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BY
JESPER BIE LARSEN

DISSERTATION SUBMITTED 2021

AALBORG UNIVERSITY
DENMARK

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CV

Jesper Bie Larsen completed his Bachelor's degree in physiotherapy in 2006 at VIA University College, Aarhus, Denmark. Following this, he practiced as a physiotherapist at the Vejle-Give hospital, Give, Denmark, the professional football club "*Vejle Boldklub*," Vejle, Denmark, and as a private physiotherapy practitioner at "*Thomsen Fysioterapi og træning*," Randers, Denmark. While working as a physiotherapist, he completed the Danish Society of Sports Physiotherapy examination to become a certified sports physiotherapist. He received his Master's degree in Health Science in 2012 at Aarhus University, Denmark. Thereafter, he lectured at University College Nordjylland Physiotherapy, Aalborg, Denmark, as a research assistant at "*Folkesundhed og Kvalitetsudvikling, Medicinsk Teknologi Vurdering og Sundhedstjenesteforskning*," Aarhus, Denmark, and as a physiotherapist at Montebello - Department of Rehabilitation, North Zealand's Hospital, Benalmádena, Spain.

Jesper Bie Larsen enrolled as a PhD-student at the doctoral school of the Faculty of Medicine at Aalborg University, Denmark, where he has been affiliated with the research interest groups Translational Pain Biomarkers and Sport Sciences – Performance and Technology. His PhD project was a collaboration between Aalborg University and Aalborg University Hospital. During his PhD study, Jesper Bie Larsen presented several posters at the international conferences: the 17th World Congress on Pain IASP (Boston, USA 2018), the OARSI World Congress on Osteoarthritis (Toronto, Canada 2019), and the 11th Congress of the European Pain Federation EFIC (Valencia, Spain 2019). In addition to the studies published in relation to the PhD thesis, he has published three other manuscripts during his time as a PhD student.

Jesper Bie Larsen was awarded the "oldermand, slagtermester Peter Ryholts" grant in 2018 by the Danish Rheumatism Association and the Lions Denmark award in 2020.

Jesper Bie Larsen is on the steering committee for the OARSI Rehabilitation Discussion Group and is the co-founder of the early-career researcher sub-committee of the OARSI Rehabilitation Discussion Group. He has completed review assignments for the Arthritis Care and Research Journal, the Osteoarthritis and Cartilage Journal, and the Scandinavian Journal of Pain.

ENGLISH SUMMARY

Osteoarthritis (OA) is a frequent condition in the elderly population and it is estimated that more than 300 million people worldwide suffer from OA. The dominant symptom of OA is pain, but the mechanisms and pathophysiology of OA pain are not fully understood. End-stage knee OA is often treated surgically with a total knee arthroplasty (TKA), but approximately 20% of patients undergoing knee-joint replacement will experience chronic pain following their surgery. The progression towards chronic pain is thought to involve a mix of local pathological processes in and around the knee joint, genetic and metabolic factors, and neuronal changes at several levels, including peripheral and/or central sensitization, and reduced descending inhibition. Numerous clinical guidelines and systematic reviews have highlighted physical activity, exercise, and education as first-line treatments for knee OA. For patients with chronic pain after TKA, no clinical guidelines or standardized treatment regimens exist and no clear treatment recommendations are available.

The overall aims of this PhD thesis were to develop a clinically applicable, bed-side test as a useful tool to examine conditioned pain modulation (CPM) (study I), to profile and compare pain, pain sensitization, the patient-reported questionnaire Knee injury and Osteoarthritis Outcome Score (KOOS) and physical performances in patients with chronic pain after knee OA or TKA (study II). Furthermore, it aimed to investigate the benefits of an intensive, multimodal rehabilitation following primary or revision TKA (study III). Lastly, it set out to design and initiate an intervention study that would improve pain, pain sensitization, and physical performances in patients with chronic pain after TKA (study IV).

Study I was a cross-sectional test-retest reliability study that included two populations of healthy, pain-free subjects (n= 22 and n= 29). Conditioned pain modulation was measured using a newly developed spring-based 6 kg pressure algometer as a test stimulus and a standard clamp, which induced pressure of 1.3 kg, as a conditioning stimulus. The test stimulus was applied to the tibialis anterior muscle belly at the dominant leg and the conditioning stimulus was applied to the ipsilateral ear lobe. The test stimulus was applied for 10 sec and the conditioning stimulus for 60 sec. Pain intensity ratings of the test and conditioning stimulus were made using a numerical rating scale (NRS) from 0-10 (with “0” representing “no pain” and “10” representing “worst pain imaginable”). To conduct the test-retest part, the second CPM test session was repeated 24-48 hours following the first test session. The results observed a “good” relative reliability (intra-class correlation; 0.67 and 0.72) for the test stimuli, although the absolute reliability indicated substantial intra-individual variation (standard error of measurement; NRS 1.9 and 2.1). No averaged CPM effect was observed in the healthy subjects, and in the population, a substantial

variation in CPM effect was observed with both CPM responders and non-responders (study I).

Study II was a cross-sectional study that included a population of 70 patients with chronic pain from knee OA (n= 46) and chronic pain after TKA (n= 24). Patients underwent a one-session assessment of pain intensity, pain sensitization parameters including mechanical pinprick pain sensitivity, temporal summation of pain and CPM, the KOOS questionnaire, and physical performances tests including the 30-second chair stand test, the 40-meter fast-paced walk test, and the stair climb test. The analysis was adjusted for body mass index. The adjusted results indicated that similar profiles for pain, pain sensitization, CPM, and KOOS were observed for the OA and the TKA populations. Between-group differences for the 30-second chair stand test (11.2 vs. 9.7 repetitions, p= 0.015), the 40-meter fast-paced walk test (29.3 vs. 31.8 seconds, p= 0.081), and the stair climb test (11 vs. 14.2 seconds, p= 0.002) were observed, with the OA group consistently performing better physically. Of note, a substantial variation in the CPM effect was seen in both CPM responders and non-responders in the OA and the TKA groups (study II).

Study III was a retrospective study, which included a population of 217 patients with primary (n= 166) or revision TKA (n= 51), who had experienced post-surgical complications, for example, persistent pain or continued functional impairments. The patients received three weeks of intensive, multimodal rehabilitation consisting of various exercise sessions to promote neuromuscular function, muscle strength, and cardiovascular capacity. Physiotherapists supervised all the rehabilitation activities and provided group-based educational sessions. As the primary outcome, the KOOS subscales of pain, symptoms, activities of daily living, and knee-related quality of life were assessed. Furthermore, pain intensities at rest and during activity and physical performances in terms of the 6 min. walking test and the stair-climbing test were evaluated. Overall, the results showed significant improvements in the KOOS subscales, pain intensities, and the physical performances for both groups following three weeks of intensive, multimodal rehabilitation. For the KOOS subscales of pain, symptoms, activities of daily living, and knee-related quality of life, the primary TKA group showed improvements of 9.8 points ($p < 0.000$), 9.4 points ($p < 0.000$), 14.2 points ($p < 0.000$), and 8.5 points ($p < 0.000$), respectively. For the revision TKA group, the same KOOS subscales showed improvements of 6.9 points ($p = 0.005$), 8.2 points ($p < 0.000$), 10.8 points ($p < 0.000$), and 8.6 points ($p = 0.001$), respectively (study III).

In summary, chronic pain reported by patients suffering from knee OA or following TKA influences pain sensitization, CPM, patient-reported outcomes, and physical performances to different extents. Overall, substantial individual variations were observed for the investigated outcomes, which may indicate the heterogeneity of the chronic pain populations. Exercise appears to improve pain, patient-reported function, and physical performances in a TKA population with post-surgical

complications, and future studies should investigate whether this observation can be verified in a population of patients with chronic pain after TKA. Study IV was initiated based on this lack of high-quality evidence regarding patients with chronic pain after TKA. Based on the findings in this thesis, some suggestions can be made regarding the clinical implications. Firstly, when undertaking future CPM studies, authors should report individual CPM effects and observations of CPM responders and non-responders. Secondly, it is proposed that the studies ensure that a thorough, multifactorial assessment, including a matrix of pain and sensitization outcomes, self-reported outcomes, and measures of physical performances, is undertaken for patients with chronic pain because of knee OA or after TKA. Such an approach would indicate which parameters require attention in the management of the individual patient's chronic pain condition.

DANSK RESUME

Slidgigt er en hyppig lidelse i den ældre del af befolkningen, og det anslås at mere end 300 millioner mennesker på verdensplan lider af slidgigt. Det dominerende symptom ved slidgigt smerter, men mekanismerne og fysiologien bag slidgigt smerterne er ikke fuldt ud klarlagt. Svær slidgigt i knæet behandles ofte kirurgisk med indsættelse af en total knæ-alloplastik (TKA), men ca. 20% af patienterne, som gennemgår denne operation, vil opleve kroniske smerter efterfølgende. Det antages at progressionen mod kronisk smerte involverer en blanding af lokale patologiske processer i og omkring leddene, genetiske og metaboliske faktorer og neurale ændringer, herunder perifer og/eller central sensibilisering samt nedsat evne til at sende smertehæmmende signaler. Talrige kliniske retningslinjer og systematiske litteraturgennemgange har fremhævet træning og patientuddannelse som primær behandling af slidgigt i knæet. For patienter med kroniske smerter efter TKA findes der ingen kliniske retningslinjer eller standardiserede behandlingsregimer, og derfor eksisterer ingen klare anbefalinger ift. behandling af denne patientgruppe.

Det overordnede formål med denne Ph.d. afhandling var at udvikle en klinisk anvendelig test til undersøgelse af smertemodulation (*conditioned pain modulation*, CPM) (studie I), udføre profilering af og sammenligne smerteintensitet, sensibilisering, spørgeskemaet *Knee injury and Osteoarthritis Outcome Score* (KOOS) og fysisk formåen hos patienter med kroniske smerter efter slidgigt i knæet eller efter TKA (studie II) samt at undersøge virkningen af intensiv, multimodal genoptræning efter primær eller revisions TKA (studie III). Derudover at designe og igangsætte et randomiseret interventionsstudie, som har til formål at mindske smerterne, mindske sensibilisering og forbedre fysisk kapacitet hos patienter med kroniske smerter efter TKA (studie IV).

Studie I var et tværsnitsdesign som undersøgte test-retest reliabiliteten af et nyudviklet tryk-algometer. Forsøgsdeltagerne var raske, smertefri forsøgspersoner (n = 22 og n = 29). Smertemodulation blev målt ved hjælp af et fjederbaseret 6 kg tryk-algometer som test stimuli og en standard klemme, som klemte med et tryk på 1,3 kg, som konditionerings stimuli. Test stimuli blev påført på muskelbugen af *tibialis anterior* på det dominante ben, og konditionerings stimuli blev påført på øreflippen på modsat side af det dominante ben. Test stimuli blev påført i 10 sekunder og konditionerings stimuli i 60 sekunder.

Smerteintensiteten af test og konditionerings stimuli blev vurderet på en numerisk rangskala (NRS) fra 0-10 (hvor "0" repræsenterede "ingen smerte" og "10" repræsenterede "den værste tænkelige smerte"). Dette setup blev gentaget 24-48 timer efter den første test session for at kunne vurdere test-retest reliabiliteten. Resultaterne viste, at den relative reliabilitet kunne betragtes som værende "god"

(*intra-class correlation*; 0,67 og 0,72) for test stimuli, hvorimod den absolutte reliabilitet viste at der var stor individuel variation (*standard error of measurement*; NRS 1.9 og 2.1). Studiet registrerede ingen CPM effekt på gruppeniveau hos de raske forsøgspersoner, og der blev observeret stor variation i CPM effekt (study I).

Studie II var et tværsnitsstudie, der omfattede en gruppe af 70 patienter med kroniske smerter som følge af enten slidgigt in knæet (n = 46) eller efter TKA (n = 24). Patienterne gennemgik en enkelt undersøgelsessession, hvor de fik vurderet deres smerteintensitet, sensibilisering, herunder smerte følsomhed og *temporal summation*, CPM, KOOS spørgeskemaet og deres fysiske kapacitet, hvilket inkluderede en 30 sekunders rejse-sætte sig test, en 40 meter gangtest, og en trappe test. Under den statistiske analyse blev resultaterne justeret for *body mass index*. De justerede resultater viste, at profilerne for smerteintensitet, sensibilisering, CPM og KOOS var sammenlignelige for gruppen med slidgigt i knæet og gruppen med TKA. Derimod var der forskel mellem grupperne for 30 sekunders rejse-sætte sig testen (11,2 vs 9,7 gentagelser, p = 0,015), 40 meter gangtesten (29,3 mod 31,8 sekunder, p = 0,081) og trappe testen (11 vs. 14,2 sekunder, p = 0,002), hvor gruppen med slidgigt præsterede de bedste resultater. Vedrørende CPM målingerne blev set en stor variation i CPM effekt hos begge grupper (study II).

Studie III var en retrospektiv undersøgelse, der omfattede en gruppe på 217 patienter med primær (n = 166) eller revisions TKA (n = 51), som havde oplevet komplikationer efter operationen, f.eks. vedvarende smerter eller nedsat fysisk formåen. Patienterne modtog tre ugers intensiv, multimodal genoptræning bestående af forskellige træningssessioner. Formålet var at forbedre neuromuskulær funktion, muskelstyrke og kredsløbs kapacitet. Alle træningssessioner var superviseret af fysioterapeuter og disse stod også for gruppebaseret patientuddannelse. Det primære effektmål var KOOS domænerne smerter, symptomer, funktion i dagligdagen og knæ-relateret livskvalitet. Desuden fik patienterne vurderet deres smerteintensitet i hvile og ved fysisk aktivitet og deres fysiske kapacitet i form af en 6 min. gangtest og en trappe test. Overordnet set viste resultaterne signifikante forbedringer i KOOS domænerne, smerteintensiteterne og den fysiske formåen efter tre ugers intensiv, multimodal genoptræning. For KOOS domænerne smerte, symptomer, funktion i dagligdagen og knæ-relateret livskvalitet viste gruppen med primær TKA forbedringer på henholdsvis 9,8 point (p <0,000), 9,4 point (p <0,000), 14,2 point (p <0,000) og 8,5 point (p <0,000). Gruppen med revisions TKA viste på de samme KOOS domæner forbedringer på henholdsvis 6,9 point (p = 0,005), 8,2 point (p <0,000), 10,8 point (p <0,000) og 8,6 point (p = 0,001) (study III).

Kroniske smerter som følge af slidgigt i knæet eller efter TKA har indflydelse på sensibilisering, CPM, patientens subjektive oplevelse af smerterne og den fysiske kapacitet. Samlet set blev der observeret stor individuel variation for de undersøgte effektmål, hvilket kan indikere heterogenitet hos patientgrupperne med kroniske smerter. Træning ser ud til at kunne forbedre smerterne, den selv-rapporterede

funktion og fysisk kapacitet i en gruppe af patienter med komplikationer efter TKA, og fremtidige undersøgelser bør undersøge, om denne observation kan verificeres i en population af patienter med kroniske smerter efter TKA. Studie IV blev igangsat på grund af den manglende evidens med hensyn til effektiv behandling af patienter med kroniske smerter efter TKA. Ud fra resultaterne i denne Ph.d. afhandling kan der foreslås nogle kliniske implikationer. For det første bør forfatterne rapportere individuel CPM effekt og ikke kun CPM effekt på gruppe-niveau, når der gennemføres fremtidige CPM undersøgelser. For det andet anbefales det at foretage en grundig vurdering af de multifaktorielle årsager, som kan have indflydelse på patienternes kroniske smerter på grund af slidgigt i knæet eller efter TKA. Dette vil give mulighed for at evaluere hvilke parametre, der kræver opmærksomhed i håndteringen af den enkelte patients kroniske smerter.

ACKNOWLEDGEMENTS

I would like to acknowledge and express my gratitude to all the patients that participated in the studies. Without their willingness to participate, despite often having had numerous visits to their general practitioner, surgeons, and hospitals in general without experiencing much improvement, study II and IV could not have been initiated or completed. Similarly, study IV could not have been initiated if not for the financial support from the Department of Health Science and Technology at Aalborg University, the Danish Rheumatism Association, the Svend Andersen Foundation, and the Lions Denmark.

This PhD thesis would not have been developed and completed without the assistance of my supervisors and collaborators. Especially, I would like to thank Professor Pascal Madeleine and Professor Lars Arendt-Nielsen for our collaboration. I am truly grateful that both of you were willing to allow me to combine your specific research areas with my own clinical experiences and ideas. Your supervision and our discussions have formed the foundation from which I am now finding my own path within the research.

My collaborators for study IV deserve credit for assisting in bringing the project to fruition: Professor Søren T Skou for always being available to discuss any issue that may emerge and his ability to propose solutions, orthopedic surgeons Ole Simonsen and Mogens Laursen for sharing their clinical experiences and linking the study to the Department of Orthopedic Surgery. Furthermore, I wish to thank senior physiotherapists Jan Kjærsgaard, Michael Flyvholm Kvols, and Christine Nørgaard and the Departments of Occupational Therapy and Physiotherapy at Aalborg, Thisted, and Farsoe hospitals for their never-ending engagement and willingness to assist with various practical issues. I have been privileged to have skillful and engaged collaborators throughout my PhD. For study II, I thank Aina Lihn, Susanne Hybholt, and the rest of the personnel at SYNEXUS Aalborg (formerly Center for Clinical and Basic Research Aalborg) for their assistance in recruiting patients. For study III, I thank Lisbeth Mogensen, Karen Schur, and the rest of the personnel at Montebello – Department of Rehabilitation for being willing to collaborate and share their clinical results.

I love going to work and immersing myself in the projects that I have commenced, but I love it, even more, when I return home to my wife Camilla, my son Anton, and my daughter Svea. Thank you for allowing me to spend so much time on research and for your presence that always reminds me of what the most important part of my life is.

/ Jesper Bie Larsen, January 2021, Aalborg

ABBREVIATIONS

ADL	Activities of daily living
BMI	Body mass index
CI	Confidence interval
CPM	Conditioned pain modulation
ICC	Intra-class correlation
KOOS	The Knee injury and Osteoarthritis Outcome Score
MCID	Minimal clinically important difference
NEMEX-TJR	The NEuroMuscular EXercise Total Joint Replacement training program
NRS	Numerical rating scale
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
PNE	Pain neuroscience education
PPT	Pressure pain threshold
QOL	Quality of life
QST	Quantitative sensory testing
SD	Standard deviation
SE	Standard error
SEM	Standard error of the measurements
TKA	Total knee arthroplasty
VAS	Visual analogue scale

PREFACE

The scientific work related to this PhD thesis is the culmination of my time as a PhD student at Aalborg University, Aalborg Denmark. During my research, I spent time at and have been collaborating with other institutions for my data collection and interventions. Data collection for study I was conducted at Sport Sciences – Performance and Technology and Translational Pain Biomarkers at Aalborg University. Data collection for study II was made at the Department of Occupational Therapy and Physiotherapy at Aalborg University Hospital, Aalborg, Denmark, and at the outpatient clinic Center for Clinical and Basic Research, Aalborg, Denmark. Data collection for study III was conducted at Montebello – Department of Rehabilitation, North Zealand's Hospital, located at Benalmádena Pueblo, Spain. Interventions and data collection for study IV is ongoing at three different locations within the Department of Occupational Therapy and Physiotherapy at Aalborg University Hospital, located in Aalborg, Farsoe, and Thisted, Denmark.

The Svend Andersen Foundation, Lions Denmark, and the Danish Rheumatism Association funded study IV. The study sponsors were not involved in executing the study, interpreting the data, or publishing the results, and all the authors are independent of the sponsors.

LIST OF PAPERS

The PhD thesis is based on four (I-IV) published manuscripts. In the thesis, the studies will be referred to according to their Roman numeral.

I. Larsen JB, Madeleine P, Arendt-Nielsen L. Development of a new bed-side-test assessing conditioned pain modulation: a test-retest reliability study. Scand J Pain. 2019 Jul 26;19(3):565-574. https://doi.org/10.1515/sjpain-2018-0353

II. Bie Larsen J, Arendt-Nielsen L, Simonsen O, Madeleine P. Pain, sensitization, and physical performances in patients with chronic painful knee osteoarthritis or chronic pain following total knee arthroplasty: An explorative study. Eur J Pain. 2021 Jan;25(1):213-224. https://doi.org/10.1002/ejp.1663

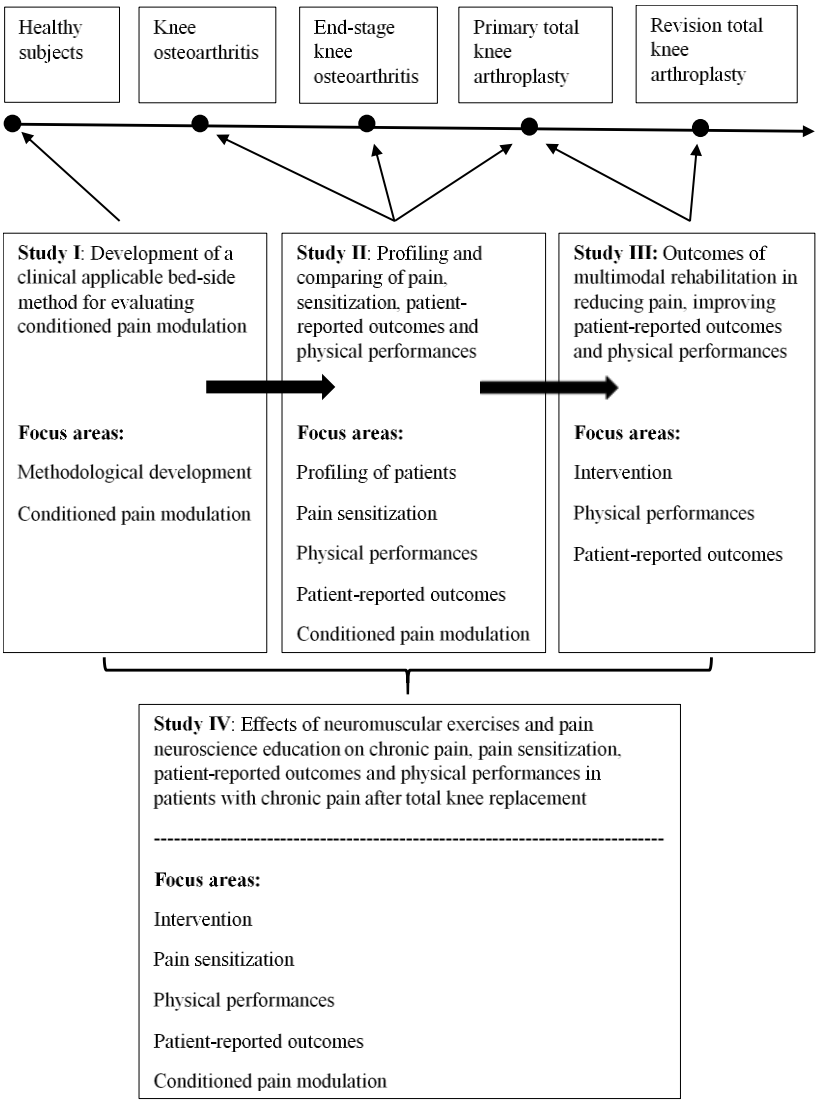
III. Larsen JB, Mogensen L, Arendt-Nielsen L, Madeleine P. Intensive, personalized multimodal rehabilitation in patients with primary or revision total knee arthroplasty: a retrospective cohort study. BMC Sports Sci Med Rehabil. 2020 Jan 10;12:5. https://doi.org/10.1186/s13102-020-0157-1

IV. Larsen JB, Skou ST, Arendt-Nielsen L, Simonsen O, Madeleine P. Neuromuscular exercise and pain neuroscience education compared with pain neuroscience education alone in patients with chronic pain after primary total knee arthroplasty: study protocol for the NEPNEP randomized controlled trial. Trials. 2020 Feb 24;21(1):218. https://doi.org/10.1186/s13063-020-4126-5

THESIS AT A GLANCE

Figure 1 illustrates the coherence between the individual studies, leading towards the intervention study (study IV).

Figure 1: Timeline from the potential development of knee osteoarthritis to total knee arthroplasty to revision total knee arthroplasty.



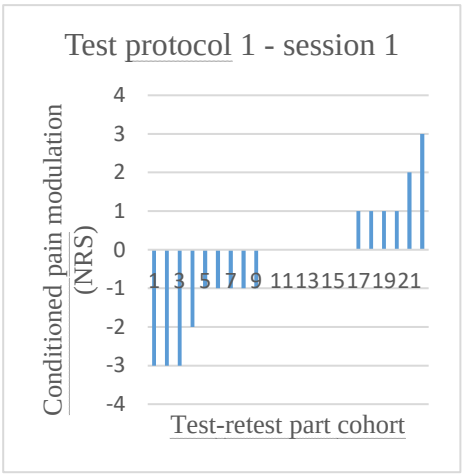
The PhD thesis aimed to develop a clinically applicable, bed-side test as a useful tool to examine conditioned pain modulation (CPM) (study I), to profile and compare pain, pain sensitization, patient-reported outcomes, and physical performances in patients with chronic pain after knee osteoarthritis (OA) or total knee arthroplasty (TKA) (study II). Furthermore, it aimed to investigate the benefits of an intensive, multimodal rehabilitation following primary or revision TKA (study III). Finally, it proposed to implement the findings from study I-III into an ongoing intervention study, which aimed at improving pain, pain sensitization, patient-reported outcomes, and physical performances in patients with chronic pain after TKA (study IV). Study IV is published as a study protocol.

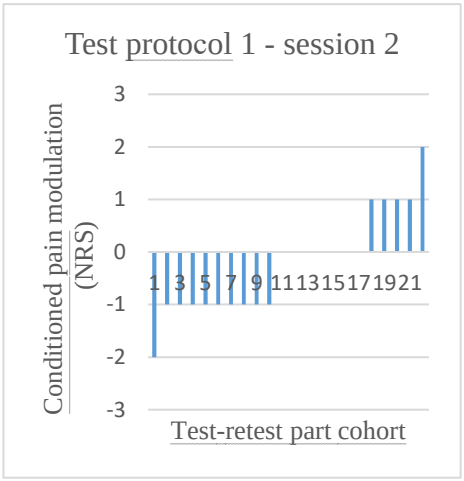
Study I:

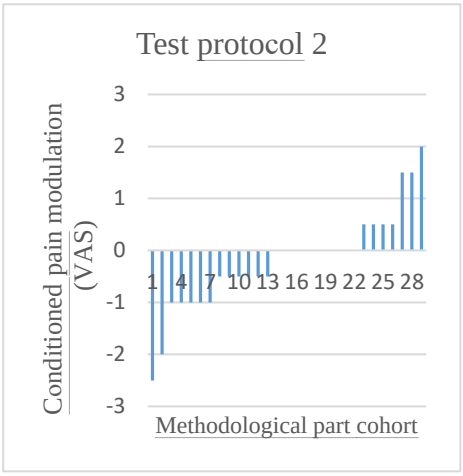
The main findings were as follows:

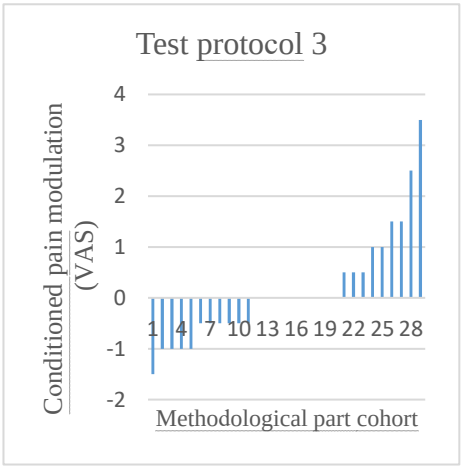
- A new, spring-based pressure algometer was developed, which can be used for applying test stimulus during CPM testing.
- The designed pressure algometer showed "good" relative reliability for test-retest test stimuli, but the absolute reliability indicated substantial intra-individual variation.
- No averaged CPM effect could be observed in a population of healthy subjects.
- When CPM data were ranked individually, a distribution with both CPM responders and non-responders was observed for all CPM test protocols (Figure 2).

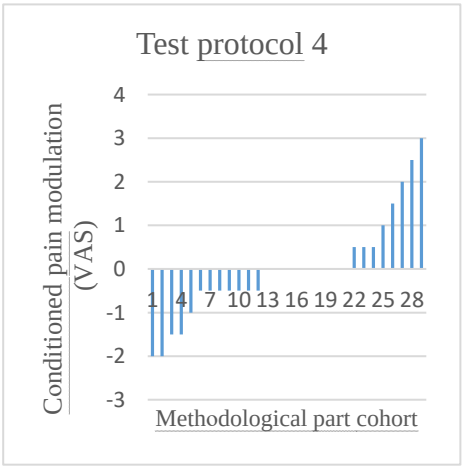
Figure 2: Individual CPM effects for all test protocols used in study I. Refer to study I for explanations of the different test protocols. Horizontal numbers refer to the number of subjects.











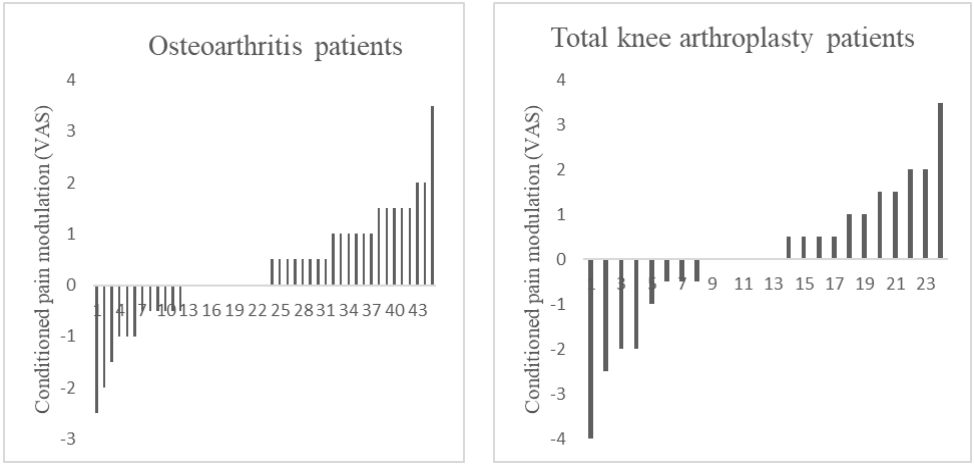
Positive values indicate facilitatory conditioned pain modulation (i.e. a non-responder).
Negative values indicate inhibitory conditioned pain modulation (i.e. a responder).
NRS: Numerical rating scale
VAS: Visual analog scale

Study II:

The main findings were as follows:

- Similar profiles for pain intensity, pain sensitization, and patient-reported outcome measures were observed for the OA and the TKA groups with chronic pain.
- Differences in physical performances were observed between groups, with the OA group consistently performing better physically.
- No averaged CPM effect could be observed in the population of patients with chronic pain because of knee OA or after TKA.
- When CPM data were ranked individually, a similar distribution as in study I with both CPM responders and non-responders was observed for both the OA and the TKA groups (Figure 3).

Figure 3: Individual conditioned pain modulation (CPM) effects for knee osteoarthritis and total knee arthroplasty patients with chronic pain. VAS: Visual analog scale. Positive values indicate facilitatory CPM (i.e. a non-responder). Negative values indicate inhibitory CPM (i.e. a responder). Horizontal numbers refer to patient numbers. Adapted from study II.

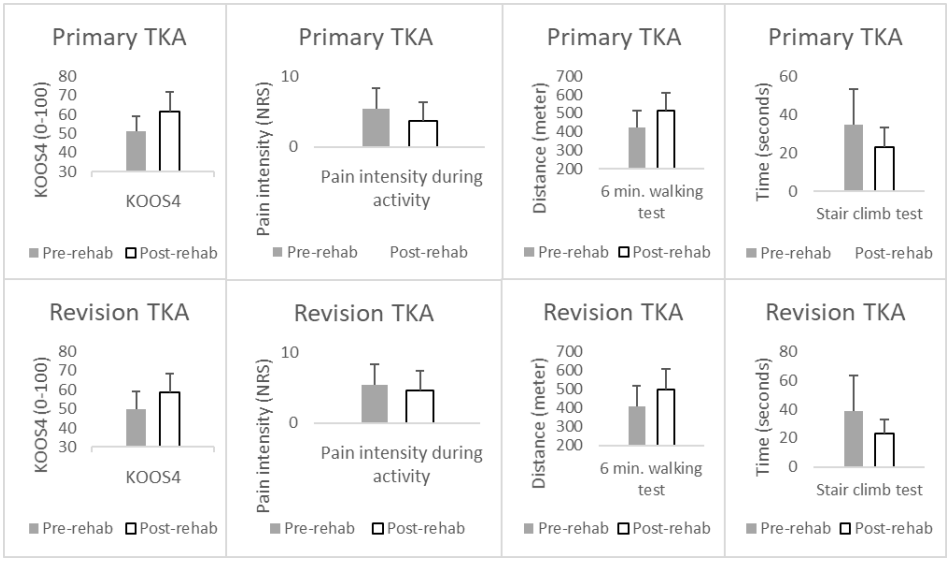


Study III:

The main findings were as follows:

- Patients with primary (n= 166) and revision TKA (n= 51) that received intensive, multimodal rehabilitation showed improvements in pain intensity, patient-reported outcomes, and physical performances. An overview of the results is shown in Figure 4.

Figure 4: Overview of outcomes for both the primary and the revision TKA groups



Knee injury and Osteoarthritis Outcome Score (KOOS)[4] is the mean of the four KOOS subscales: pain, symptoms, activities of daily living, and knee-related quality of life. Pre-rehab: Scores before rehabilitation. Post-rehab: Scores after rehabilitation. Error bars indicate standard deviation. TKA: Total knee arthroplasty. NRS: Numerical rating scale.

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CHAPTER 1. INTRODUCTION

1.1. OSTEOARTHRITIS AND TOTAL KNEE ARTHROPLASTY: MAGNITUDE AND BURDEN OF DISEASE

Osteoarthritis (OA) is a frequent condition in the elderly population and it is estimated that more than 300 million people worldwide suffer from OA (1,2). In the overall Danish population, 21% suffers from OA and for the age group of 65+ years, the prevalence of OA ranges from 40-50% (3). This makes OA the second-most prevalent disease in Denmark, and it accounts for more cases than hypertension, migraine/recurrent headache, and diabetes (3). More specifically, hip and knee OA have the most significant effect on the overall OA burden and a global knee OA prevalence of 3.8% has been estimated (4). Expressed as a global disability, hip and knee OA ranked 11th among 291 conditions when years lived with a disability was evaluated in 2016, which was a rise from rank 17th in 1990 (4). For the Nordic countries (Denmark, Sweden, Norway, Iceland, Greenland, and Finland), hip and knee OA ranks 15th among the 30 leading causes of years lived with disability in 2015. Moreover, from 1990-2015, it had the fifth-highest relative increase in years lived with a disability (5).

End-stage knee OA is often treated surgically with a total knee arthroplasty (TKA) (1,4) and it has been estimated that patients diagnosed with knee OA have a 30-50% lifetime risk of undergoing TKA (6,7). Due to aging, increased obesity rates, and a more sedentary lifestyle, the number of people with hip and knee OA is expected to increase in the future (1,4,8). Therefore, the number of TKAs performed has been growing and is expected to continue to rise (9,10). It has been estimated that if the increasing rate of TKA surgeries from 2003 to 2013 in Australia continues, 276% more TKA surgeries will be performed in 2030 compared to those in 2013 (11). In Denmark, 9.700 patients underwent a TKA in 2018, which is a rise of 14% compared to previous years (2011-2017), during which the surgery rate for TKA remained unchanged (12). In Denmark, a total of 1.100 patients had a revision TKA in 2018. The most common reasons for revision surgery was the aseptic loosening of an implant (19%), infection (18%), instability (18%), and pain without loosening of the implant (11%) (12).

At an individual level, the burden of OA affects pain levels, physical performance, and quality of life (QOL) (13). Moreover, increased mortality in OA populations compared to general populations has been observed, especially regarding the risk of death from cardiovascular disease (14-18). Socioeconomically, people with OA have an increased risk of sick leave, a reduced employment rate, and early retirement, and the productivity costs of work loss are expected to increase by 46% from 2010 to 2031

in Canada (19). Recently, the total medical and non-medical expenses caused by OA are estimated to be an annual cost of $ 460 billion in the USA (20).

1.2. OSTEOARTHRITIS AND TOTAL KNEE ARTHROPLASTY: PATHOLOGY AND SYMPTOMS

1.2.1. PATHOLOGY

Osteoarthritis is a disease that occurs in the synovial joints. It is most commonly observed in the hips, knee, hand, and spine joints and often affects several joints (5,21,22). Contrary to earlier assumptions, OA is now considered a *whole disease* and not only a disease related to the articular cartilage (23). The onset of OA can be caused by cell stress and extracellular matrix decomposition in the joint (21,24). The quality of the extracellular matrix is crucial for preserving the functional properties of the cartilage (21). The OA can be initiated from an abnormality in any of the synovial joint tissues, including articular cartilage (25), subchondral bone (26), ligaments (25), menisci (27), periarticular muscles (28), peripheral nerves (25), and/or synovium (29). These abnormalities can be caused by biomechanical (26,30), biochemical (31), and/or genetic factors (32). Osteoarthritis is characterized by degenerative changes in the articular cartilage and subchondral bone as the result of lack of joint regeneration (21,25,30). These changes lead to synovitis and thickening of the joint capsule (21,33). The loss of cartilage and the subsequent osteophyte formation causes joint space narrowing and structural changes in the bone (21,26,31). The structural changes of the bone and joint can gradually develop into malalignment of the joint (26). This stage of OA progression represents a vicious circle, leading to increased load-bearing of the affected focal areas of cartilage and bone. Thus, further cartilage damage and remodeling of the underlying bone occur, which creates further malalignment and degradation (26,30).

1.2.2. SYMPTOMS

Pain is the dominant symptom of OA (22,34-36). Other symptoms include joint stiffness (21,22,25,34,37), crepitus (21,22,37), swelling (21,22,37), reduced joint movement (21,22,37), and joint instability (22,37). These symptoms can progressively impose impaired sleep (25), mood changes (25), decreased QOL (25), and pain-related psychological distress (22,37). Furthermore, physical performance limitations (22,25,34,37), such as the impaired ability to walk and climb stairs, can limit the participation of previously appreciated activities, which leads to further reduced QOL (25).

In the initial phase of OA, pain is often intermittent and mainly occurs during weight-bearing activities. When the pain becomes more frequent and unpredictable, patients tend to characterize their pain as intolerable (22). This progression and chronification of pain, along with unacceptable activity limitations and severe end-stage OA, often

leads to these patients being offered a total knee arthroplasty (TKA) (10,22). The TKA procedure is regarded as a successful treatment for OA and has shown excellent results from a prosthesis perspective (38,39). However, it is estimated that about 20% of patients undergoing knee joint replacement will experience chronic pain following their surgery (10,22,40,41). The chronic postoperative pain is often followed by functional limitations with reduced walking distance and difficulties with climbing stairs and rising from a chair (39). Low QOL (40,42), and poor patient-reported outcomes (42) are exhibited when experiencing chronic pain after TKA. Psychological symptoms in terms of depression (38,43), anxiety (43,44), pain catastrophizing (45-47), fear-avoidance behavior (48) and poor pain self-efficacy(49) have all been associated with chronic pain following TKA. However, conflicting evidence for these psychological traits is present (50), making the impact of these parameters uncertain (49).

Following the TKA surgery, problems can arise that can lead to a revision TKA. The most common causes of revision TKAs are infection, aseptic loosening of the implant, and periprosthetic fracture (10,51). Revision TKAs have also been used as a treatment for unexplained (e.g. not due to implant or infection factors) chronic pain after TKA (52), but the benefits of this have been questioned because of the low rates of treatment success (53). The positive effects, often seen after a primary TKA, are not as evident after revision TKA (52,54) and, therefore, revision TKAs do not appear to be an effective treatment of unexplained chronic pain after TKA (40,52,53).

1.3. OSTEOARTHRITIS AND TOTAL KNEE ARTHROPLASTY: CHRONIC PAIN AND PAIN SENSITIZATION

1.3.1. CHRONIC PAIN

In their taxonomy, the International Association for the Study of Pain stipulates that when the pain has been present for at least three months, it is defined as chronic pain (55). The exact factors that influence the transition from acute to chronic pain are not completely understood (34). Initially, the OA pain is intermittent and is often related to loading and weight-bearing activities, which is believed to be a typical trait for nociceptive OA pain (56). The nociceptive pain input can originate from structural changes in the OA joint and synovitis (57). This can lead to peripheral sensitization (57), which is commonly observed as a reduction in pressure pain thresholds (PPT) (56,58). Over time, the continued nociceptive input can result in pain sensitization (see section 1.3.2), which can become a contributor to the chronic pain pathophysiology (22,56,57).

The mechanisms and pathophysiology of OA pain are complex (57) and not fully understood (56). The progression towards chronic pain is thought to involve a combination of local pathological processes in and around the joint, genetic and metabolic factors, and neuronal changes at several levels, including peripheral and/or

central sensitization, reduced descending inhibition, and atrophy of cortical areas (56). The causes of chronic pain after TKA are largely unexplained (59). Similar to the chronic pain mechanisms in OA, peripheral and central sensitization has been observed in chronic pain patients following TKA (59,60). Patients have been shown to have complex causes of pain and, overall, it has been suggested that the chronic pain in patients after TKA is predominantly centrally driven (59,60). Similarly, in patients with chronic pain after revision TKA, signs of widespread pain, hyperalgesia, and enhanced temporal summation have been observed, indicating pain sensitization (61).

Chronic pain should be considered in a biopsychosocial framework, which highlights the multifactorial reasons for chronic pain (35,36,62,63). Thus, the severity of chronic pain can be influenced by factors such as sleep (22,25), mood/depression (22,43), systemic inflammation (64), and pain catastrophizing (45-47). Therefore, a biopsychosocial approach is important when managing patients with chronic pain (62,65).

1.3.2. PAIN SENSITIZATION

Pain sensitization has been proposed as an important factor in developing chronic pain (66,67). The International Association for the Study of Pain defines sensitization as "*Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs*" and distinguishes between central and peripheral sensitization (68). Central sensitization refers to "*increased responsiveness of nociceptive neurons in the central nervous system*" whereas peripheral sensitization refers to "*increased responsiveness and reduced threshold of nociceptive neurons in the periphery*" (68). Sensitization was initially described in animal models (69). In animals, it is possible to assess the development of sensitization using invasive measurements in the spinal cord and brain (70,71). In humans, it is possible to measure sensitization as a proxy, parallel to the output in animals (70). Animal studies have observed findings of hyperalgesia and allodynia (i.e. pain experienced due to a stimulus that would not normally induce pain) in pain-sensitization models, which infer that these mechanisms, when observed in humans, could be interpreted as signs of pain sensitization (71).

The mechanisms behind pain sensitization are not completely elucidated (56) and are thought to include both central and peripheral aspects, which can lead to the development and maintenance of chronic pain (72). This pain hypersensitivity is thought to be caused by initial nociceptive inputs, leading to amplification of neural signals and hyperexcitability of nociceptors (56,66,67,72). These structural changes can occur due to the plasticity of the nervous system (66,67,72). An important element of central sensitization is the "wind-up," which refers to repetitive stimuli that lead to temporal summation of pain and, thereby, a pain response (72). If central sensitization is present, this hyperexcitable state will lead to enhanced temporal summation, which

will generate a higher pain response than in healthy controls (72,73). Pain sensitization can manifest itself as allodynia (67,74) (pain response from a non-noxious stimulus), hyperalgesia (67,73,74) (increased pain response from a noxious stimulus), and widespread pain symptoms (67,74,75). Several studies have observed pain sensitization in OA patients (58,76), TKA patients (59,60), and in patients after revision TKA (61), thereby highlighting the importance of pain sensitization for the development and maintenance of chronic pain in chronic pain conditions (56,72).

Descending inhibition is another mechanism of interest in pain sensitization, and this mechanism has been described as a further important factor behind the development of chronic pain (77,78). In animal studies, the inhibitory control of nociceptive excitability, through lower brainstem mediated inhibitory mechanisms, can be observed (70,79). Originally, this was termed diffuse noxious inhibitory control in animals (80). In humans, this descending inhibition mechanism is referred to as conditioned pain modulation (CPM) (80) and describes the mechanisms by which the brain can modulate pain-facilitating signals using pain inhibitory signals (70,81). In humans, it is not possible to differentiate between inhibition and facilitation, and only the net sum can be assessed (70,80). Therefore, CPM is thought to reflect the balance between descending pain inhibitory and facilitatory mechanisms (56,80,82,83). In most healthy subjects, a CPM effect can be observed (78), although variations occur (81,84), whereas in patients with chronic pain conditions, often no CPM effect is observed (79,81,85,86). However, it is not uncommon to observe variation in the distribution of CPM responders and non-responders (83,86-89). This variation of CPM effect in patients with chronic pain is not fully understood (90).

Pain sensitization can be measured using different methods and no gold standard for evaluating pain sensitization exists (76,91,92). Quantitative sensory testing (QST) has been used for mechanistic profiling of pain mechanisms and pain sensitization (76,93,94). These methods include the measurement of mechanical and thermal detection thresholds, wind-up, mechanical and thermal pain threshold and sensitivity, a thorough protocol for QST has been developed (95,96). However, QST tests are time-consuming, require the introduction and teaching of the methods and costly equipment, which hinders the implementation of these methods in routine clinical settings (97-99). This highlights the need for the development of clinically applicable bed-side tools. Currently, it is suggested that the measurement of pain sensitization could include evaluation of temporal summation of pain, pain thresholds using PPT algometers, and pain hypersensitivity using pinpricks or a brush, which should be evaluated in localized and extra-segmental areas (73,97). Conditioned pain modulation evaluation has been proposed, which would use the cold presser test as conditioning stimulus and PPTs as test stimulus (83,100), and cuff-induced pressure pain as both conditioning and test stimuli (101,102). Challenges of implementing these methods into routine clinical settings are present due to the requirement of laboratory equipment, such as an ice-water bath or computer-controlled cuff pressure algometry. This warrants the development of clinically applicable CPM tools (103).

1.4. OSTEOARTHRITIS AND TOTAL KNEE ARTHROPLASTY: TREATMENT OF CHRONIC PAIN, PAIN SENSITIZATION, AND PHYSICAL PERFORMANCES

1.4.1. CLINICAL PRACTICE GUIDELINES

Numerous clinical guidelines and systematic reviews have highlighted exercise and education as first-line treatments for hip and knee OA (104-109). The introduction of OA management programs, such as GLA:D (110), backed by evidence-based knowledge (111), has led to joint replacement surgery being recommended as the last treatment option (109) (Figure 5).

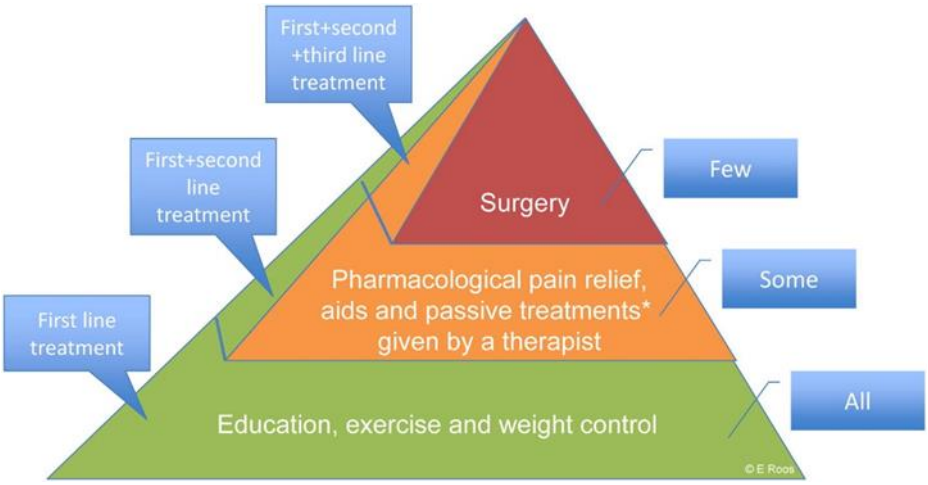


Fig. 5. The osteoarthritis treatment pyramid. Osteoarthritis of the hip and knee is best managed using education, exercise, and weight control with the addition of pharmacological and surgical interventions when needed. All patients should be offered first-line treatment, while some will need second-line treatment, and few will need third-line treatment. *Passive treatments include manual therapy, acupuncture, and other treatments given by a therapist and not requiring an active lifestyle change by the patient. Figure and text are reprinted with permission (109).

While pharmacological treatment has been conditionally recommended as a treatment for OA (104), evidence suggests that exercise is prescribed less frequently than pharmacological or surgical treatments (112). Analysis from the United States has shown that opioid and non-opioid medications were prescribed more frequently than physiotherapy and counseling for the management of chronic musculoskeletal pain, including OA (113). No clinical or standardized regimens are available to patients with chronic pain after TKA (114,115). Since no clear treatment recommendations are available, treatment is more likely to be based on the health-care practitioner's

experiences and preferences rather than on evidence-based knowledge. High-quality studies examining possible treatment options are, therefore, warranted (114,115).

1.4.2. EXERCISE AS TREATMENT

Exercise is defined as "*a subcategory of physical activity that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of one or more components of physical fitness is the objective*" (116). Given this broad definition, a variety of different types of exercise as treatment exists. Overall, exercise can be categorized as aerobic or strengthening and can be performed as land-based or aquatic exercise, or it may focus on neuromuscular coordination (117). The use of exercise as a treatment for OA has recently been shown to elicit moderate-to-high effects on pain and physical performances (118,119), with no single type of exercise superior to another (106,117,120).

The mechanisms behind the effect of exercise on chronic pain are not fully understood (65,121,122). It has been suggested that central, peripheral, systemic, and psychological effects occur because of exercising (117,123,124). Reduced pain sensitivity following exercise is often referred to as exercise-induced hypoalgesia (125-127). Exercise is thought to induce activation of the endogenous opioid and serotonin systems and through enhanced activation of the CPM system, which results in endogenous analgesia (123,125,128). The systemic effects have been proposed to occur due to an increase in anti-inflammatory cytokines, possibly resulting in reduced systemic inflammation (124,129,130). However, the influence of exercise on systemic inflammation is not fully known (117). The psychological effects of exercising may relate to less pain catastrophizing, less fear of movement, and improved self-efficacy, which are elements involved in the presence of chronic pain (123,131). Furthermore, the sensorimotor function can be mediated by pain (35,117). This can result in alterations in motor unit recruitments and incomplete activation of the muscles, which can lead to poor coordinated timing of muscle contractions, joint instability, and lack of postural control (132-134). Exercise has been shown to induce functional gains in muscle strength, proprioception, and mobility in patients with chronic pain following exercise (117,121,135). Such peripheral improvements are associated with pain relief in knee OA patients (121,127,135). Improvements in physical performances following exercise have been observed in patients with knee OA and after TKA, including improved walking distance and speed (111,136-139), improved ability to climb stairs (137,138,140), improved ability to perform functional tasks such as chair rises (137,140) and timed up and go (111,138), and increased muscle strength (139,141).

Neuromuscular exercise has been widely used as a treatment for hip and knee OA and after TKA surgery (111,139,142,143). Neuromuscular exercise consists of functional, weight-bearing exercises, which focus on the quality of the movements as well as optimal activation and loading of the muscles, thereby enhancing sensorimotor

control, joint alignment, and postural control (134,143). Neuromuscular exercises have been demonstrated to be effective in treating pain and improving physical performances in patients with hip and knee OA (134,139,144) and as an early post-operative treatment after joint replacement (111), but they have not been investigated as a treatment option for patients with chronic pain after TKA.

1.4.3. PAIN EDUCATION AS TREATMENT

Education as a treatment for patients with chronic pain has traditionally been based on a biomedical approach, but the increased knowledge of the multifactorial reasons behind chronic pain has led to a shift in the education focus towards a biopsychosocial approach (145,146). The predominantly patient-centered focus, rather than an anatomical focus, is believed to be important for the management of chronic pain (63,147). This has led to the development of pain neuroscience education (PNE), which focuses on explaining the multifactorial nature of chronic pain, the characteristics of acute and chronic pain, how pain can become chronic (plasticity of the nervous system), and the multifactorial factors that can influence the presence and experience of chronic pain (146,148). Pain neuroscience education has been suggested as a useful type of education for patients with chronic pain (147,148). Pain neuroscience education aims to re-conceptualize the beliefs about pain and decrease the potential threat experienced from the pain, which involves less pain catastrophizing and less kinesiophobia (146,147,149). Studies that implement PNE as part of the pain management have shown mixed results with either similar effects on pain outcomes as usual care (i.e. traditional education) (146,150), clinically non-significant changes (147), improved pain outcomes (151,152), or improvement in psychological parameters, such as pain catastrophizing and kinesiophobia (146,147,151-153). Pain neuroscience education has been proposed to be most efficient when delivered in conjunction with exercise (149,152). Pain neuroscience education has mainly been investigated for its role in treating chronic musculoskeletal disorders (147,151,152) or as a preoperative treatment to prevent post-operative pain (146,150). It has never been used as a later phase post-operative treatment for patients with chronic pain after TKA.

1.4.4. TREATMENT OF PAIN SENSITIZATION

Pain sensitization appears to play an important role in the development and maintenance of chronic pain (56), and it attracted interest in the exploration of how pain sensitization evolves and the establishment of effective treatment options. Non-conservative interventions, for example, knee-replacement surgery, have been examined for their effect on pain sensitization. Since pain sensitization is believed to be initiated by peripheral nociceptive input (56,66,67,72), surgical treatment has attempted to eliminate the source of the nociceptive input based on the assumption that this might reverse or "remove" the pain sensitization (154). Results are conflicting and some studies have reported a decrease in pain sensitization following TKA (155-

157), whereas others report no effect on pain sensitization following TKA (158,159) or even widespread sensitization in patients with pain following revision TKA (61). Several studies have examined the effect of pain sensitization on treatment outcomes and found pain sensitization to predict a worse outcome after TKA (100,160,161), although a systematic review concluded that the findings of the predictive value regarding chronic postoperative pain are inconsistent (162).

Conservative interventions have also been investigated as treatments of pain sensitization and have consisted of physical activity, exercise, education, as well as manual therapy and pharmacological treatment, which are beyond the scope of this thesis. As with the outcomes following surgical interventions, conflicting evidence exists. Most studies demonstrate that exercise decreases pain sensitization (157,163-165), but have also been shown not to modulate pain sensitization (159). In a systematic review and meta-analysis, exercise decreased pain sensitization immediately following exercise, but not after a period of exercising (166). The authors concluded that limited evidence formed the base for their findings (166). Pain sensitization in knee OA patients has been shown to predict non-response from physiotherapy treatment that consisted of exercise programs (167). Pain neuroscience education has been proposed as a treatment option for pain sensitization (148,168), possibly by reducing pain catastrophizing and kinesiophobia (146,147,149). As with the other listed interventions, results are conflicting with evidence pointing both towards decreased pain sensitization following PNE in some studies (149,169) and no changes in pain sensitization in other studies (164,170). Overall, pain sensitization appears to be somewhat treatment-resistant, and more research regarding this topic is required to establish an effective treatment (148,171). Because of the complex and multifactorial mechanisms behind chronic pain and pain sensitization, it has been argued that studies combining multimodal interventions, for example, exercise and education, are warranted (172).

1.5. SUMMARY OF BACKGROUND

Figure 6 provides a summary of the background.

Figure 6: Fact box

Multifactorial mechanisms underlie chronic pain due to knee OA or after TKA and include several factors, such as local pathological processes in the joint, genetic and metabolic factors, and pain sensitization.

Pain sensitization appears to be an important feature of chronic pain mechanisms, highlighting the need for clinically applicable bed-side tools to measure pain sensitization in routine clinical settings.

Clinical guidelines have firmly established recommendations of conservative treatments, such as exercise and education for knee OA patients. No evidence-based clinical guidelines or treatment recommendations are available for patients with chronic pain after TKA.

Neuromuscular exercise is effective for decreasing pain and improving physical performances in knee OA patients, and pain neuroscience education has been proposed as a useful treatment for chronic pain. This suggests that a combination of neuromuscular exercises and pain neuroscience education could potentially be an effective treatment for patients with chronic pain after TKA.

1.6. AIMS AND HYPOTHESIS OF THE PHD PROJECT

The PhD thesis aims to

1) Examine pain, pain sensitization, CPM, patient-reported outcomes, and physical performances in patients with chronic pain after knee OA or TKA by using quantitative pain assessment and evaluating outcomes after conservative interventions.

The specific aims and hypotheses of the individual studies:

Study I:

1) Develop a new and feasible screening test to evaluate CPM in clinical settings.

It was hypothesized that a simple, handheld, spring-based pressure algometer as test stimulus and a standard clamp as a conditioning stimulus would be able to induce a CPM effect in healthy subjects and that the proposed method would be reliable.

Study II:

2) Profile and compare pain outcomes, pain sensitization, patient-reported outcomes, and physical performances in patients with chronic pain from knee OA or after TKA using clinically applicable bed-side methods to evaluate pain sensitization and CPM. Furthermore, to examine associations between physical performances, patient-reported function, pain intensity, and quantitative sensory profiling outcomes.

The hypothesis was that indications of pain sensitization (defined as temporal summation of pain) would be more prevalent in patients with chronic pain after TKA compared to OA patients.

Study III:

3) Analyze the benefits of a three-week intensive, multimodal rehabilitation regimen on pain, patient-reported outcomes, and physical performances in patients with pain and impaired physical performances after primary or revision TKA.

It was hypothesized that pain intensity, patient-reported outcomes, and physical performances would improve after the three-weeks of intensive, multimodal rehabilitation.

Study IV:

4) Investigate the effects of a 12-week neuromuscular exercise program combined with PNE on pain outcomes, pain sensitization, patient-reported outcomes, and physical performances in patients with chronic pain after TKA.

The study hypotheses propose that treatment consisting of neuromuscular exercises in conjunction with PNE can decrease pain intensity and pain sensitization and improve patient-reported outcomes and physical performances after 12 months.

CHAPTER 2. METHODS

2.1. STUDY DESIGN

Study I was a test-retest reliability study and study II was a cross-sectional profiling study. Study III and IV were/are intervention studies. Study III was a retrospective cohort study and study IV is an ongoing randomized controlled superiority trial (RCT) with a 1:1 treatment allocation. The study IV manuscript is a protocol for the ongoing trial.

2.2. POPULATIONS

2.2.1. STUDY I

Study I consisted of two cohorts of healthy subjects. The cohort for reliability evaluation consisted of 22 subjects and the cohort for the methodological evaluation consisted of 29 subjects. All subjects were recruited using postings on the Aalborg University campus site. According to the inclusion criteria, subjects had to be between 18-40 years old, did not have any pain, and were not allowed to consume alcohol or pain medication on the days of the test. The reliability part was conducted according to the Guidelines for Reporting Reliability and Agreement Studies (173). The study was conducted according to the Helsinki declaration and the local ethics committee of the North Denmark Region approved the study (N-20170088). Oral and written information were provided to the subjects prior to inclusion and informed consent was obtained from all subjects (study I).

2.2.2. STUDY II

Study II included a population of 70 patients with chronic pain from knee OA (n= 46) and chronic pain after TKA (n= 24). Potential eligible patients were identified using patient medical journals from the Department of Orthopedic Surgery, Aalborg University Hospital, Denmark, and from the outpatient clinic Center for Clinical and Basic Research, Aalborg, Denmark. Patients were eligible to participate if they fulfilled the inclusion criteria of 1) knee OA diagnosis according to the American College of Rheumatology criteria (174) based on clinical and radiographic evidence of $\geq$ grade 2 or having a primary TKA, 2) duration of pain for at least six months, 3) average daily pain intensity for the last week of at least 4/10 on a numerical rating scale (NRS, with “0” representing “no pain” and “10” representing “worst pain imaginable”), 4) aged between 40-80 years, and 5) body mass index (BMI) between 19-40 kg/m2. Exclusion criteria were 1) secondary causes of arthritis to the knee, 2) surgery (including arthroscopy) of the knee within the three months before inclusion, 3) acute pain affecting lower limb or back at the time of participation, and 4)

rheumatoid arthritis, neurologic illnesses or primary pain area other than the knee. The study adhered to the guidelines from the Strengthening the Reporting of Observational Studies in Epidemiology Statement (175). The study was conducted according to the Helsinki Declaration and was approved by the local ethics committee of the North Denmark Region (N-20170088). Oral and written information were provided to the subjects prior to inclusion and informed consent was obtained from all subjects (study II).

2.2.3. STUDY III

Study III included a population of 217 patients with primary (n= 166) or revision TKA (n= 51). All patients were referred to a three-week rehabilitation stay at Montebello, Department of Rehabilitation, North Zealand's Hospital, Denmark. To be referred to the rehabilitation department, patients must have had post-surgical complications, for example, persistent pain, continued functional impairment, lack of effect from initial post-surgical rehabilitation, infection, or implant failure. The patient's surgeon or family physician evaluated whether post-surgical complications were present. Because retrospective, register-based data was used for the analysis, the local ethics committee of the North Denmark Region waived the need for ethical approval. The Danish Data Protection Agency approved the study (study III).

2.2.4. STUDY IV

The ongoing RCT aims to include 120 patients with chronic pain after primary TKA. Patients will be recruited from the Department of Orthopedic Surgery, Aalborg University Hospital, Denmark. Using a computer-generated random numbers system, the included patients are being randomized in a 1:1 ratio to receive either 1) a neuromuscular exercise program (NEMEX-TJR) and PNE or 2) PNE alone. Screening of eligibility is conducted for patients referred to the orthopedic department as well as those using the hospital's research database to identify patients with TKA. Inclusion criteria are 1) age between 40-80 years, 2) BMI between 19-40 kg/m^2, 3) primary TKA due to OA and for at least 12 months post-operatively, 4) duration of knee pain for at least 6 months, and 5) average daily pain intensity for the last week of at least 4/10 on NRS. Major exclusion criteria were 1) chronic pain due to implant failure that requires revision surgery, 2) secondary reasons for arthritis in the knee, 3) primary pain area other than the knee (e.g. low back pain), or neurological illnesses. The study protocol conformed to the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (176), and study interventions were described according to the Template for Intervention Description and Replication checklist (177) and the Consensus on Exercises Reporting Template checklist (178). The study is being conducted according to the Helsinki declaration, and the local ethics committee of the North Denmark Region has approved the study (N-20180046). Before patient inclusion, the trial was registered at ClinicalTrials.gov

(NCT03886259). Oral and written information are provided to the subjects prior to inclusion and informed consent is being obtained from all subjects (study IV).

2.3. INTERVENTIONS

2.3.1. STUDY III

Patients referred to the rehabilitation department will undertake a standardized, multimodal rehabilitation regimen over three weeks. The rehabilitation regimen consisted of group-based exercise derived from evidence-based exercise programs (143,179). The general focus of the various exercise sessions was to promote neuromuscular function, the flexibility of muscles and joints, postural control, walking ability by re-training gait patterns, muscle strength, and cardiovascular capacity. Patients attended two to four exercise sessions per day, with each session lasting 30-50 min. For further information on the specific exercises and exercise frequency and magnitude, please refer to the additional files of the study III manuscript. Load, difficulty level, and magnitude of exercise sessions were personalized according to the individual level of the patients and were based on parameters such as physical ability, pain, and fatigue. Patients attended educational sessions that provided information on pain self-management, the prosthetic knee implant, the importance of exercising, and the planning of continued exercising and self-management following discharge. Physiotherapists supervised all rehabilitation activities, including the educational sessions (study III).

2.3.2. STUDY IV

Interventions are taking place at three local Departments of Occupational Therapy and Physiotherapy (Aalborg, Farsoe, and Thisted), which are all part of the Aalborg University Hospital. Patients allocated to the neuromuscular exercise and PNE group are undergoing a 12-week rehabilitation period with bi-weekly exercise sessions that consist of the NEMEX-TJR program (143). The NEMEX-TJR program (for details see Ageberg et al. 2010) consists of a warm-up session of ergometer cycling, which is followed by a circuit program. The circuit program focuses on postural control, joint positioning and alignment, muscle strength, and functional exercises to improve the activities of daily living. The neuromuscular exercises are conducted in two to three sets with 10 to 15 repetitions in each set. Physiotherapists that are specially trained in the NEMEX-TJR program supervise all exercise sessions, thereby allowing individualization, for example, progression or regression of exercise difficulty. If the patients experience a major flare-up of pain related to exercise, the intensity and volume of the exercise are reduced until symptoms “are as usual” (143). Since the patients experience chronic pain, a time-contingent approach is used instead of a pain/symptom-contingent approach (154)).

The content of the PNE sessions is the same for both groups. The PNE consists of two group-based sessions of one hour each. One session takes place before the first exercise session and the other session takes place after six weeks of exercising. The PNE-alone group also receives the two sessions separated by six weeks. A PNE-trained physiotherapist conducts the sessions, which focus on topics such as the multifaceted causes of chronic pain and pain sensitization, including terms such as hyperalgesia, allodynia, and self-management. The group-based sessions allow for questions and experience sharing between the patients. Following the sessions, a short information leaflet, summing up the content of the educational sessions, is provided to the patients (study IV).

2.4. ASSESSMENT AND OUTCOMES

An overview of all outcome measures included in the thesis can be seen in table 2.

2.4.1. STUDY I

The assessment of CPM was performed at the laboratories of the Department of Health Science and Technology at Aalborg University. The experimental procedure for the reliability part lasted approx. 10 minutes and the procedure was repeated after 24-48 hours after the first session. For the methodological part, one session was performed, which lasted approx. 30 minutes.

For both study cohorts, demographic information regarding age, sex, and dominant leg were retrieved before testing. In the test-retest part, the CPM effect was measured using a spring-based 6 kg pressure algometer (SMI, Aalborg University) as the test stimulus and a standard clamp, which induced a pressure of 1.3 kg, as conditioning stimulus. While the subjects were lying in a relaxed, supine position, the test stimulus was applied to the tibialis anterior muscle belly at the dominant leg and the conditioning stimulus was applied to the ipsilateral ear lobe. For the test-retest part, the test stimulus was applied for 10 sec, followed by a pain intensity rating of the test stimulus using a 0-10 NRS (with “0” representing “no pain” and “10” representing “worst pain imaginable”) (180,181). Following the pain rating, the clamp was attached to the earlobe for 60 sec, followed by a pain intensity rating of the conditioning stimulus using an NRS. This was followed by the immediate application of the test stimulus for 10 sec, while the conditioning stimulus was still applied to the ear lobe. Lastly, the subjects rated the pain intensity of the test stimulus on an NRS, this time while the conditioning stimulus was present. To conduct the test-retest part, the second CPM test session was repeated 24-48 hours following the first test session (study I).

For the methodological part, the three test protocols were conducted in a randomized order, and tests were separated by a 10 min. break to avoid any carry-over effects. Test areas, subject position, and test procedures were identical with the areas

described in the test-retest part. The pressure algometer induced a force of 6 or 10 kg and the standard clamps induced a force of 1.3 kg each. An overview of the different CPM test protocols can be seen in Table 1. Pain intensity ratings for the methodological part were measured using a visual analogue scale (VAS, with one end representing "no pain" and the other end representing "worst pain imaginably) (180,181). The author of the thesis performed all CPM tests in both study cohorts (study I).

Table 1: Overview of experimental test protocols for the test-retest part and the methodological part.

Test protocol	Test stimulus	Conditioning stimulus
1 (Test-retest part)	6 kg spring-based pressure algometer applied for 10 sec	One standard clamp (1.3 kg) applied for 60 sec
2 (Methodological part)	10 kg spring-based pressure algometer applied for 10 sec	Two standard clamps (1.3 kg each) applied for 60 sec
3 (Methodological part)	10 kg spring-based pressure algometer applied for 10 sec	One standard clamp (1.3 kg) applied for 120 sec
4 (Methodological part)	6 kg spring-based pressure algometer applied for 10 sec	One standard clamp (1.3 kg) applied for 120 sec

2.4.2. STUDY II

The outcome assessment took place at the Department of Occupational Therapy and Physiotherapy at Aalborg University Hospital, Aalborg, Denmark, or at the outpatient clinic Center for Clinical and Basic Research, Aalborg, Denmark. The examination took place during a single session, which took approximately two hours. Patient characteristics were retrieved before assessing the outcomes and included age, sex, BMI, the time since knee OA diagnosis, and the time since surgery. The testing sequence was predetermined and started with pain and pain-sensitization-related outcomes, completion of patient-reported outcome measures, and finally, the physical performance tests. During the pain and pain sensitization examination, patients lay in a comfortable, supine position. The author of the thesis conducted all outcome assessments in the study (study II).

Pain intensity

Assessment of pain intensity was conducted by asking the patients to rate "the average pain intensity in the knee over the last week" on an NRS in which the perceived pain intensity was chosen from a range between 0-10 with "0" representing "no pain" and "10" representing "worst pain imaginable" (study II).

Pain sensitization

The quantitative sensory profiling of pain sensitization was conducted using clinical applicable bed-side tests (Figure 7). The bed-side screening tool consisted of mechanical pinprick pain sensitivity, mechanical temporal summation, and CPM.

Mechanical pinprick pain sensitivity was examined using a nylon filament of 0.7mm (Chicago Medical Supplies, Chicago, USA). The nylon filament was applied perpendicular to the skin (90° angle) until the filament was slightly bent, which occurs when a force of 75 grams is applied. The patients rated the pain intensity of the single pinprick on an NRS. This procedure was performed at two test areas, both localized at the most affected knee (index), 10 cm above the knee on the ventral thigh and extra-segmentally at the muscle belly of flexor digitorum superficialis, located on the medial side of the forearm.

Mechanical temporal summation was examined using the nylon filament described above. First, a single pinprick stimulus was applied perpendicular to the skin and the patients were asked to rate the pain intensity on an NRS. Thereafter, a series of 10 repeated pinprick stimuli were applied within an area of 1 cm^2 with a repetition rate of 1/second, which is similar to the single pinprick stimulus, and after the 10^{th} pinprick stimulus, patients rated the pain intensity on an NRS. The test was performed at the same test areas as for the mechanical pinprick pain sensitivity test.

Conditioned pain modulation was assessed using the bed-side CPM method developed in study I. As a test stimulus, the 6 kg pressure algometer was applied for 10 sec on the mid part of the tibialis anterior muscle on the contralateral side of the index knee. Following this, test stimulus pain intensity was rated on a VAS slider. As a conditioning stimulus, a standard clamp inducing a force of 1.3 kg was attached to the ipsilateral ear lobe for 60 sec. After 60 sec, the conditioning stimulus pain intensity was rated using a VAS slider and followed by the re-application of the test stimulus for 10 sec, while the clamp was still attached to the ear lobe. Thereafter, the test stimulus pain intensity was rated using a VAS slider (study II).

Figure 7: Illustration of the bed-side tools used for the quantitative sensory profiling of pain sensitization. 1: Standard clamps. 2: Nylon filament. 3: Spring-based pressure-algometer.

Patient-reported outcome measures

As patient-reported outcomes, the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire was included. The KOOS consists of five domains that encompass pain, symptoms, ADL, sports and recreational activities, and knee-related QOL. Each domain includes several items, which are scored on a 5-point Likert scale, ranging from 0 (none) to 4 (extreme) and the overall outcome score ranges from 0 (worst) to 100 (best) (182). The score of each domain was recorded as the outcome (study II).

Physical performances

Assessment of physical performance related to activities of daily living followed the recommendations from OsteoArthritis Research Society International (OARSI) (183)

and included the 30-second chair stand test, the 40-meter fast-paced walk test, and the stair climb test. The chair-stand test has the patient rising and sitting down as many times as possible in 30 seconds. Patients were instructed to place their arms across the chest and when rising and to fully extend their knee and hips. The numbers of repetitions were the outcome score (183,184). For the 40-meter fast-paced walk test, patients were instructed to walk as fast as possible along a 10-meter walkway, turn around a cone, walk back again, and repeat this for a total distance of 40 meters. Regular walking aids, such as a cane, were allowed if patients felt this was necessary. The time it took to complete the 40 meters of walking was registered as the outcome score (183,184). The stair-climb test consisted of nine stairs, which the patients were instructed to ascend and descend once as fast as possible. Patients were allowed to use the handrail to maintain balance if needed. The time it took to complete the test was registered as the outcome score (183,184) (study II).

2.4.3. STUDY III

The assessment of outcomes was part of the rehabilitation department's test battery for evaluating the overall effects of the treatment during the hospital stay. Therefore, assessments were made after hospitalization and again before discharge. Demographic information regarding age, sex, BMI, and time-since-surgery were registered. As the primary outcome, the patient-reported outcome measure KOOS, which was introduced and used in study II, was completed. For this study, the KOOS domain sports and recreational activities were not included, since it represents strenuous activities, such as running, jumping, and kneeling, and surgeons often explain to their patients that such activities are contraindicated. Assessment of pain intensity was made by asking the patient to rate the pain intensity during activity (e.g. walking, biking, or stair climbing) using an NRS. The physical performances of the patients was evaluated using tests recommended by the OARSI (183,184). The 6 min. walking test assesses the walking ability and aerobic capacity. Patients were told to walk along a 21 m long walkway, circumvent a cone, walk back again, and then repeat this for 6 min. Patients were instructed to walk as fast as possible and the number of meters covered during the test was the outcome score (183,184). The stair-climb test (introduced in section 2.4.2) consisted of a staircase of 22 steps, which the patients were asked to ascend and descend once as quickly as possible. The time it took to complete the task was the outcome score. The physiotherapists working at the rehabilitation department in the study period performed the outcome assessments (183,184) (study III).

2.4.4. STUDY IV

The assessment of outcomes is taking place at the Department of Occupational Therapy and Physiotherapy at Aalborg University Hospital, Aalborg, Denmark. The assessment of outcomes is conducted at baseline before randomization and is repeated at 3, 6, and 12 months after initiation of the intervention. Assessment sessions take

approximately two hours. Blinded outcome assessors are assessing the participating patients. The experiences with the development and use of the CPM paradigm in study I and II, the experiences with bed-side sensitization outcome measures in study II, the experiences with patient-reported outcomes and physical performances in study II and III, and the observed benefits of exercise as a treatment in study III led to the outcomes included in study IV. A detailed description of the included outcome measures forms part of the study protocol. The primary outcome is the KOOS[4], which is the mean score of the KOOS domains of pain, symptoms, ADL, and knee-related QOL (111). The secondary outcomes are categorized as patient-reported outcomes, pain and pain sensitization related outcomes, and physical performance outcomes (Table 2).

Table 2: List of outcomes included in the thesis. Outcomes are categorized as pain and pain-sensitization related, patient-reported, or related to physical performances. For a specific description of the outcomes, refer to the individual studies.

Outcome measures	Study I	Study II	Study III	Study IV
Pain and pain sensitization				
Pain intensity		x	x	x
Pain location				x
Pressure pain thresholds				x
Pinprick hyperalgesia		x		x
Mechanical temporal summation		x		x
Dynamic mechanic allodynia				x
Deep somatic hyperalgesia				x
Conditioned pain modulation	x	x		x
Patient-reported outcomes				
Knee injury and Osteoarthritis Outcome Score		x	x	x
PainDETECT				x

Fear-avoidance beliefs questionnaire				x
Global perceived effect				x
Pain catastrophizing scale				x
Physical performances				
Chair stand test		x		x
Walk test		x	x	x
Stair climb test		x	x	x
Maximal isometric quadriceps and hamstrings muscle strength				x
Leg extension power				x

Furthermore, adverse events because of the intervention, adherence to the intervention, and whether other treatments were received are continuously registered. Before baseline testing, demographic parameters, such as age, gender, BMI, time-since-surgery, comorbidities, and scores on the Hospital Anxiety and Depression Scale are recorded (study IV).

2.5. ANALYSES AND STATISTICS

2.5.1. STUDY I

A convenient sample of subjects was recruited for the study. Conditioned pain modulation effect was calculated as the difference between the pain intensity rating for the test stimuli with and without conditioning stimulus. The terminology used was that positive values indicated a CPM effect (i.e. a CPM responder) and negative values indicated no CPM effect (i.e. a CPM non-responder). The paired-samples t-test was used to evaluate the statistical significance of the CPM effect. As a measure of relative reliability, intra-class correlation coefficients (ICC) ($ICC_{2,1}$ for absolute agreement) were calculated, and as a measure of absolute reliability, the standard error of measurements (SEM) was calculated. Intra-class correlation coefficients can be interpreted as “poor reliability” if <0.4, as “fair reliability” if between 0.4 to 0.59, as “good reliability” if between 0.6 to 0.75, and as “excellent reliability” if greater than

0.75 (81,185). The standard error of measurement reflects the measurement error. Therefore, it can be interpreted as an estimate of the variation if tests were repeated without any changes occurring in the subjects (186) (study I).

2.5.2. STUDY II

Study II was part of a multicenter study, aiming at developing a bed-side test tool for evaluating pain sensitization (Sachau et al. manuscript under review). Therefore, no separate sample size calculation was made for study II. Mechanical temporal summation was calculated as pain intensity rating from repeated stimuli subtracted with the pain intensity rating from the single stimulus. Temporal summation of pain represents aspects of pain sensitization (58). The difference in test stimuli pain intensity ratings with and without conditioning stimulus reflects the CPM effect. Contrary to the terminology used in study I, a positive value indicated a facilitatory CPM response and a negative value indicated an inhibitory CPM response. The change of terminology was based on the recommendations from Yarnitsky et al., (187). Patients with signs of facilitated CPM were referred to as non-responders and patients with signs of inhibitory CPM were referred to as responders. Lack of inhibitory CPM represents aspects of impaired central pain inhibition (58).

Evaluation of normal distribution of data was made by assessing histograms, QQ-plots, and Shapiro-Wilk tests. There was a significant difference in BMI between the OA and the TKA group, why an ANCOVA test adjusting for BMI was conducted for the continuous outcomes. Analysis of associations between the physical performances, in other words, the 30-second chair stand test, the 40-meter fast-paced walk test, and the stair climb test (dependent variables) and pain intensity, mechanical pinprick pain sensitivity, temporal summation, CPM, and the KOOS subscales ADL and sports and recreational activities (independent variables) were conducted in each group separately. The analysis was conducted by applying multivariate linear regression models, using the enter method with an adjustment for age, sex, and BMI. The calculated β-coefficients suggest how strongly the independent variables influenced the dependent variables. The R^2 value is an indication of the ratio of variability explained by the independent variable or the adjusted regression model. Based on the explorative design of the study, exact p-values and effect sizes are reported to enhance interpretation and discussion of the between-group differences. Effect sizes were calculated as Hedges ´g and interpreted as < 0.2 = “very small,” 0.2 = “small,” 0.5 = “medium,” 0.8 = “large,” 1.2 = “very large,” and 2.0 = “huge” as provided by Sawilowsky (188) and Cohen (189) (study II).

2.5.3. STUDY III

For the primary outcome KOOS, an improvement of 8-10 points from baseline to re-test has been proposed as a minimal clinically important difference (MCID) (190). Data was evaluated for normal distribution using histograms, QQ-plots, and the

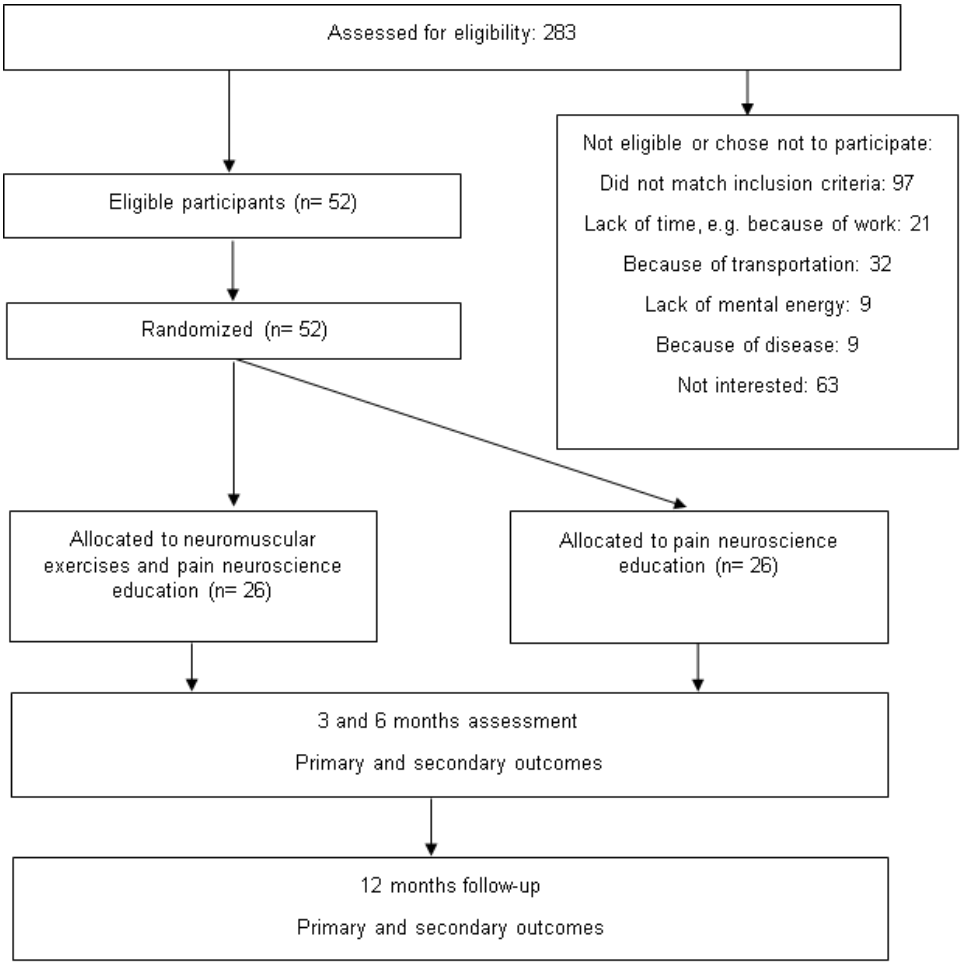
Shapiro-Wilk tests, and paired samples t-tests were applied for normal distributed and continuous outcomes. Non-normal distributed outcomes were analyzed using the Wilcoxon signed-rank test. To enhance interpretation, effect sizes were calculated as Cohen's $d = (Mean_2 - Mean_1) / SD_{pooled}$. Interpretation of effect sizes followed the suggestion by Cohen (189); 0.2 = "small," 0.5 = "medium" and 0.8 = "large" (study III).

2.5.4. STUDY IV

A sample size calculation was conducted using a difference of 10 points in the KOOS[4] as an MCID (190). The sample size calculation showed that to achieve a study power of 90% to detect an improvement of at least 10 points between groups for the KOOS[4], 49 patients would be required in each group. To account for possible dropouts and missing data, 60 patients will be included in each group. The intention-to-treat principle will be used for the statistical analysis regarding the primary outcome. Data is expected to be normally distributed and, therefore, data analysis will use a repeated measure mixed model with patients as random effect and time (i.e. baseline, 3, 6, and 12 months) and treatment (i.e. neuromuscular exercises and PNE or PNE alone) as fixed effects. Secondary outcomes will be analyzed in a similar way to the primary outcome. A per-protocol analysis will be made for the primary outcome in which patients with poor adherence to the interventions will be excluded. Poor adherence will be defined as attending less than 75% of the exercise sessions and not attending both PNE sessions. Similarly, a per-protocol analysis will exclude patients who receive additional surgery in their index knee during the follow-up period (study IV).

The ongoing RCT will include 120 patients of which 60 patients will be allocated to receive neuromuscular exercises and PNE, and the other 60 patients will receive PNE alone. The flow diagram (Figure 8) illustrates the status of recruitment (as of 05.01.2021). Due to the difficulty in recruiting patients and the COVID-19 pandemic, no results can yet be presented.

Figure 8: Flow chart for patient recruitment in the ongoing randomized controlled trial.



For all studies, the significance level was set to $P<0.05$. All analyses were made using the statistical software SPSS (version 25, SPSS Inc., Chicago, IL, USA).

CHAPTER 3. RESULTS

3.1. STUDY I:

Characteristics of the study populations are presented in Table 3.

Table 3: Characteristics for study I populations.

	Test-retest part (n= 22)	**Methodological part (n= 29)**
Age (mean ± SD)	23.6 (±2.4)	21.5 (±1.6)
Sex (males, %)	15 (68%)	9 (31%)
Dominant leg side* (right, %)	18 (82%)	26 (90%)

***** Leg side was determined by asking the question "which leg would you use to kick a football." Adapted from study I.

Averaged conditioned pain modulation effect

Conditioned pain modulation effects are shown in Table 4. It can be seen that none of the test protocols elicited significant averaged CPM effects. The number of subjects classified as having an inhibitory CPM effect (i.e. a CPM responder) varied between study cohorts and within test protocols (see Figure 1 in thesis at a glance). Conditioned pain modulation responder rates were nine (40%), 10 (45%), 13 (45%), 11 (38%), and 12 (41%) for test protocol 1 (session 1 and 2), test protocol 2, test protocol 3, and test protocol 4, respectively.

Table 4: Conditioned pain modulation (CPM) effect in study I. Positive values indicate a CPM effect.

	Conditioned pain modulation effect (95% CI)
NRS (test protocol 1 – session 1) §	0.3 ^{ns} (-0.37 ; 1.01)
NRS (test protocol 1 – session 2) §	0.2 ^{ns} (-0.20 ; 0.66)
VAS (test protocol 2) ^	0.2 ^{ns} (-0.17 ; 0.55)
VAS (test protocol 3) ^	- 0.1 ^{ns} (-0.55 ; 0.28)

VAS (test protocol 4) ^	0.0 [ns] (-0.45 ; 0.45)

NRS: Numerical rating scale. VAS: Visual analog scale. ns: Non-significant. CI: Confidence intervals. §: Study cohort for the test-retest part. ^: Study cohort for the methodological part.

The mean (±SD) conditioning stimulus pain intensities for test protocol 1 (session 1 and 2), 2, 3, and 4 were 4.4 (±1.7), 3.9 (±1.7), 2.9 (±1.8), 2.2 (±1.7), and 2.4 (±1.6), respectively.

Reliability measures

Table 5 shows the reliability outcomes for both relative (ICC) and absolute reliability (SEM) for the test stimuli with and without conditioning stimulus. Significant correlations for measurements both with and without conditioning stimulus were observed (ICC $model_{2.1}$ for absolute agreement, P: <0.000 and <0.000, respectively). The ICC coefficients were interpreted as "good" relative reliability.

Table 5: Test-retest measures of relative and absolute reliability

	Reliability study – test protocol 1 (n= 22)	
	ICC (95% CI)	SEM (NRS)
Test stimulus without conditioning stimulus (session 1 vs. session 2)	0.67* (0.36 ; 0.85)	1.9
Test stimulus with conditioning stimulus (session 1 vs. session 2)	0.72* (0.44 ; 0.87)	2.1

ICC: Intra-class correlation coefficient. SEM: Standard error of measurement. NRS: Numerical rating scale.*: p-value < 0.000. Adapted from study I.

Additional outcome measures can be found in the original manuscript (study I).

3.2. STUDY II

Patient demographics for both OA and TKA patients are shown in Table 6.

Table 6: Patient characteristics for the population in study II. Values are mean (SD) unless otherwise stated.

	Osteoarthritis patients (n: 46)	Total knee arthroplasty patients (n: 24)
Age (years)	66.4 (8.2)	66.5 (7.2)
BMI (kg/m2)	28.0 (3.7)	30.8 (4.5)*
Sex (males, %)	27 (59%)	9 (37 %)
Time since knee OA diagnosis (years) §	11.1 (7.6)	NA
Time since surgery (years) ^	NA	4.0 (1.9)

BMI: Body Mass Index. NA: Not applicable. * p-value = 0.007 between groups. § Time since osteoarthritis diagnosis is the period from being diagnosed with knee osteoarthritis to the day of the test. ^ Time since surgery is the period from the day of total knee arthroplasty surgery to the day of the test. Adapted from study II.

Pain intensity and pain sensitization

The BMI adjusted outcomes for pain and quantitative sensory profiling are listed in Table 7.

No between-group differences were observed for the adjusted pain and pain sensitization outcomes. Consequently, effects sizes were interpreted as "very small" for pain intensity (0.06), localized temporal summation (0.00), extra-segmental temporal summation (0.09), and CPM (0.15), and as "small" for localized (0.23) and extra-segmental (0.29) mechanical pinprick pain sensitivity.

Table 7: Results from pain intensity and quantitative sensory profiling. Estimates are adjusted for BMI and presented as mean (SE).

	Osteoarthritis (n: 46)	Total knee arthroplasty (n: 24)	Between-group difference (95% CI)	p-values
Pain intensity (NRS)	5.3 (0.3)	5.0 (0.4)	0.3 (-0.67 to 1.17)	0.589

Mechanical pinprick pain sensitivity, index knee (NRS)	1.4 (0.3)	1.1 (0.4)	0.3 (-0.64 to 1.20)	0.552
Mechanical pinprick pain sensitivity, extra-segmental (NRS)	1.2 (0.2)	0.9 (0.3)	0.3 (-0.42 to 1.01)	0.412
Mechanical temporal summation, index knee (NRS)	1.6 (0.2)	1.6 (0.3)	0.0 (-0.84 to 0.90)	0.949
Mechanical temporal summation, extra-segmental (NRS)	1.1 (0.2)	1.1 (0.2)	0.0 (-0.55 to 0.57)	0.974
Conditioned pain modulation § (VAS)	0.2 (0.2)	0.2 (0.3)	0.0 (-0.76 to 0.61)	0.828

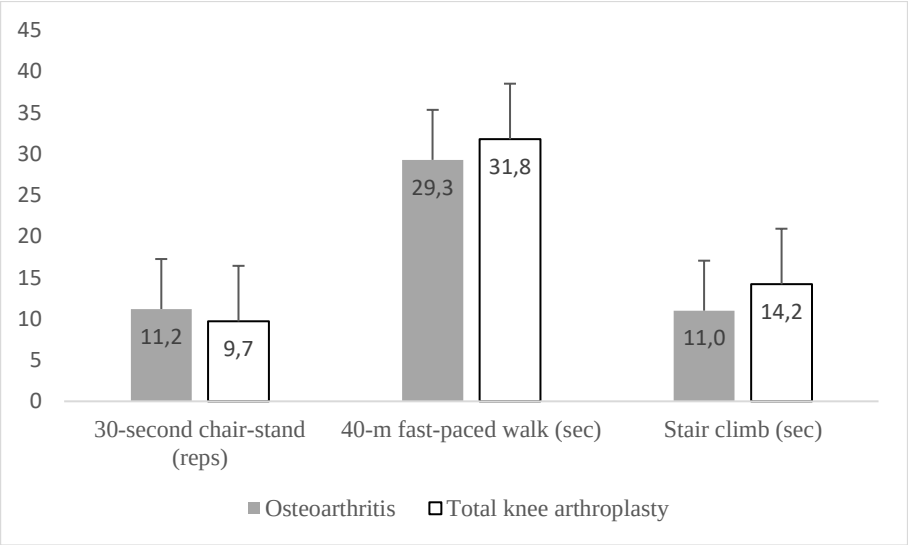
SE: Standard error. NRS: Numerical rating scale. VAS: Visual analog scale. CI: Confidence interval. § Positive values indicate facilitatory conditioned pain modulation. Adapted from study II.

No significant averaged CPM effect was observed in either group (P= 0.084 and 0.851, for the OA and the TKA groups respectively). The VAS pain intensity of the conditioning stimulus was 6.7 (±2.6) in the knee OA group and 5.4 (±2.3) in the TKA group. When CPM was analyzed and ranked for each individual, a distribution with both facilitatory and inhibitory CPM responses was observed (see Figure 1 in thesis at a glance).

Physical performances

It was observed that the OA group performed consistently better compared to the TKA group for the 30-second chair stand test (P= 0.015), the 40-meter fast-paced walk test (P= 0.081), and the stair-climb test (P= 0.002) (Figure 9). Effect sizes were interpreted as “medium” for the 30-second chair stand test (0.74) and the 40-meter fast-paced walk test (0.64) and as “large” for the stair climb test (0.98).

Figure 9: Outcomes, adjusted for body mass index, for the physical performances for both groups. Please note that units include seconds and repetitions.



Exact values are listed for each outcome. Adjusted means are presented with standard error. Reps: Repetitions. Sec: Seconds.

Patient-reported outcome measures

For the KOOS subscale sports and recreational activities, a significant difference was observed with the OA group reporting the best outcome (Table 8). For the KOOS subscales pain, symptoms, ADL and knee-related QOL, and minor and non-significant between-group differences were detected. Effects sizes were interpreted as "small" for the subscales pain (0.21), symptoms (0.41), ADL (0.21), and knee-related QOL (0.31) and as "medium" for the subscale sports and recreational activities (0.73)

Table 8: Outcomes for the KOOS subscales. Estimates are adjusted for BMI and presented as mean (SE).

	Osteoarthritis (n: 46)	Total knee arthroplasty (n: 24)	Between-group differences (95% CI)	p-values
KOOS pain	59.2 (2.5)	57.2 (3.5)	2.0 (-6.8 to 10.7)	0.653
KOOS symptoms	53.6 (2.2)	49.7 (3.0)	3.9 (-3.7 to 11.5)	0.311
KOOS ADL	61.9 (2.2)	61.4 (3.1)	0.5 (-7.2 to 8.2)	0.898

KOOS sports and recreational activities	26.3 (2.8)	12.2 (3.9)	14.1 (4.3 to 23.8)	0.005
KOOS knee-related quality of life	39.7 (2.3)	34.9 (3.2)	5.6 (-2.5 to 13.6)	0.171

KOOS: Knee injury and Osteoarthritis Outcome Score. SE: Standard error. BMI: Body mass index. ADL: Activities of daily living. Adapted from study II.

Associations for the osteoarthritis group

The KOOS sports and recreational activities and facilitatory CPM were significantly (p= 0.032 and p= 0.043, respectively) associated with the 30-second chair stand test (R^2 change: 0.094 and 0.088, respectively). Localized temporal summation was significantly (p= 0.031) associated with the 40-meter fast-paced walk test (R^2: 0.081). Localized temporal summation and facilitatory CPM were significantly (p= 0.007 and p= 0.029, respectively) associated with the stair climb test (R^2: 0.108 and 0.072, respectively). Estimates for the non-significant independent variables are presented in Table 3 of the study II manuscript.

Associations for the total knee arthroplasty group

The independent variables localized and extra-segmentally mechanical pinprick pain sensitivity were significantly (p= 0.035 and 0.017, respectively) associated with the 30-second chair stand test (R^2: 0.169 and 0.137). The independent variables KOOS ADL and sports and recreational activities were significantly (p= 0.012 and p= 0.026, respectively) associated with the 40-meter fast-paced walk test (R^2: 0.210 and 0.172, respectively). The independent variables KOOS ADL and sports and recreational activities were significantly (p= 0.017 and p= 0.001, respectively) associated with the stair climb test (R^2: 0.159 and 0.253, respectively). Estimates for the non-significant independent variables are presented in Table 4 of the study II manuscript.

3.3. STUDY III

Patient characteristics are shown in Table 9.

Table 9: Patient characteristics for the study III population. Values are mean (SD) unless otherwise stated.

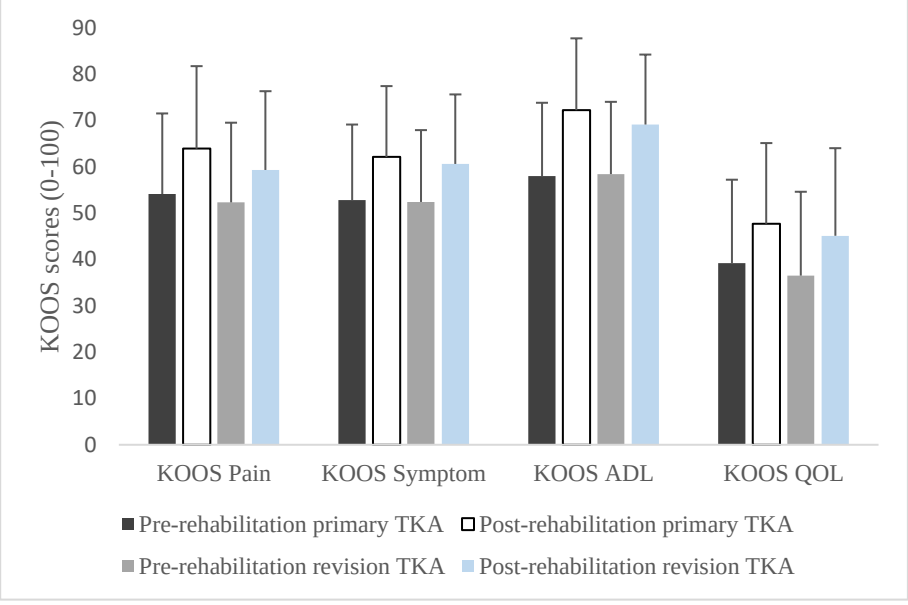
	Primary total knee arthroplasty (n: 166)	Revision total knee arthroplasty (n: 51)
Age (years)	64.0 (8.6)	62.2 (8.8)

BMI (kg/m^2)	28.9 (4.3)	28.3 (5.0)
Sex (males, %)	52 (31)	21 (41%)
Index leg (right, %)	87 (52 %)	30 (59 %)
Time-since-surgery (months)*	3.7 (5.9)	2.7 (2.4)

BMI: Body Mass Index. * Time-since-surgery: The period from the day of surgery (primary or revision total knee arthroplasty) to the date of hospitalization. Adapted from study III.

Significant improvements for the primary outcome KOOS were observed for both groups (Figure 10). For the primary TKA group, improvements ranged from 9.8 (95% CI 7.6 to 12.0, p< 0.000), 9.4 (95% CI 7.3 to 11.5, p< 0.000), 14.2 (95% CI 12.2 to 16.2, p< 0.000) and 8.5 (95% CI 6.1 to 10.9, p< 0.000) for the KOOS subscales pain, symptoms, ADL and knee-related QOL. For the revision TKA group, improvements ranged from 6.9 (95% CI 2.2 to 11.7, p= 0.005), 8.2 (95% CI 4.0 to 12.4, p< 0.000), 10.8 (95% CI 6.8 to 14.7, p< 0.000) and 8.6 (95% CI 3.5 to 13.8, p= 0.001) for the KOOS subscales pain, symptoms, ADL and knee-related QOL, respectively.

Figure 10: Knee injury and Osteoarthritis Outcome Score from baseline to post-rehabilitation for both groups.



KOOS: Knee injury and Osteoarthritis Outcome Score. ADL: Activities of daily living. QOL: Quality of life. TKA: Total knee arthroplasty. Error bars indicate standard deviation.

Effect sizes for the primary TKA group were interpreted as “medium” for KOOS pain (0.57), KOOS symptoms (0.58), and KOOS knee-related QOL (0.51) and as “large” KOOS ADL (0.88). For the revision TKA group, effects were interpreted as “small” for the KOOS pain (0.38) and KOOS knee-related QOL (0.46) and as “medium” for KOOS symptoms (0.54) and KOOS ADL (0.70).

The results for pain intensity during activity, the 6 min. walking test and the stair climb test for both groups can be seen in Table 9. All secondary outcomes improved significantly and effect sizes were interpreted as “medium” for pain intensity during activity (0.62) and the stair-climbing test (0.77) and as “large” for the 6 min. walking test (0.96) for the primary TKA group and as “small” for the pain intensity during activity and as “large” for the 6 min. walking test (0.81) and the stair climb test (0.82) for the revision TKA group. Additional outcome measures can be retrieved in the original manuscript (study III).

Table 9: Secondary outcomes for both groups in study III. Values are mean (SD) unless otherwise stated.

	Primary total knee arthroplasty (n: 166)			Revision total knee arthroplasty (n: 51)		
	Before rehab	Post-rehab	Change (95% CI)	Before rehab	Post-rehab	Change (95% CI)
Pain intensity during activity (NRS)	5.4 (2.9)	3.7 (2.6)	1.7* (1.3; 2.1)	5.4 (2.9)	4.6 (2.8)	0.8* (0.2; 1.3)
6 min. walking test (meters)	421.9 (91.6)	513.1 (97.9)	91.1* (82.4; 100.0)	407.7 (108.9)	496.6 (111.8)	88.8* (72.0; 105.7)
Stair climbing test (seconds)	34.8 (18.6)	23.2 (10.3)	11.6* (9.7; 13.4)	38.6 (24.7)	23.1 (9.8)	15.5* (10.6; 20.4)

NRS: Numerical Rating Scale. *: p-value < 0.005. Adapted from study III.

CHAPTER 4. DISCUSSION

In this section, the presented results are compared and discussed, both within the study I – IV and related to existing evidence from the literature. Possible mechanisms underlying the effect of exercise and the interaction between the multiple factors behind chronic pain and the significance thereof is addressed. The strengths and limitations of the specific studies and the overall thesis are discussed. Lastly, a conclusion based on the main findings from study I – IV is presented in combination with the relevant implications and perspective.

4.1. SUMMARY OF MAIN FINDINGS

The overall aim of the thesis was to examine pain outcomes, pain sensitization, CPM, patient-reported outcomes, and physical performances in patients with chronic pain after knee OA or TKA, by using quantitative pain assessment and evaluating outcomes following conservative interventions. Study I sought to develop a clinically applicable method to examine CPM. The results indicated "good" relative reliability (81,185) of the test stimuli, though the absolute reliability indicated substantial individual variation. No averaged CPM effect was observed in the healthy subjects, and in the population, a substantial variation in the CPM effect was observed in CPM responders and non-responders. Study II aimed at profiling and comparing outcomes regarding pain intensity, pain sensitization, CPM, patient-reported outcomes, and physical performances in populations with chronic knee OA pain and chronic pain following TKA. The results indicated that similar profiles for pain intensity, pain sensitization, CPM, and patient-reported outcomes were observed for the OA and the TKA population. Contrary to these findings, differences in physical performances were observed, with the OA group consistently performing better physically. As in study I, no averaged CPM effect was observed and a substantial variation in the CPM effect was seen, including both CPM responders and non-responders in the OA and the TKA groups. Study III investigated the effects of intensive, multimodal rehabilitation in a population of patients with post-surgical complications following primary or revision TKA. The results showed improvements in pain intensity, patient-reported outcomes and physical performances following three weeks of intensive, multimodal rehabilitation. Based on the lack of evidence regarding the management of chronic pain after TKA, study IV was initiated. This ongoing randomized controlled trial investigates the effect of exercise and PNE in a population of patients with chronic pain after TKA.

4.2. CHRONIC PAIN AND PAIN SENSITIZATION IN PATIENTS WITH KNEE OSTEOARTHRITIS AND TOTAL KNEE ARTHROPLASTY

By definition, pain is termed as chronic when it lasts for at least three months (55). In study II and study IV, the inclusion criteria of at least six months of pain was used, and for study IV, patients have to be at least 12 months post-operative (study II and IV). These criteria were applied to ensure that patients experienced chronic pain and features of pain sensitization and that no spontaneous recovery following the TKA procedure could be expected. This was based on findings that suggested that the duration of pain can be associated with increased pain sensitization (93) and that outcomes after TKA could improve for up to 6-12 months post-operatively (191,192).

Pain sensitization has been proposed as an important mechanism behind chronic pain (66,67,171). However, since pain sensitization can be measured only as a proxy and not directly (70,71,74), it is difficult to accurately conclude whether a patient is sensitized. Typically, heightened pain responses to painful stimuli (i.e. hyperalgesia), pain responses from non-noxious stimuli (i.e. allodynia), increased pain response from accumulated stimuli of equal intensity (i.e. temporal summation of pain), and the presence of widespread pain are interpreted as indications of pain sensitization (67,71,73-75). Especially, temporal summation of pain has been referred to as a symptom of a central pain mechanism, which indicates the presence of pain sensitization (58,71,167). Evaluation of pain sensitization outcomes has been proposed as a continuum of signs of pain sensitization more than the presence of or no presence of pain sensitization (71,171)).

Traditionally, somatosensory parameters have been examined using the QST protocol from the German Research Network on Neuropathic Pain (95,96), but more recently, studies have attempted to develop and evaluate possible bed-side methods to investigate pain sensitization that is not too time-consuming or requires expensive equipment ((99,193). Such bed-side methods are used in study II and IV and provide information on hyperalgesia, allodynia, and temporal summation of pain, which are mechanisms believed to indicate pain sensitization (99,193). Pain sensitization is thought to be driven and/or maintained by peripheral, nociceptive inputs (71,74,194,195). Studies demonstrate that elimination of the peripheral, nociceptive input can diminish pain sensitization (71,155,196,197). These observations indicate that pain sensitization could be reversed when the peripheral nociceptive inputs were removed, for example, following successful joint replacement surgery. It remains unknown why some patients suffering from long-lasting chronic pain (e.g. from knee OA) experience chronic pain after TKA and show signs of pain sensitization, whereas others will experience pain relief following TKA. The results and analysis from study IV will allow for an evaluation of how pain sensitization will change during the intervention period and the subsequent follow-up period. Such analysis could reveal whether improvements in pain intensity, patient-reported outcomes, and physical

performances can be achieved with or without changes in pain sensitization, which will allow to evaluate the impact of pain sensitization on these parameters.

4.3. CONDITIONED PAIN MODULATION

Study I aimed to develop an easy-to-use CPM method that could be applied in clinical settings. In the population of healthy subjects, no averaged CPM effect was observed. Instead, a substantial variation in CPM responders and non-responders were observed. In general, a CPM effect can be elicited in healthy subjects and impaired CPM can be observed in populations with chronic pain (81,83,85). However, several studies have observed substantial variation in CPM effects (84,86,87,89,90,198-201). It has been shown that the individual CPM effect is influenced by age (77,83,85,202), sex (83-85,201), test sites (199), type of test stimulus (198,203), and type of conditioning stimulus (198-200). To date, no specific CPM test paradigm can be identified as superior to other CPM test paradigms (80,89,187) and different types of test and/or conditioning stimuli can elicit different CPM responses in the same individual (198-200,203).

Klyne et al. (204) found that using PPT as a test stimulus was more valid for observing CPM effects compared to using pain responses as a test stimulus. In studies I and II, a pain response from the pressure algometer test stimulus was used to evaluate the CPM effect. Therefore, the lack of observed CPM effect in the healthy subjects in study I could have been influenced by the pressure pain response as a test stimulus and the CPM effects might have been different if measured using PPT. In study I, an ICC of 0.67 for test stimulus without conditioning stimulus and 0.72 for test stimulus with conditioning stimulus indicated that "good" relative reliability was achieved (81,185). Contrary to the relative reliability, the SEM values of 1.9 for test stimulus without conditioning stimulus and of 2.1 for test stimulus with conditioning stimulus indicated that absolute reliability was somewhat low, which was illustrated by a substantial individual variation in the CPM effect. Most CPM reliability studies focus on the relative reliability and, in general, these studies observe good-to-excellent relative reliability (81,101,198). Absolute reliability (e.g. SEM) is a measure of the measurement error of the observations and has, therefore, been suggested as a method to indicate whether a "true" CPM effect has been elicited (205). As observed in study I and II, substantial individual variations in the CPM effect has been detected in other studies evaluating absolute reliability (200,205). The substantial individual variations have been suggested to illustrate that different pain systems could be activated by different combinations of test and conditioning stimuli (e.g. cutaneous or deeper tissue stimulation) (198,200). However, this assumption needs further investigation.

In study I, both NRS and VAS were used as outcome measures for the pain response from the test stimuli. For the test-retest part, an NRS was used to evaluate pain intensity as it is frequently used in clinical settings and is an easy method to implement (97). In the methodological part, a VAS was used to evaluate pain intensity. The

method was changed since it was considered a possible bias that subjects were able to recall the exact first pain rating (without conditioning stimulus) when evaluating the second pain rating (with conditioning stimulus). Therefore, using a VAS slider was considered less prone to bias. The VAS and NRS have been observed to generate very similar pain intensities when used simultaneously (206). Therefore, the VAS was used to measure the pain intensity responses in study II.

Study II observed no significant, averaged CPM effect in the population with chronic pain because of knee OA or after TKA, which is in line with findings from other chronic pain populations (81,90,207). As seen in study I, a substantial variation between CPM responders, non-responders, and patients with no change in pain responses was observed. This implies that it might not provide sufficient information to only evaluate averaged CPM effects, but is important to evaluate individual CPM data to gain insight on individual variation. A recent CPM study demonstrated that approximately half of the included population of healthy subjects showed no signs of CPM effect (i.e. a non-responder) and that the CPM effect, measured as a change in pain intensity ratings, varied from -100% (pain inhibition, i.e. responder) to +112.5% (pain facilitation, i.e. non-responder) (201). Other studies observing substantial individual variations in CPM effect in healthy subjects, and which, therefore, include responders and non-responders, have proposed that averaged group-level CPM analysis may not be appropriate (89,103). Based on the novel observations from studies I and II as well as findings in recent CPM studies (89,103,201), it is recommended that future CPM studies should focus on individual information regarding CPM effect and responder or non-responder classification. However, how to truly classify individuals as responders or non-responders remains debatable and several suggestions have been made to determine a "true" CPM effect, allowing possible measurement errors to be taken into consideration (89,199,200,205,208). It remains to be investigated whether chronic pain patients with differences in CPM responses also exhibit different pain trajectories and, therefore, might respond differently to treatment interventions. The focus must remain on individual profiling of the CPM effect in chronic-pain patients to investigate this in future studies. It is expected that the completion of study IV will shed some light on this unclear aspect of pain modulation.

4.4. ASSOCIATIONS FOR PATIENTS WITH KNEE OSTEOARTHRITIS AND TOTAL KNEE ARTHROPLASTY

The explorative findings in study II revealed that signs of pain sensitization (measured as mechanical temporal summation) were associated with poorer physical performances in the OA group and that patient-reported function (KOOS subscales ADL and sports and recreational activities) were associated with physical performances in the TKA group (study II). While these findings should be considered as hypothesis-generating and have limitations (see section 4.8), the differences in

associations, despite similar pain profiles, are interesting and should be further investigated in studies with adequate statistical power.

The observed associations between pain sensitization and physical performances in the OA group confirm other findings in knee OA (209) and low back pain populations (210), although different methods to assess pain sensitization were used. Study II used mechanical temporal summation at the index knee as the indication for pain sensitization, whereas Guérard et al. used the presence of widespread pain and Echeita et al. used the questionnaire Central Sensitization Inventory (209-211). Similar to the findings in study II, both Guérard et al. and Echeita et al. observed variation in associations for physical performances and pain sensitization ((209,210). This intra-individual variation, where some pain sensitization outcomes are associated with physical performances and others are not, underlines that the exact mechanisms behind pain sensitization and the evaluation of physical performances are unexplained. It remains to be fully understood why signs of pain sensitization manifest differently in various outcomes and why pain sensitization can also be differently associated with physical performances. Studies have shown that physical performances are influenced by factors such as age, sex, BMI, physical activity levels, and pain catastrophizing, which adds further to multifactorial factors underlying these associations (35,209,210,212). Moreover, studies have shown that functional impairments and muscle weakness are present following knee joint replacement (213-216), which illustrates that such factors may also influence the pain experience, the self-reported function, and the physical performances after TKA. This reflection could vindicate that multimodal assessment of key elements (e.g. pain severity and intensities, quantitative sensory profiling of pain sensitization and CPM, patient-reported outcomes, and physical performances) in chronic knee pain patients should be undertaken to capture the individual factors of the patient's situation as a whole. Such an approach could potentially form the basis of personalized treatment.

4.5. PATIENT-REPORTED OUTCOMES IN PATIENTS WITH KNEE OSTEOARTHRITIS AND PRIMARY OR REVISION TOTAL KNEE ARTHROPLASTY

The KOOS questionnaire, consisting of the subscales pain, symptoms, ADL, sports and recreational activities, and knee-related QOL, revealed similar findings in study II and study III (results for pre-rehabilitation). Following the intensive, multimodal rehabilitation in study III, an improvement in all KOOS subscales was observed, elevating the KOOS scores to the highest values observed in study II and III. The KOOS subscale sports and recreational activities, which were included in study II, showed the lowest values, indicating that strenuous activities, such as squatting, kneeling, and twisting on the knee, impose the most difficulties. The KOOS sports and recreational activities subscale was not part of study III since many surgeons consider such activities to be contraindicated after TKA. Therefore, this domain was omitted during the patient assessment (study III).

In study III and IV, the KOOS questionnaire is the primary outcome. In intervention studies, it is important to evaluate whether an observed improvement can be considered a clinically, meaningful change (217-219). In studies III and IV, an MCID of 8-10 points and 10 points, respectively, are used as cut-off values to indicate a minimum change that can be regarded as clinically significant (190,220,221). However, the establishment of MCID values remains debatable and variations have been observed because of different methods to calculate the MCID, different patient populations, and differences in follow-up periods (217,219,222,223). Consequently, Singh et al. suggested an MCID of 8 points in a study of knee OA patients referred to an orthopedic surgeon, who had two weeks follow-up (223), whereas Goodman et al. suggested an MCID of 21 points for the KOOS pain subscale and 14 points for the KOOS ADL subscale in a population of patients having received TKA two years earlier (222). Lastly, Lyman et al., in their population of patients undergoing TKA and having two years of follow-up, suggested MCID values of 18 points for the KOOS pain subscale, 7 points for the KOOS symptoms subscale, 16 points for the KOOS ADL subscale, 17 points for the KOOS sports and recreational activities subscale, and 14 points for the KOOS knee-related QOL subscale (217). In summary, no universally accepted MCID values for the KOOS exists (219). Furthermore, it remains debatable whether values such as MCID should be reported at group-level or as percentages of individual subjects fulfilling the specified criteria (224).

4.6. PHYSICAL PERFORMANCES IN PATIENTS WITH KNEE OSTEOARTHRITIS AND PRIMARY OR REVISION TOTAL KNEE ARTHROPLASTY

Physical performance outcomes are recommended as measures to monitor the progress of treatment modalities in patients with chronic pain (183,225-227). Activities of daily living, such as walking, stair climbing, getting in and out of bed, and rising from a chair, are functions that are often impaired in patients with chronic pain because of knee OA or after TKA (22,25,34,37,39). In study II, significant differences for the 30-second chair stand test and the stair-climb test were observed between the OA and TKA groups. Similar pain and pain sensitization outcomes between the groups indicates that other factors are important for the physical performances in patients with chronic pain after TKA. Firstly, it could be explained by low levels of physical activity after TKA, which leads to impaired physical performances. Studies have shown that patients undergoing TKA failed to adhere to the general health recommendations of being physically active, in other words, activity of moderate intensity for 30 minutes at least five days per week (228-230). No data for physical activity levels were collected in study II and, therefore, this assumption cannot be verified. Secondly, chronic pain after TKA could be related to pre-operative pain sensitization and higher pre-operative pain intensities as this can be associated with poorer outcome following TKA (41,231,232). It has been suggested that chronic pain after TKA is often a sign of a complex manifestation of pain mechanisms (75), which could affect the physical performances in this patient

population. No pre-operative observations were available for the TKA population to assess these associations. Lastly, psychological traits such as pain catastrophizing, fear-avoidance, and anxiety are known to influence chronic pain and physical performances (43-48) and could, therefore, have influenced the results. Since outcomes for psychological parameters were not evaluated in study II, this assumption cannot be investigated. Study IV includes outcomes such as pain catastrophizing and fear-avoidance beliefs and will be able to examine the association between these psychological traits and physical performances.

4.7. EXERCISE AND PAIN NEUROSCIENCE EDUCATION AS TREATMENT IN PATIENTS WITH PRIMARY OR REVISION TOTAL KNEE ARTHROPLASTY

Study III evaluated an intensive, multimodal rehabilitation regimen, which provided novel insight into the benefits of exercise in a population of patients with complications following a TKA surgery. In general, exercise is recommended as a treatment for chronic pain (65,105,117,120,131,233). Exercise is also recommended following TKA to regain the ability to engage in activities of daily living and to optimize physical performances, although variation is observed in effect sizes and the long-term effect (140,192,213,216,234,235). Furthermore, studies are often undertaken in the early post-operative phase and not during later stages when chronic pain might have developed (213,234). Consequently, no RCT has evaluated whether exercise is an effective treatment modality for patients with chronic pain after TKA, thus explaining why an RCT was initiated (study IV).

Study III analyzed the clinical data of patients experiencing post-surgical complications after primary or revision TKA and observed medium-to-large effect sizes for both patient-reported and physical performance outcomes (study III). Despite being a retrospective, non-controlled study, the results indicate that it could beneficial to use exercise for patients with chronic pain following TKA, and it warrants further validation of this observation. Therefore, study IV was initiated to evaluate whether exercise remains a viable treatment option in an RCT. Contrary to the multimodal treatment approach used in study III, study IV uses the NEMEX-TJR program (study IV). Because of the mixture of exercise treatments (e.g. neuromuscular exercises, flexibility exercises, re-training of gait patterns, resistance training, and cardiovascular training) in study III, it cannot be established which type of exercises are the most beneficial or if the combination of exercise types provides additional benefit. Overall, no specific type of exercise has demonstrated superiority to others when evaluating the effect in populations with OA pain (106,117,236,237), musculoskeletal pain (65,120), or rehabilitation following TKA (216,235). Therefore, it appears that exercise, regardless of type and mode, is beneficial for treating chronic pain in various conditions (65,106,117,120,131,192,216,235-237). Likewise, the optimal intensity, dosage, and frequency of exercise have not been established either

(65,106,117,120,236,238) and are frequently mentioned as important research areas for future investigations (65,106,120,192,216,238).

Several mechanisms behind the beneficial effects of exercise have been suggested (see section 1.4.2 and 1.4.4). Studies have attempted to predict the effect of physiotherapy treatment (167) or examine associations between pain mechanisms and outcomes following TKA (50), neuromuscular exercises (239), and pharmacological treatment (240). No measures of, for example, pain sensitization or pain catastrophizing were retrieved in study III, which could have assisted in interpreting the mechanisms behind the improvements. Such outcomes are included in study IV and will, in time, determine which pain mechanisms can be modulated by neuromuscular exercises and PNE. In study IV, PNE is introduced to patients to re-conceptualize their understanding of their chronic pain (146,147,149,153), which has been shown to decrease pain catastrophizing and kinesiophobia (146,147,151,152). In a recent viewpoint paper, Louw et al. (241) argue that PNE alone would only have a minimal effect on chronic pain. It was argued that exercise and movement should be the focus of the treatment interventions and that PNE should be used in conjunction with exercise (241). Other studies have pointed out that PNE in conjunction with exercise appears to provide superior results compared to exercise or PNE alone (149,152). Since PNE has not been evaluated as a treatment for chronic post-operative pain, but only as a pre-operative approach, it remains to be seen whether this treatment modality is effective in patients with chronic pain after TKA.

4.8. STRENGTH AND LIMITATIONS

Several limitations from the studies should be acknowledged. For the CPM methods introduced in study I and II, no control condition was used. Therefore, the changes in pain ratings could reflect random variation and not facilitatory or inhibitory CPM responses. Study I and II use different terminology when referring to the CPM effect, which could confuse interpretation, although both studies clearly state how the CPM effect, responders, and non-responders are defined (study I and II). Study II was an explorative, cross-sectional study in which causal effects cannot be investigated. Study II was not powered to detect and establish associations and, therefore, these results should be evaluated as hypothesis-generating more than as conclusive (study II). However, the inclusion of pain intensity, pain sensitization, CPM, patient-reported outcomes, and physical performances should be considered a strength, which facilitated the evaluation of physical performances in the context of chronic pain patients. Psychological traits have been shown to interfere with chronic pain and this could have influenced the findings in studies II and III. Study IV does include such psychological measures and these results will be able to account for these possible influencing factors. Due to the observational nature of study III, no control group was included, and the study cannot evaluate the effect of time on the results. Likewise, no long-term follow-up is available after the discharge and, therefore, it is not known whether the benefits from intensive, multimodal rehabilitation will persist over time.

However, the structure and practicalities in study III reflect the real-world practice and the findings could be regarded as indications of effectiveness. The overall strengths of study IV are the inclusion of multiple outcomes, for example, pain intensity, pain sensitization, CPM, patient-reported outcomes, physical performances, and muscle strength in a randomized trial. These future novel findings will provide insight into the mechanisms behind chronic pain after TKA, what treatment effect from exercise and PNE can be expected in this population, and whether long-term effects can be observed (study IV).

CHAPTER 5. CONCLUSION

This PhD thesis addressed issues related to chronic pain, pain sensitization CPM, patient-reported outcomes, and physical performances in patients with chronic pain after knee OA or after TKA. Study I developed a clinically applicable method to examine CPM. The novel method showed good relative reliability but somewhat low absolute reliability. No group-level CPM effect was observed in the population of healthy subjects, and a substantial variation in the CPM effect for the individuals was registered, which consisted of CPM responders and non-responders. In study II, the profiling and comparison of pain intensity, pain sensitization, CPM, and patient-reported outcomes exhibited similar between-group outcomes in the knee OA and TKA populations with chronic pain. However, there were between-group differences regarding the physical performances, with the knee OA group illustrating the best physical performances. The CPM effect findings illustrated substantial variation in the populations of CPM responders and non-responders. Study III found that intensive, multimodal rehabilitation resulted in improvements in pain intensity, the KOOS questionnaire, and the physical performances of the 6 min. walking test and the stair-climbing test. Based on the limited evidence regarding the management of chronic pain after TKA, study IV was initiated. This ongoing randomized controlled trial investigates the effect of exercise and PNE in a population of patients with chronic pain after TKA. In summary, chronic pain reported by patients suffering from knee OA or following TKA impacts pain sensitization, CPM, patient-reported outcomes, and physical performances to different extents. Overall, substantial individual variations were observed for the investigated outcomes, which may indicate the heterogeneity of the chronic pain populations underlined by the unclear etiology and pathogenesis of chronic pain in these patients. The findings in this thesis have limitations based on the cross-sectional nature of studies I and II and the retrospective, non-controlled design of study III. Therefore, no causal effects can be drawn and results should be interpreted with caution. Study IV will remediate some of these limitations because of the randomized controlled trial study design.

5.1. PERSPECTIVES

Over the last decade, research into pain mechanisms behind chronic pain has intensified. Despite the many efforts to investigate these mechanisms, there is no clear understanding of the neurophysiology underlying chronic pain or of the effectiveness of interventions in treating the patient's chronic pain. Well-powered and controlled trials are needed to move this research area forward, and the results from the ongoing RCT (study IV) will provide novel knowledge regarding the possible effects of exercise and PNE. Bed-side testing and the use of clinically applicable tools for assessing pain sensitization and CPM are a research area that has recently received attention (99,103,193). The development and use of clinically applicable tools to examine pain mechanisms in patients with chronic pain will facilitate individual

profiling, which could form the base for personalized medicine. Based on the substantial individual variation of pain, pain sensitization, patient-reported outcomes, and physical performances in populations with chronic pain because of knee OA or after TKA, individualized treatment could be an effective way of targeting specific pain mechanisms and deficits in individual patients.

Based on the findings in this thesis, some perspectives for the clinical implications can be made. Firstly, when undertaking future CPM studies, authors should report individual CPM effects and observations of CPM responders and non-responders. Such an approach would allow for separate analysis of what impact the presence or non-presence of a CPM effect could have instead of making interpretations on group-level. Secondly, it is proposed to ensure that a thorough assessment of pain intensity, pain sensitization, patient-reported outcomes, and physical performances are undertaken for patients with chronic pain because of knee OA or after TKA. This would facilitate evaluating the parameters that require attention in the management of the individual patient's chronic pain condition.

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APPENDICES

Appendix 1: Study I

Appendix 2: Study II

Appendix 3: Study III

Appendix 4: Study IV

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