADe INFLAMMATION

Traditionally, OA is considered a non-inflammatory disease when compared with other forms of arthritis (e.g. rheumatoid arthritis). Various subgroups of OA patients can be categorized with different low-grade systemic inflammatory profiles [202]. It is well-known that synovitis (inflammation of the synovial membrane) is present in more than 50% of knee OA patients [92], and synovitis is associated with OA pain [59,92]. Preclinical studies have shown that pro-inflammatory cytokines sensitize the peripheral nerves [200]. Pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor alpha (TNF-α) have been found upregulated in synovial fluid in OA patients and associated with increased pain reports [59,65]. Localized pressure hyperalgesia is a common finding in severe OA when compared with healthy subjects [15], and inflammatory processes are most likely one of the reasons for this localized hyperalgesia.

Systemic upregulation of inflammatory markers has been detected in a subgroup of severe knee OA patients [202]. Severe knee OA is associated with widespread hyperalgesia [15], but it is currently unknown if this is due to low-grade systemic inflammation. Epidemiological studies have found that low-grade inflammation is associated with increases pain sensitivity [94,201], and therefore inflammation should be considered as an important factor when assessing patients with OA pain.

2.4.3 COGNITIVE FACTORS

Higher clinical pain levels in OA have been associated with high levels of pain catastrophizing [30,153,205,212], fear of movement [205], pain self-efficacy [205], anxiety [84,205], and depression [84]. Studies focusing on training of pain coping skills have found these effective for managing OA pain [34,211] suggesting that targeting cognitive pain-related beliefs might be an option for non-surgical and non-pharmacological treatment of OA pain. Duloxetine (a serotonin and norepinephrine reuptake inhibitor) is approved for the treatment of depression, but studies have shown pain relieving effects when administrated to patients with knee OA [229]. Duloxetine might target a subgroup of OA patients with depression, and alternatively, emerging evidence suggests that duloxetine can restore losses in pain inhibitory control [241], which is often impaired in patients with severe OA [15]. This is further supported by the 2019 OARSI guideline, in which duloxetine is conditionally recommended for OA patients with widespread pain and/or depression [21]. Unfortunately, the number needed to treat (NNT) for duloxetine is 7, which could suggest that only a subgroup of patients with knee OA will benefit from duloxetine [40].

2.5 RECOMMENDED TREATMENTS FOR PAINFUL OSTEOARTHRITIS

No treatment is currently available to cure OA, and therefore treatment of OA is focused on alleviating pain, improving joint function, and increasing quality of life. "Regenerative medicine" has been proposed as a cure for OA focusing on intra articular injections or bone marrow migration of stem cells, aiming to repair the damaged cartilage, but currently no implemented treatment has been developed. Being a fascinating area of research, however, the current thesis will not focus on regenerative medicine for OA due to the high risk of bias [160].
2. Osteoarthritis is a major clinical worldwide issue. Instead, it will focus on some of the treatments recommended by the Osteoarthritis Research International (OARSI), which can be divided into non-surgical and surgical therapies. They will be briefly reviewed below.

2.5.1 NON-SURGICAL TREATMENT OF OSTEOARTHRITIS

Non-surgical treatment of OA consists of multiple pharmacological and non-pharmacological options [21,208,228]. The 2019 OARSI guidelines on non-surgical management of knee OA strongly recommend arthritis education, land-based exercise programs, and weight management if needed [21]. In addition, the 2019 OARSI guidelines strongly endorse the use of topical NSAIDs and conditionally (with high consensus) recommend oral non-selective NSAIDs and COX-2 inhibitors [21]. Intra-articular corticosteroids are conditionally recommended (with low consensus), and this is not included in the current dissertation since recent studies suggest limited pain relief and risk of cartilage damage due to multiple injections of corticosteroids compared with injections of saline [135]. Further, there is ongoing discussion whether the effect is due to hyaluronic acid or the corticosteroids itself [181].

This dissertation will focus on non-surgical treatments with COX-2 inhibitors and non-selective NSAIDs as these are very commonly used for OA treatments and considered effective [90,100].

2.5.1.1 SELECTIVE AND NON-SELECTIVE NSAIDS

The analgesic effect of NSAIDs has been widely documented [90,100] even though the mechanisms of action are not completely understood [71]. It is known that NSAIDs (and paracetamol) inhibit the synthesis of prostaglandins through modulation of cyclooxygenase (COX). A preclinical studies have found that non-selective NSAIDs and paracetamol increase the activity of the cannabinoid system [4], and that the effect of NSAIDs and selective COX-2 inhibitors dependents on an intact serotonin system [71]. In addition, human studies suggests that COX-2 inhibitors can modulate widespread hyperalgesia [8,128,183], which further suggests that COX-2 inhibitors act on the central pain pathways.

It is important to highlight that long-term use of NSAID is potentially harmful [128], and therefore NSAIDs should be used effectively with short duration (weeks). NSAIDs should be administered in combination with paracetamol as the combination yields a larger effect in OA than each of the drugs alone [156]. It seems that the most optimal paradigm for OA pain is 1 g paracetamol and 400 mg Ibuprofen three times daily (a total of 3 g paracetamol and 1.2 g ibuprofen daily). This yields an analgesic effect with limited adverse events [49].

2.5.2 SURGICAL TREATMENT OF OSTEOARTHRITIS

Several surgical procedures are performed for OA with the most common ones being arthroscopic surgery and total joint arthroplasty (TJA) [244]. The current thesis will not focus on arthroscopy surgery as the long-term pain relieving evidence supporting this procedure has been questioned in the last decade when compared with other standard treatments for OA pain [70,104,172,220]. Instead, this thesis will focus on TJA, and the rational will be discussed below.
2.5.2.1 TOTAL JOINT ARTHROPLASTY

TJA might seem to be the ideal treatment if OA was a purely localized pain disorder as the damaged joint is replaced by a prosthesis and thereby eliminates the peripheral pain driver. TJA is a frequently performed procedure \[37\], and patients ongoing TJA have better improvements in pain, function, and quality of life compared with patients receiving non-surgical treatment \[209\]. It is problematic, however, that 20% of TKA and 10% of THA patients experience chronic postoperative pain \[26\]. The primary clinical indication for TKA and THA is OA (94-97% of cases) \[192\]. The number of THA and TKA are increasing worldwide \[2,42,105,116,203,204\]. The number of Danish TKA and THA seem to have stabilized in the last few years as also stated in the Danish Knee \[151\] and Hip \[157\] Arthroplasty Registry yearly reports, but the most recent report seems to indicate an increase in 2018 compared with previous years \[152\].

2.6 THE FOCUS OF THE CURRENT DISSERTATION

The focus on this dissertation will be on TJAs and NSAIDs as they are standard treatments which are widely used for OA pain, but it seems evident that some patients respond better to these treatments than others. This dissertation will aim to identify patients who are poor responders to these standard OA treatments.
3. PERSONALIZED PAIN MEDICINE

“Personalized medicine” or “precision medicine” aims to provide the correct treatment to the right patient. Currently, personalized medicine is mainly developed within cancer, but the concept might also apply to pain medicine. Management of pain is difficult, and therefore many treatment diagnostic algorithms have been developed to target different chronic pain patient groups. Many of these algorithms are based around a “trial and error”-concept where patients are introduced to many pharmaceutical treatments before the correct one is found. This process is lengthy, potentially harmful due to side effects, costly, and very ineffective. The concept of “Personalized Pain Medicine” revolves around assessing the underlying mechanisms for pain and treating these mechanisms. Advanced treatment options exist today, but assessment of pain is still lacking, and the clinical use is limited.

This dissertation aims to exemplify how sensory profiles using QST may be used to predict responses to standard OA therapies for patients with OA and to investigate if this concept can be used in a different chronic pain population.

3.1 PREDICTORS FOR POOR RESPONSE TO STANDARD THERAPIES FOR PAINFUL OSTEOARTHRITIS

This dissertation is focused on the possible predictive value of sensory profiles for treatment responses to surgery and pharmacological interventions, but it is important to underline that multiple other factors are currently being utilized to predict poor outcome after standard therapies for painful OA. These factors are briefly discussed below.

3.1.1 PAIN CATASTROPHIZING

High levels of pain catastrophizing has been suggested to be a predictor for chronic postoperative pain following TKA [64, 188, 190]. Pain catastrophizing can be reduced [187], and therefore studies have aimed to reduce preoperative levels of pain catastrophizing to reduce chronic postoperative pain. Two recent studies were able to reduce preoperative levels of pain catastrophizing, but unable to see effects of chronic postoperative pain scores when compared with patients receiving usual care [29, 189]. Similar, modulating pain catastrophizing prior to exercise therapy does not improve the pain relieving effect of exercise therapy in patients with hip OA [24]. These findings could suggest that pain catastrophizing might be a predictor of poor outcome after therapy for patients with OA, but that modulating pain catastrophizing might not improve the treatment outcome.

3.1.2 EPIGENETICS

Micro and long non-coding RNAs (miRNA and lnRNA, respectively) are, among others tasks, responsible for regulation of the inflammatory cascades [213], and therefore epigenetics is a new and interesting avenue for pain research. A recent proof-of-concept study demonstrated that upregulation of preoperative miRNA-146a-5p combined with high preoperative pain predicted postoperative pain relief following TKA [67]. A previous study [119] found differences in miRNA-146a comparing painless and painful peripheral neuropathies, and multiple other studies have associated miRNAs with pain in patients with e.g., osteoarthritis [27], rheumatoid
3.1.3 SENSORY PROFILES

Sensory profiles based on QST have previously been used to predict chronic postoperative pain following e.g., thoracic surgery [240], groin hernia repair surgery [1] and abdominal surgery [234] or the analgesic effect of e.g. duloxetine in patients with diabetic neuropathy [241] or migraine [107], pregabalin in patients with painful chronic pancreatitis [154], or to classify patients with peripheral neuropathy as responders to oxcarbazepine [45].

Prior to the work described in this dissertation, three studies were published on the use of QST as predictors in patients with OA with two studies finding that preoperative 1) electrical pain thresholds [124] and 2) widespread pressure hyperalgesia [235] were associated with chronic postoperative pain following TKA. In addition, Martinez et al., 2007 [132] studied preoperative allodynia, mechanical pain thresholds, heat pain thresholds, and cold pain thresholds in 20 patients with knee OA and found no predictive value of these assessment to postoperative pain at four months follow-up. The following sections will address how to assess sensory profiles using QST in OA and the current evidence on profiles in patients compared with healthy subjects.
4. PROFILING USING QUANTITATIVE SENSORY TESTING (QST)

QST is neurological examination of somatosensory function, and multiple standardized protocols exist [52,195,233]. The most comprehensive and most widely used protocol is the German Research Network on Neuropathic Pain (DFNS) protocol for neuropathic pain [195], which includes seven tests focused on thermal and mechanic detection and pain thresholds, allodynia, and wind-up with an assessment time of approx. 60-90 minutes.

While thermal hyperalgesia and hypoesthesia have been reported in OA when compared with healthy subjects [96,106,114,142], it is commonly accepted that deep structures are more affected by pain sensitivity in musculoskeletal pain [62,129], and therefore pressure stimuli are often utilized [15,76]. Severe OA is commonly associated with localized and widespread pressure hyperalgesia, facilitated temporal summation of pain (TSP), and impaired conditioned pain modulation (CPM) [15]. It is important to note, however, that while patients and healthy subjects are different on group levels, some patients are less pain sensitive than others [164], and this variability might be useful in the prediction of pain after standard OA treatments. The following sections will discuss the pain mechanisms and assessment of localized and widespread pressure hyperalgesia, TSP, and CPM.

4.1 LOCALIZED AND WIDESPREAD HYPERALGESIA

Hyperalgesia is defined as an increased pain from a stimulus that normally provokes pains [138]. Pressure hyperalgesia is assessed using pressure pain thresholds (PPTs) and different versions of pressure algometers. The pressure should be delivered slowly and at a constant rate when assessing PPTs, and the assessments require training to increase the reliability. PPTs are most often assessed using a 1 cm² probe with a 30 kPa/sec increase, and this assessment demonstrates interclass coefficients (ICC) values of 0.60 – 0.96 for both within days and in between weeks [6,98,214] and months [79,130], which is considered good-to-excellent [63]. In addition, the inter-tester reliability is considered good-to-excellent [98].

Localized pressure hyperalgesia can be assessed when applying PPTs in an area of injury in e.g., pain patients and can be compared with the same anatomical area in an asymptomatic healthy subject. Generally, it is accepted that knee OA is associated with localized and widespread pressure hyperalgesia. Figure 2: Illustration of assessments of pressure pain thresholds (PPTs) at the knee (assessment of localized hyperalgesia) and at the arm (assessment of widespread hyperalgesia). In general, lower PPTs will be found for patients with severe knee osteoarthritis (OA) compared with healthy subjects at both the local and remote site.

Figure 2: Illustration of assessments of pressure pain thresholds (PPTs) at the knee (assessment of localized hyperalgesia) and at the arm (assessment of widespread hyperalgesia). In general, lower PPTs will be found for patients with severe knee osteoarthritis (OA) compared with healthy subjects at both the local and remote site.
Mechanistic Pain Profiling of Patients with Osteoarthritis

Lower PPTs around the knee joint (anatomical markers around patella) compared with age- and gender-match healthy subjects [15,155], which suggests localized pressure hyperalgesia. Widespread pressure hyperalgesia can be assessed when applying PPTs outside (preferably extra-segmentally) the area of injury in pain patients and comparing this to the same anatomical area in an asymptomatic healthy subject. Widespread hyperalgesia is often found in severe knee OA when assessing the PPTs at e.g., the arm compared with age- and gender-match healthy subjects [15]. Widespread hyperalgesia suggests sensation of central pain mechanisms and might be associated with impairment of descending pain inhibitory control systems [76], which is also commonly found in severe knee OA [15] and other painful conditions [11].

Thermal stimuli can be utilized to assess cold and warm detection thresholds (WDT and CDT, respectively) and heat and cold pain thresholds (HPT and CPT, respectively) [194] and can be used to assess localized and widespread hyperalgesia to thermal stimuli. Thermal stimuli are widely used in the DFNS protocols, and Aasvang et al., 2010 [1] demonstrated that preoperative painful ratings to suprathreshold heat stimuli were associated with chronic postoperative pain following groin hernia repair surgery. In addition, Edwards et al., 2006 [56] have found that pretreatment HPT was associated with the analgesic effect of opioids in patients with postherpetic neuralgia, and Demant et al., 2014 and 2015 utilized the DFNS protocol to classify patients with peripheral neuropathic pain into subgroups defined by irritable nociceptors, which had a lower number needed to treat for oxcarbazepine [45] and lidocaine patches [44] compared with subgroups classified by non-irritable nociceptors.

4.2 SENSITIZATION OF CENTRAL PAIN MECHANISMS

The wind-up process of dorsal horn neurons can be assessed in animals [38] and reflects the excitability of dorsal horn neurons [178]. Assessing wind-up requires placement of electrodes into the spinal cord of the animal, which is not feasible in human studies. TSP is the human surrogate model of the wind-up process [10]. TSP can be assessed using painful heat [231], pinprick [163], electrical [154], or pressure stimuli [164]. In general, the assessment of TSP relies on a train of painful stimuli, which are applied rapidly and with the same intensity [177,184] while the subject is instructed to rate the pain for all of the stimuli or to rate the first and the last stimuli (see figure 4).

Studies have found facilitated TSP in chronic pain conditions such as fibromyalgia [11,80,179,217] and severe osteoarthritis [9,12,36,58,219] compared with healthy subjects, indicating a sensitization central pain mechanisms. Facilitated TSP is believed to be associated with NMDA receptor activation since administrating NMDA-antagonists can decrease TSP [80].

4.2 SENSITIZATION OF CENTRAL PAIN MECHANISMS
4. Profiling Using Quantitative Sensory Testing (QST)

Figure 3: (A) Temporal summation of pain (TSP) relies on continuously fast stimuli with the same intensity. (B) TSP is calculated as the pain score to these painful stimuli over time, and TSP scores e.g., chronic pain patients and healthy controls, can be compared.

4.3 DESCENDING PAIN INHIBITORY CONTROL

In 1979, Le Bars et al. [23] found that noxious stimuli could evoke activity of convergent wide-dynamic-range neurons in the dorsal horn, which could be inhibited by another tonic noxious stimuli in rats. This was the first study to explain the “pain-inhibits-pain” phenomenon and was termed “diffuse noxious inhibitory control” (DNIC), which was used in many years to describe the same mechanisms in humans and animals. In 2010, conditioned pain modulation (CPM) was recommended to be used when referring to human studies and DNIC when discussing animal studies [238] as the mechanisms are similar, but not the same [43].

CPM can be assessed using a test and a conditioning stimuli, and multiple different stimuli modalities have been utilized over the years. In general, healthy subjects will demonstrate a decrease in pain sensitivity to the test stimulus while exposed to the conditioning stimulus when compared with the test stimulus without the conditioning stimulus (figure 5).

The reliability of CPM testing has been questioned [102], but it seems to be depended on the combination of the test and conditioning stimuli [93]. Different protocols are utilized by various laboratories where the test stimulus is either applied during the conditioning stimulus or just after termination of the conditioning stimulus [239], which is also likely to interfere with reliability. The studies described in the current thesis will rely on a CPM paradigm, in which the test stimulus is assessed during the conditioning stimulus and will either describe the CPM paradigms using pressure conditioning and test stimuli [8,169] or the combination of a pressure test stimulus and a cold pressor conditioning stimulus [163]. Studies on these paradigms have reported good-to-excellent reliability [79,93].
Figure 5: Assessment of conditioned pain modulation (CPM). Assessment of CPM requires a test stimulus and a conditioning stimulus, and multiple paradigms of test and conditioning stimuli have been utilized. In general, an increase in test stimulus will be observed when applying the conditioning stimulus in healthy subjects, and this increase in test stimulus seems absent in multiple chronic pain disorders.
5. MECHANISTIC PAIN PROFILING OF PATIENTS WITH OSTEOARTHRITIS

The studies presented here have all utilized longitudinal designs and assessments before and after TKA or treatment with NSAIDs (selective COX-2 inhibitors or non-selective NSAIDs) plus paracetamol.

Prior to the publications of the above papers, two studies on TKA had previously been published describing an association between preoperative electrical pain thresholds [124] and widespread hyperalgesia [235] and chronic postoperative pain. In addition, Martinez et al., 2007 [132] found no association between preoperative allodynia, mechanical pain thresholds, heat and cold pain thresholds, and chronic postoperative pain. Similar, Noiseux et al., 2014 [149] assessed mechanical pain threshold, heat pain threshold, and pressure pain thresholds assessed around the knee in patients scheduled for TKA and did not find the presence of moderate-to-severe postoperative pain at a 6-month follow-up.

The presentation of papers will focus on associations between QST (alone or in combination) and the pain outcomes after standard OA treatments. The coefficient of determination (R²) will be described for both correlations and linear regressions.

The following sections will shortly describe each individual paper, a discussion on how these findings fit into the literature and finalize with an overall discussion and conclusions from the studies. An overview of the eight studies is found in table 1.
<table>
<thead>
<tr>
<th>Paper Number</th>
<th>Reference</th>
<th>Year</th>
<th>Type of Intervention</th>
<th>Number of Patients</th>
<th>QST Parameters</th>
<th>Follow-up Time</th>
<th>Dependent Parameter</th>
<th>Models and Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Petersen et al. [163]</td>
<td>2015</td>
<td>TKA</td>
<td>78</td>
<td>PPTs, mTSP, pCPM</td>
<td>12 MO</td>
<td>Pain intensity</td>
<td>Regression: $mTSP$ and PreOP VAS: $R^2 = 0.13$</td>
</tr>
<tr>
<td>2</td>
<td>Petersen et al. [164]</td>
<td>2016</td>
<td>TKA</td>
<td>103</td>
<td>cPPT, cPTT, cTSP, cCPM, PPTs</td>
<td>12 MO</td>
<td>Pain relief</td>
<td>Regression: $R^2 = 0.379$, using $cPPT$ and VAS</td>
</tr>
<tr>
<td>3</td>
<td>Izumi et al. [96]</td>
<td>2017</td>
<td>THA</td>
<td>40</td>
<td>cPPT, cPTT, cTSP, cCPM, cSS, PPTs, CDT, CPT, WDT, HPT, MPT</td>
<td>6 weeks</td>
<td>Pain relief</td>
<td>Correlation: $R^2 = 0.270$ using TSP</td>
</tr>
<tr>
<td>4</td>
<td>Petersen et al. [167]</td>
<td>2018</td>
<td>TKA</td>
<td>130</td>
<td>CDT, CPT, WDT, HPT, mTSP</td>
<td>12 MO</td>
<td>Pain intensity</td>
<td>Regression: $PreOP mTSP$, WDT, HPT and KL $R^2 = 0.119$</td>
</tr>
<tr>
<td>5</td>
<td>Larsen et al. [117]</td>
<td>2020</td>
<td>TKA</td>
<td>131</td>
<td>cPPT, cPTT, cCPM</td>
<td>12 MO</td>
<td>Pain intensity</td>
<td>Regression: $R^2 = 0.205$ using pre-OP CPM and PCS</td>
</tr>
<tr>
<td>6</td>
<td>Arendt-Nielsen et al. [8]</td>
<td>2016</td>
<td>COX-2 inhibitors and placebo</td>
<td>37</td>
<td>PPT, pTSP, pCPM</td>
<td>28 days</td>
<td>Change in pain intensity for non-responders</td>
<td>Correlation: $pTSP$ predicting a non-response: $R = 0.421 - 0.639$</td>
</tr>
<tr>
<td>7</td>
<td>Petersen et al. [166]</td>
<td>2019</td>
<td>NSAID and paracetamol</td>
<td>132</td>
<td>cPPT, cPTT, cTSP</td>
<td>21 days</td>
<td>Change in pain intensity</td>
<td>Regression: $R^2 = 0.269$ using VAS and $cTSP$</td>
</tr>
<tr>
<td>8</td>
<td>Petersen et al. [169]</td>
<td>2019</td>
<td>NSAID and paracetamol</td>
<td>42</td>
<td>Offset analgesia, cCPM</td>
<td>21 days</td>
<td>Change in pain intensity</td>
<td>Correlation: $R^2 = 0.186$ using cCPM and VAS</td>
</tr>
</tbody>
</table>

Table 1: Papers including in the dissertation using quantitative sensory testing (QST) to predict chronic postoperative pain and analgesic effects. QST modalities: **CDT**: Cold Detection Threshold, **CPT**: Cold Pain Threshold, **cPPT**: Cuff-induced Pressure Pain Threshold, **cPTT**: Cuff-induced Pressure Tolerance Threshold, **CPM**: Conditioning Pain Modulation (c: cuff pressure test and condition stimuli, p: pressure test stimulus, # cold pressor tests as condition stimulus), **HPT**: Heat Pain Threshold, **MPT**: Mechanical Pain Threshold, **PPT**: Pressure Pain Threshold, **TSP**: Temporal Summation of Pain (c: using cuff stimuli, m: using mechanical pinprick stimuli, p: using pressure stimuli), **WDT**: Warm Detection Threshold. Other abbreviations: $R$: Coefficient of determination. $§$: Calculated for this dissertation only and not presented in the original paper. The data presented here are modified from Petersen et al., 2020 [170].
5.1 DISCUSSION OF THE PAPERS INCLUDED IN THIS DISSERTATION

Paper 1 aimed to investigate whether assessments of preoperative central pain mechanisms were associated to chronic postoperative pain after TKA. Paper 1 assessed 78 patients with severe knee OA before, 2 months after, and 12 months after TKA using self-reported pain scores (VAS), PPTs, TSP, and CPM. The study was the first to demonstrate that the combination of facilitated preoperative TSP and high preoperative pain intensity predicted high clinical pain 12 months after surgery with a $R^2 = 13\%$ using a linear regression model. The $R^2$ was not presented in the original paper, but was calculated for paper 9.

Paper 1 was the first study to demonstrate an association between preoperative TSP and chronic postoperative pain. Previously, assessment of central pain mechanisms had demonstrated that preoperative widespread hyperalgesia was associated to high WOMAC scores 13 months after TKA surgery and that impaired preoperative CPM was associated with chronic postoperative pain intensity after thoracic surgery and major abdominal surgery. The combination of these findings suggested that preoperative assessments of central pain mechanism activity might provide predictive information on chronic postoperative pain.

Paper 2 aimed to identify if preoperative combinations of TSP and CPM profiles could identify a subgroup of patients in higher risk of chronic postoperative pain. This study was mainly a consequence of previously developed "pain sensitivity index", in which subgroups of OA patients reported high clinical pain in combination with facilitated TSP and impaired CPM.

Paper 2 assessed 103 patients with severe knee OA before and 12 months after TKA. Self-reported pain scores were assessed before and 12 months after TKA, and pain relief following TKA was calculated as the difference between pre- and postoperative pain scores. In this study, patients were subgrouped based on preoperative CPM and TSP using the average of TSP and CPM from the cohort as cut-off values. Based on this, four groups were described with 1) facilitated TSP and impaired CPM, 2) facilitated TSP and non-impaired CPM, 3) non-facilitated TSP and impaired CPM, and 4) non-facilitated TSP and non-impaired CPM. Paper 2 found that the group of preoperative, impaired CPM and facilitated TSP had worst pain relief 12 months after TKA compared with patients with impaired CPM alone or facilitated TSP alone. Using a linear regression model, this paper found that the combination of preoperative low cPDT and high preoperative VAS scores was predictive of higher postoperative pain scores ($R^2 = 38\%$). The $R^2$ value was not presented in the original paper, but calculated for paper 9.

Prior to Paper 2, it was established that certain patients with knee OA were more sensitive than others and that these patients could be classified by TSP and CPM. Paper 2 supported the previously published data that preoperative, impaired CPM and facilitated TSP were risk factors for chronic postoperative pain. Interestingly, a study on patients with chronic pain was published just after paper 2, which supported the idea that CPM and TSP could be utilized to subgroup patients with high clinical pain scores. The predictive model in paper 2 demonstrated that preoperative widespread pressure hyperalgesia and high preoperative pain was associated with low pain relief after TKA, which supported the study by Wylde et al., 2013.
Mechanistic Pain Profiling of Patients with Osteoarthritis

In 2015, Wylde et al. found that preoperative widespread pressure hyperalgesia was not associated with 12 months postoperative WOMAC scores for patients undergoing TKA, but predictive for patients undergoing THA. This was in conflict with their previous study.

Paper 2 further supported that preoperative assessments of central pain mechanisms are associated with chronic postoperative pain following TKA.

Prior to Paper 3, subgroups of patients with OA with facilitated TSP and impaired CPM had been identified based on KL and clinical pain intensity scores. In addition, King et al., 2013 demonstrated that patients with severe knee OA were more sensitive to pain heat stimuli. Aasvang et al., 2010 demonstrated a weak association between preoperative heat pain thresholds and chronic postoperative pain after groin hernia repair surgery, and Lunn et al., 2013 found associations between preoperative heat pain thresholds and acute postoperative following TKA.

Paper 3 aimed to assess if preoperative thermal stimuli were predictive of chronic postoperative pain following TKA. It was from the same cohort as Paper 2 with the overall aim to assess a large range of QST parameter before and after TKA. In total, 200 patients were included in the study, but the cuff algometer (which was described in Paper 2) was added as an amendment after the first 65 patients were included. In paper 3, 70 patients were excluded due to missing data, which was mainly due to technical difficulties using the thermal stimulator. The patients in paper 3 were categorized as patients with chronic postoperative pain if the patients did not yield at least 30% reduction in pain comparing pre- and 12 month postoperative pain scores.

Paper 3 utilized a linear regression and found that preoperative WDT, HPT, KL, and TSP all contributed to the predictive value of the model (R² = 12%), but TSP was the only significant, independent predictor. The R² was not presented in the original paper, but was calculated for paper 9.

Paper 3 showed that patients with low KL might be in risk of poor pain alleviation following TKA, which was supported by Riis et al., 2014. In addition, paper 3 supported the notion that patients with low KL and high pain might display high pain sensitivity levels argued previously, and paper 3 further added that these patients might be in risk of poor pain alleviation following TKA.

Paper 3 did find associations between preoperative WDT and HPT and chronic postoperative pain intensities, which supported the previous findings on acute and chronic postoperative pain.

In Paper 4, aimed to advance the predictive models by including QST and other known preoperative risk factors for chronic postoperative pain. Prior to recruitment, no studies found associations between preoperative CPM and chronic postoperative pain following TKA. Previous preoperative CPM had been associated with chronic postoperative pain following thoracic surgery and abdominal surgery. Today, two studies have found preoperative CPM associated with chronic postoperative pain following TKA. Preoperative pain catastrophizing has been suggested as a strong preoperative predictor for pain 6 and 24 months after TKA surgery, and studies suggest an interaction between CPM and pain catastrophizing. In addition, studies have found widespread pressure hyperalgesia in patients categorized as neuropathic pain-like components compared with patients categorized as nociceptive pain-like components according to the PainDetect questionnaire.
Mechanistic Pain Profiling of Patients with Osteoarthritis

Studies have found preoperative widespread hyperalgesia to be associated with chronic postoperative pain after TKA [14,164,235]. Furthermore, preoperative high PainDetect scores have been found associated with high 6 months postoperative pain scores after TKA compared with low preoperative PainDetect scores [115].

Studies indicated that preoperative QST in combination with other known pre- and perioperative risk factors might improve the predictive models [1,32,124,186,210] (including paper 1, 2, 5 [163,164,167]). Therefore, Paper 4 [117] aimed to assess predictive value of preoperatively established preoperative predictors for chronic postoperative pain after TKA such as pain intensity, CPM, pain catastrophizing, and PainDetect scores alone and in combination.

Paper 4 [117] demonstrated statistically significant correlations between chronic postoperative pain and preoperative pain intensity (R² = 18%), CPM (R² = 3%), pain catastrophizing (R² = 11%), and PainDetect scores (R² = 9%). A linear regression model utilizing the four preoperative predictors could significantly predict chronic postoperative pain (adjusted R² = 21%). Paper 4 [117] was the first to combine preoperative pain intensities, CPM, pain catastrophizing, and PainDetect scores in one predictive model for chronic postoperative pain following TKA and found that the combination of these factors yielded a better predictive value than each of the elements alone.

Paper 5 [96] aimed to explore if the previous findings from the TKA studies could be utilized for pain after THA. Paper 5 [96] assessed 40 patients with hip OA before and six weeks after THA using the pain intensity scores (VAS) and cold and warm detection and heat and cold pain thresholds, PPTs, TSP, and CPM. The study found that preoperative TSP was associated with postoperative pain (R² = 19%) and postoperative pain relief (R² = 27%).

Paper 5 [96] was the first to report that preoperative TSP was associated with postoperative pain and postoperative pain relief after THA. Wylde et al., 2015 [236] found that preoperative widespread hyperalgesia was associated with WOMAC scores 12 months after THA, which was not the case in paper 5 [96] although both studies support the notion that preoperative assessment of central pain mechanisms is associated with postoperative pain after THA.

Paper 5 [96] included data on thermal stimuli as previous studies had demonstrated associations between preoperative thermal stimuli and acute [73,125,159,218,230] and chronic [1] postoperative pain. No association between preoperative thermal stimuli and postoperative pain was reported in paper 5 [96], which could be due to a relatively small sample size or the fact that most previous papers demonstrating a predictive value utilized suprathreshold stimuli [1,73,125,218,230].

Paper 5 [96] is limited by the follow-up as assessment which was six weeks after surgery, and therefore these findings do not necessarily report chronic postoperative pain.
Paper 6 primarily focused on the modulatory effect of etoricoxib (a COX-2 inhibitor) on clinical pain intensity and PPT, TSP, and CPM. Paper 6 was based on a randomized, double-blind, placebo-controlled, 2-way crossover study assessing clinical pain intensity, PPTs, TSP, and CPM before and after a 4-week placebo or etoricoxib treatment paradigm in 37 patients with knee OA. Paper 6 is incorporated in this dissertation as a prediction model on the effect of COX-2 inhibitors was included. Paper 6 demonstrated that four weeks of COX-2 inhibitors decreased clinical pain intensities, and it was the first study to demonstrate a decrease in TSP following COX-2 inhibitors when compared with placebo. Furthermore, this paper was the first to demonstrate an association between pre-treatment facilitated TSP and poor analgesic response (R² = 18-41%) in a subset of patients with knee OA characterized as non-responders. Paper 6 was the first to demonstrate an association between pre-treatment facilitated TSP and poor analgesic response in patients with knee OA. Edwards et al., 2016 [53] found that pre-treatment impaired CPM was associated with poor analgesic response to topical NSAIDs in patients with knee OA, which supported the finding in paper 6 suggesting that pain sensitive patients with knee OA might not respond well to COX-2 selective and topical non-selective NSAIDs. NSAIDs and paracetamol are standard treatments for pain in OA [21], and paper 7 further investigated the association between QST and responses to NSAIDs and paracetamol, which had already been briefly investigated by Edwards et al., 2016 [53] and in paper 6. Paper 7 assessed 132 patients with knee OA before and after 3 weeks of NSAIDs (400 mg ibuprofen daily) and paracetamol (3000 mg daily) using self-reported pain scores and cPDT, cPTT, and TSP. Paper 7 was the first to demonstrate that non-responders (either less than 30% or 50% pain relief) to 3 weeks of NSAIDs and paracetamol are categorized by pre-treatment facilitated TSP. Using a linear regression model, paper 7 found that pre-treatment TSP and pre-treatment clinical pain predicted the analgesic effect of NSAIDs and paracetamol with a R² = 27%. Study 7 [166] was the first large-scale study applying QST profiling on pharmaceutical therapies in knee OA, and it supported the finding by Edwards et al., 2016 suggesting that pain sensitive OA patients are less likely to benefit from NSAIDs. Paper 8 elaborated on the findings by Edwards et al., 2016 suggesting that impaired descending pain inhibitory function was associated with poor analgesic response to topical NSAIDs. In a preclinical study, Graham et al., 2013 suggested that an intact serotonin system was needed for an analgesic response to NSAIDs, and serotonin seemed to be an important neurotransmitter for the descending pain inhibitory control [19,122]. Therefore, paper 8 assessed if assessment of descending pain inhibitory control could predict the analgesic effect of 3 weeks of NSAIDs and paracetamol.
5. Mechanistic Pain Profiling of Patients with Osteoarthritis

Daily and paracetamol (3000 mg daily). Using a linear regression model, pretreatment clinical pain and CPM were predictive of the analgesic effect with a $R^2 = 19\%$. The data presented in paper 8 [169] were greatly limited by missing data due to the malfunction of the thermal testing device for assessing offset analgesia.

It has been argued that the response of NSAIDs and paracetamol is dependent on an intact serotonin system [71]. Preclinical trials connect the serotonin system to descending pain inhibition [19, 20, 122], the human surrogate model for assessing descending pain inhibition is CPM [237], and impaired CPM can be restored by the administration of serotonin-noradrenaline reuptake inhibitors in patients with painful diabetic neuropathies [241].

Paper 8 [169] demonstrated that impaired CPM was associated with poor response to NSAIDs and paracetamol, which might support the notion that a response to NSAIDs and paracetamol is dependent on an intact serotonin system if CPM is an indirect measure of serotonin activity.

Sangesland et al., 2017 [199] reviewed the literature on preoperative QST and the association with postoperative pain. Sangesland et al., 2017 [199] did not include associations between QST and analgesic effects to pharmacological interventions, and from 2017 to 2020, 10 new studies were published on QST and the association with chronic postoperative pain. Therefore, Paper 9 [170] aims to give an update on the association between QST and chronic postoperative and analgesic effects to pharmacological interventions.

In April 2020, Pubmed and EMBASE were systematically searched for all papers on the predictive value of QST in relation to chronic postoperative pain and responses to pharmacological treatments. Inclusion for the surgical papers was prediction models evaluating at least one preoperative QST parameter with an assessment of pain at least three months after surgery. Surgical studies on acute and subacute postoperative pain were excluded since QST seemed to have less predictive value in the early postoperative phase [199]. Pharmacological studies including predictive models which evaluated at least one QST parameter and a pain-related outcome after a pharmacological treatment were included. Studies evaluating pain-free subjects and studies evaluating the short-term effect of pharmacological interventions (minutes to hours) were excluded.

Paper 9 [170] identified 25 surgical and 11 pharmacological papers with 17 surgical papers and 11 pharmacological papers demonstrating an association between preoperative or pretreatment QST and chronic postoperative pain or response to pharmacological treatment. Deep pressure stimuli, TSP, and CPM were the most frequently assessed QST modalities, and TSP (50%) and CPM (approx. 44%) were most frequently associated with chronic postoperative pain or response to pharmacological treatment.

Paper 9 [170] highlighted that the predictive power of prediction models (both correlations and more advanced prediction models) ranged from 12% to 67%.

Paper 9 [170] is included in this dissertation to give an overview of the field on QST as predictors for chronic postoperative pain and responses to pharmacological treatments. Paper 9 [170] was the first to systematically review all studies on QST as a predictor for surgical and pharmacological outcomes and identified 36 studies with 28 studies (approx. 78%) reporting a statistically significant association between preoperative or pretreatment QST and chronic postoperative pain and responses to pharmacological treatments.
The most consistent predictors were TSP (reported in 14 studies and found as predictor in seven studies, 50%) and CPM (reported in 17 studies and found as a predictor in seven studies, 41%). Even though multiple studies find QST parameters as predictors for chronic postoperative pain or analgesic effect of pharmacological interventions [1,7,107,115,124,127,154,163,164,166,169,186,8,210,224,234–236,240,241,14,32,44,45,53,56,99], paper [170] questions if these associations are clinically meaningful as the predictive power differs substantially between studies.
6. GENERAL DISCUSSION

Papers 1-8 describe the work on preoperative or pretreatment QST as potential predictors for chronic postoperative pain and analgesic effect of NSAIDs and paracetamol in patients with OA. All eight papers find statistically significant associations, but the systematic review (paper 9) questions if the associations are clinically relevant.

6.1 THE PREDICTIVE VALUE OF QST PROFILING IN OSTEOARTHRITIS

As discussed in paper 9, multiple studies have assessed preoperative and pretreatment QST in patients with OA, and the results are mixed. Paper 9 highlighted that 10 out of 12 surgical (83%) and four out of four pharmacological (100%) studies demonstrate significant QST predictors for chronic postoperative pain or response to pharmacological interventions in patients with OA. In addition, O’leary et al., 2018 found pretreatment facilitated TSP and widespread pressure hyperalgesia to be associated with a limited pain relieving response to physiotherapy in patients with knee OA, which further supports a predictive value for QST in patients with OA. This is supported by a recent study by Hansen et al., demonstrating an association between pretreatment TSP and pain relief following exercise therapy of patients with knee OA. In 2016, an IASP taskforce suggested “nociplastic” as new pain phenotype to reflect changes in the nociceptive system. The “nociplastic” suggestion did receive some criticism, but it may be suitable for the patients described in this dissertation who are characterized as “centrally sensitized”, and who do not respond well to the standard OA treatment suggested by OARSI.

It is important to highlight that conflicting literature on the predictive value of QST to OA therapy does exist. Arendt-Nielsen et al., 2018 assessed 100 patients with OA and found no association between PPTs at the knee or the lower leg of patients with knee OA and response to exercise therapy. Martinez et al., 2007 investigated 20 patients with OA and found no association between preoperative allodynia or pain thresholds to mechanical, heat and cold stimuli, and chronic postoperative pain after TKA. Finally, Noiseux et al., 2014 assessed 193 patients with OA and found no association between preoperative mechanical heat and pressure pain thresholds and the presence of moderate-to-severe chronic postoperative pain. Conclusively, more studies seem to suggest a statistically significant association between QST and chronic postoperative pain and analgesic effect in OA than studies rejecting this hypothesis.

One could speculate that there could be a publication bias in mainly reporting statistically significant results. A search on Clinical.gov will reveal that approx. 25 studies have been conducted using the search terms “osteoarthritis” and “Quantitative Sensory Testing”, and some of these studies have not been published yet, which could indicate a selection bias towards publishing.
6.2 “WE ONLY HAVE TIME TO DO ONE TEST – WHICH ONE SHOULD IT BE?”

The above mentioned question is relevant when implementing something as complicated and time consuming as QST into a busy clinical workday, but the answer is not easy. The following sections will attempt to answer the question by observing it from three different angles, namely 1) the studies based on my research, 2) the studies on osteoarthritis in general, and 3) the studies on different pain populations.

6.2.1.1 STUDIES INCLUDING IN THIS DISSERTATION

The current dissertation utilized pressure (paper 1[163], 2[164], 3[96], 5[117], 6[8], and 7[166]) and thermal pain thresholds (paper 3[96] and 5[117]), TSP (paper 1[163], 2[164], 3[96], 4[167], 6[8], and 7[166]), and CPM (paper 1[163], 2[164], 3[96], 5[117], 6[8], and 7[169]) in predictive studies on OA. Pressure pain thresholds assessed remotely from the OA affected knee (possible sign of spreading pressure hyperalgesia) were evaluated in four of my surgical studies and found predictive for chronic postoperative pain in one study (25%) [164] and not predictive of analgesic effect after pharmacological interventions in three studies (0%). TSP was evaluated in four of my surgical studies and predictive of chronic postoperative pain in three (75%) [96,163,167] and assessed in two pharmacological studies and predictive for the analgesic effect in both studies (100%) [8,166]. CPM was assessed in four of my surgical studies and predictive for chronic postoperative pain in one study (25%) [117]. Thermal stimuli were evaluated in two surgical studies and predictive in one study (50%) [167]. Based on this dissertation, TSP is most frequently assessed and most frequently found as predictive, and therefore, TSP could be that “one test”, which should be included in future research.

6.2.1.2 STUDIES ON OSTEOARTHRITIS IN GENERAL

The question can also be answered from a more generalized OA perspective including all studies on OA including QST as predictors. Pressure pain thresholds have been assessed in 11 surgical studies and were predictive of chronic postoperative pain in five studies (36%, of note: pressure pain thresholds were predictive for chronic postoperative pain after total hip, but not total knee arthroplasty in Wylde et al., 2015 [236]) [115,164,235,236], and assessed in four pharmacological studies, but not predictive of the analgesic effect (0%). TSP have been evaluated in seven surgical studies and found predictive for chronic postoperative pain in five studies (71%) [96,115,163,167,186] and assessed in three pharmacological studies in which it was found predictive of analgesic effect in two studies (67%) [8,166]. CPM has been assessed in eight surgical studies and found predictive of chronic postoperative pain in three (38%) [32,117,224] and evaluated in three pharmacological studies and predictive of analgesic effect in two studies (67%) [53,169]. Thermal stimuli have been assessed in four surgical studies and found predictive in one study (25%) [167]. In addition, exercise induced hyperalgesia was evaluated in one surgical study and predicted chronic postoperative pain [224], and offset analgesia was assessed in one pharmacological study, but did not predict any analgesic effect [169]. Mechanical pin prick pain has been assessed in two surgical studies, but not found predictive for chronic postoperative pain [132,149]. Finally, allodynia was evaluated in one surgical study, but not found predictive for chronic postoperative pain [132].
6. General Discussion

6.2.1.3 STUDIES ON DIFFERENT PAIN POPULATIONS

Paper 9 [170] summarized the studies using QST as predictors for chronic postoperative pain and analgesic effects and identified 25 surgical and 11 pharmacological studies. Paper 4 [117] was not included in paper 9 [170] so the current number of surgical papers is now 26. Conclusively, TSP has been assessed in 14 studies and found predictive in seven studies (50%) [8, 115, 163, 166, 167, 186, 210], CPM has been evaluated in 18 studies and found predictive in eight studies (44%) [53, 117, 169, 224, 234, 240, 241], and pressure pain thresholds have been assessed in 18 studies and found predictive in 5 studies (28%) [14, 115, 164, 235, 236]. Based on these studies, it is concluded that TSP was most frequently assessed and most frequently found as a predictor for chronic postoperative pain and analgesic effect.

Based on the studies on OA in general, TSP seems to be most frequently assessed and most frequently found as a predictor for chronic postoperative pain or analgesic effect.

6.2.1.4 CAN WE ANSWER THE QUESTION?

Based on the above analysis, TSP seems to be the most consistent predictor for chronic postoperative pain and analgesic effect. It is important to highlight, however, that a lot (+50%) of the above mentioned studies have been conducted in patients with musculoskeletal pain, which tends to favor pressure stimuli as the QST modality [145]. TSP does not seem to be elevated in patients with e.g., peripheral neuropathic pain [195, 226], and therefore TSP might not be predictive of treatment response in these patients. Finally, it is very important to highlight that TSP (or other QST assessment) might be significantly associated with chronic postoperative pain or analgesic effect, but the predictive strength remains low, and therefore, it is advisable to include additional known predictors in future studies.

6.3 METHODOLOGICAL CONSIDERATIONS

Linear regression models are often used as the predictive tool in the QST literature, which is also the case for the work presented here. It is worth noticing that linear regression models assume that the dependent factor is linear, which might not be the case for clinical pain intensities. Future studies should consider applying more advanced statistical methods to identify if this will improve the predictability of QST.

In this dissertation, the different assessment techniques are self-limiting as multiple different approaches of TSP (pinprick [87, 163, 167], automated pressure algometry [8] and cuff algometry [164, 166]) and CPM (conditioning stimulus using the cold pressor test [163], ischemic cuff induced pain [8], and cuff algometry [117, 164, 169]) have been utilized. As highlighted in paper 9 [170], standardization of QST assessments would increase the comparability between studies, which could push the field forward. On a positive note, the work presented here covers a wide range of different stimuli modalities such as mechanical pin prick, heat and cold stimuli, and deep pressure stimuli and, therefore, substantially adds to the literature discussing which stimuli might be important for predicting treatment outcomes in OA.

QST reliability constitutes an issue in the literature, and CPM has attracted attention recently [102, 103]. Reliability studies are conducted either using sessions within days or between days (or weeks). Koo et al., 2016 defines test-retest reliability to “reflect the variation in measurements taken by an instrument on the same subject under the same conditions” [111]. In a
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QST study, this means that reliability studies should aim to establish identical sessions using the same subjects and ensure that the subjects are influenced by the same conditions. The interclass correlation coefficient (ICC) is often reported in QST reliability studies [79, 93, 225], and this relies on a ranking system in which a better ICC score is obtained if subjects remain within the same rank in between sessions [111]. It is nearly impossible to obtain perfect test-retest reliability of QST parameters due to the fact that everyday factors such as quality of sleep [108, 161, 215], stress [91, 109], or negative affect [54, 57] influence QST. Studies suggest that these factors might also hold predictive value for pain alleviating response to therapy [126, 176, 190], and therefore, future studies should focus on understanding the variability of QST parameters and potentially utilizing the variability to strengthen the prediction models.
7. CONCLUSION

The current work demonstrated significant associations between QST poor response to standard surgical and pharmacological treatments in patients with OA, indicating that highly pain-sensitive patients with OA are less likely to benefit from standard care. In addition, a systematic review has established that temporal summation of pain is the most consistent predictor of chronic postoperative pain and responses to pharmacological treatments. Finally, the predictive strength for quantitative sensory testing remains low and, therefore, encourages a multimodal assessment of patients for future predictive studies.
8. THE FUTURE: DEVELOPMENT OF THE CONCEPT “PERSONALIZED MECHANISTIC PAIN MEDICINE”

Personalized medicine is defined as medical care tailored towards the individual patient. This challenges the traditional “staircase treatment” regimes for OA composed of initial education, exercise, and weight control followed by NSAIDs plus paracetamol and surgery if needed [196].

Early selection of patients based on the mechanisms generating the pain and treatments targeting these mechanisms is hypothesized to improve pain treatment in OA (see figure 6 for illustration of the concept).

Figure 6: Today, osteoarthritis is treated in the order of 1) physiotherapy (and weight loss if needed), 2) NSAIDs, and 3) surgery. Ideally, early selection of patients best suited for a given therapy would optimize the treatment regime. In addition, some patients might not benefit from physiotherapy, NSAIDs plus paracetamol, or surgery and should be offered therapies.

The possibility for selecting patients who do not benefit from TJA or NSAIDs may exist. How to select patients for the right treatment has not been utilized yet. An understanding of the underlining mechanisms for pain and the contribution of other factors is needed to support this hypothesis.

It seems clear that multiple factors such as opioid use [131], sleep deprivation [215], pain catastrophizing [221], and physical performance [86] do affect QST, and these factors also seem important for pain relieving therapies.

To exemplify this theory in another context, high levels of pain catastrophizing have been associated with high levels of postoperative pain [22, 51, 173–175, 197]. Therefore, Riddle et al., 2019 [189] aimed to decrease preoperative pain catastrophizing using cognitive behavioral therapy compared with standard care in 346 patients with OA, and to investigate if this reduced the chronic postoperative pain following TKA. Riddle et al., 2019 [189] were able to modify preoperative pain catastrophizing, but no differences were reported in postoperative pain levels at 12-month follow-up, which has been supported in another recent RCT on patients scheduled for TKA [29]. Despite the inability to reduce chronic postoperative pain by
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Riddle and colleagues, the idea of targeting mechanisms, presumably associated with chronic postoperative pain, is good. Similar to Riddle et al., 2019 [189], future Personalized Mechanistic Pain Medicine studies must be conducted with the aim to target mechanisms, which presumably generate pain (or contribute to pain) in order to investigate possible new treatment options. For instance, sleep deprivation leads to up-regulation of IL-6 [95], and IL-6 is known to sensitize peripheral free nerve endings, which results in localized and widespread hyperalgesia [200]. High IL-6 is associated with high pain scores in patients with OA [59]. Increased physical activity is associated with better sleep [242], and high intensity exercise interventions can reduce the severity of chronic insomnia [182]. In addition, preclinical trials have reported a shift in macrophages type 1 (pro-inflammatory) to type 2 (anti-inflammatory) after high intensity exercise [120], and modulation of micro-RNAs has been observed in healthy subjects following 12 weeks of high intensity exercise [146] indicating an anti-inflammatory response to high intensity exercise. Therefore, exercise therapy might benefit patients with e.g., poor quality of sleep, high inflammation, and widespread hyperalgesia.

Similar, the function of descending pain inhibitory control is believed to rely on serotonin and noradrenaline [17,20]. CPM is assumed to be the human proxy for the assessment of descending pain inhibitory control [237]. Duloxetine is a serotonin-noradrenaline reuptake inhibitor, and duloxetine was recently recommended by the OARSI for OA pain treatment for patients with widespread pain and/or depression [21]. Patients with diabetic neuropathies and impaired patients have been found to respond well to four weeks of duloxetine, and CPM seems to be restored after pain relieving duloxetine treatment [241]. Studies have found that a subset of knee OA patients display impaired CPM compared with healthy subjects [11,15] or other OA patients [164]. A recent RCT [110] administrated pre- and postoperative duloxetine to pain sensitive knee OA patients scheduled for TKA and found this to reduce pain intensities at postoperative week 6 and 12 compared with placebo. This study needs further validation, but could be another example of how a targeted effort towards pain mechanisms might improve the treatment in future.
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