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PAIN AND SENSITIZATION IN KNEE OSTEOARTHRITIS AND PERSISTENT POST-OPERATIVE PAIN

BY
SØREN THORGAARD SKOU

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Pain and sensitization in knee osteoarthritis and persistent post-operative pain

PhD Thesis

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Preface

The scientific work presented in this PhD thesis was accomplished at Aalborg University Hospital and Aalborg University, Aalborg, Denmark, during my time as a PhD student at the Orthopaedic Surgery Research Unit from September 2011 to January 2015.

The data collection for papers I and II was conducted at Centre for Sensory Motor Interaction (SMI) at Aalborg University, while the data collection for paper III was conducted in the Department of Occupational Therapy and Physiotherapy in Aalborg and in the specialized, orthopedic outpatient clinics in Farsø and Frederikshavn at Aalborg University Hospital.

The studies reported in papers I and II were funded by The Danish Rheumatism Association, The Danish National Advanced Technology Foundation, Aase and Ejnar Danielsen's Foundation, Lions Club Denmark, and The Danish Council for Technology and Innovation (09-052174). The study reported in paper III was partially funded by The Danish Rheumatism Association and The Association of Danish Physiotherapists Research Fund. The funders did not have any role in the studies other than to provide funding and all authors were independent of the funders.

List of papers

This PhD thesis is based on the following three manuscripts:

I. Skou, ST; Graven-Nielsen, T; Rasmussen, S; Simonsen, O; Laursen, MB; Arendt-Nielsen, L. Widespread sensitization in patients with chronic pain after revision total knee arthroplasty. Pain. 2013; 154(9):1588-1594.
II. Skou, ST; Graven-Nielsen, T; Rasmussen, S; Simonsen, O; Laursen, MB; Arendt-Nielsen, L. Facilitation of pain sensitization in knee osteoarthritis and persistent postoperative pain – a cross-sectional study. Eur J Pain. 2014 Aug;18(7):1024-31. doi: 10.1002/j.1532-2149.2013.00447.x. Epub 2013 Dec 24.
III. Skou, ST; Roos, EM; Simonsen, O; Laursen, MB; Rathleff, MS; Arendt-Nielsen, L; Rasmussen, S. The efficacy of multimodal non-surgical treatment on pain and sensitisation in patients with knee osteoarthritis: an ancillary analysis from a randomised controlled trial. Ready for submission for Osteoarthritis and Cartilage when primary results from the RCT has been accepted.

Thesis at a glance

Figure 1 depicts the relationships between the studies. The aim of this thesis was to investigate pain and sensitization in osteoarthritis (OA)-related post-operative pain (Study I), compare this to painful knee OA and explore whether the spreading of sensitization differs within the patient populations based on local knee sensitization (Study II), and investigate whether multimodal non-surgical treatment improves pain and sensitization outcomes in patients with knee OA (Study III).

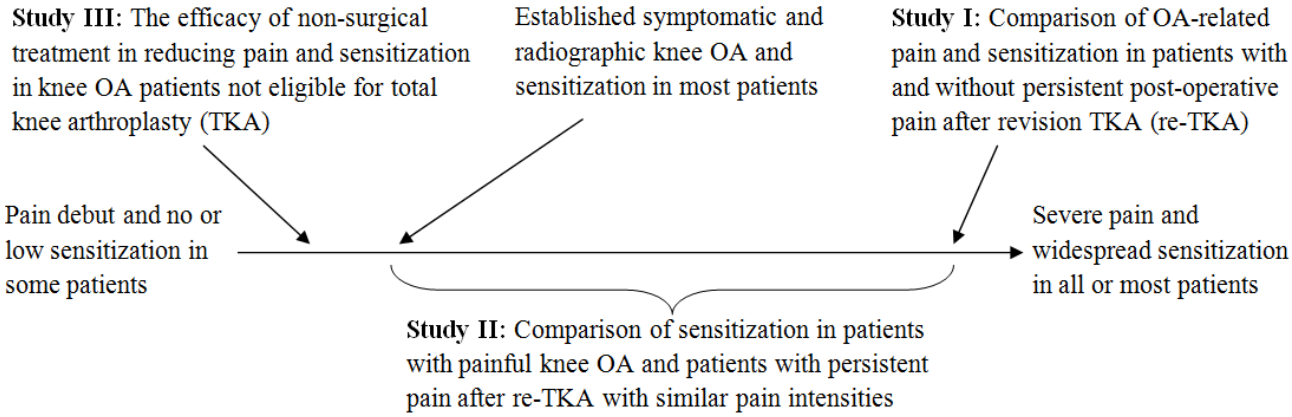
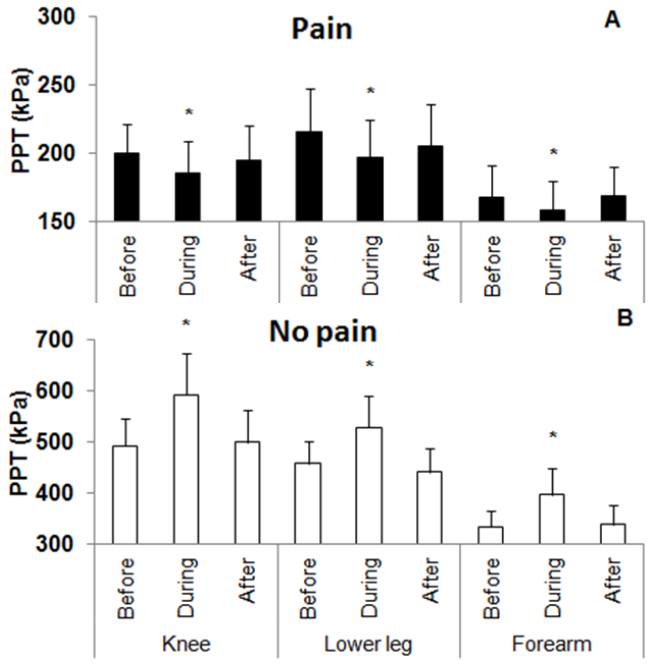


Figure 1. Continuum of osteoarthritis (OA)-related pain and sensitization

Study I.



Patients with pain after revision of total knee arthroplasty (re-TKA) compared to those without pain demonstrated:

- More body sites with pain; and
- More pronounced widespread sensitization as indicated by
  - decreased pressure pain thresholds and pressure tolerance thresholds;
  - facilitated temporal summation, and
  - impaired conditioned pain modulation (Figure 2).

Figure 2. Conditioned pain modulation.[1]

[1] Mean pressure pain thresholds (PPT) manually assessed in patients with (A) and without pain (B) after revision total knee arthroplasty (re-TKA). The PPTs were recorded before, during, and after conditioned pain modulation by tonic arm pain in the knee region, at the lower leg, and at the forearm. The assessments were averaged between the leg with re-TKA and the contralateral leg. PPTs were significantly different during compared to before the painful conditioning stimulation (*, $P < 0.05$). Error bars indicate SEM.

Study II.

Despite similar pain intensities, patients:

- with post-operative pain had more facilitated temporal summation than those with knee OA
- with high knee pain sensitivity showed a more prominent spreading of sensitization than those with low knee pain sensitivity (Figure 3).

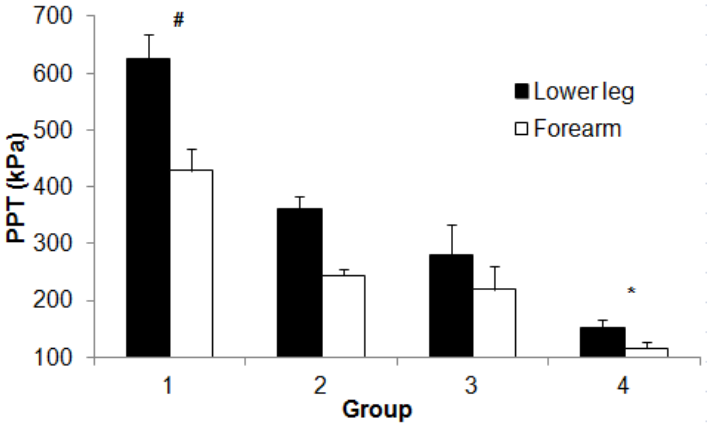


Figure 3. Pressure pain thresholds.[2]

Study III.

Patients undergoing a combined, individualized treatment consisting of education, neuromuscular exercise, weight loss, insoles, and pain medication have greater improvements after 3 months than patients receiving usual care in:

- Peak pain intensity and pain intensity after 30 min of walking; and
- Number of body sites with pain;
- But not in sensitization locally at the knee or at sites distantly to the knee (both groups improved; Figure 4).

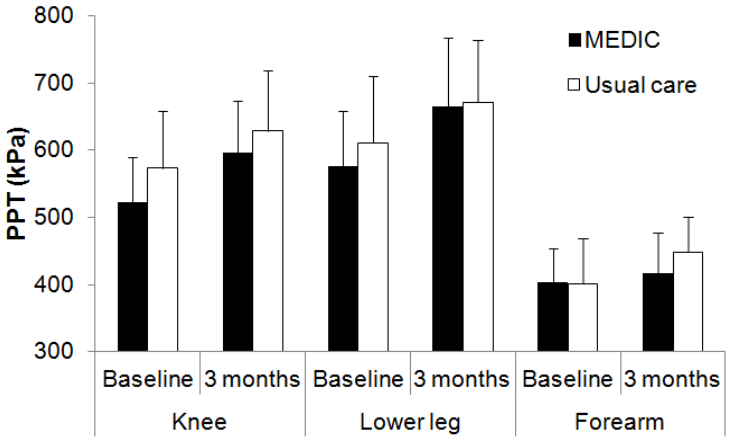


Figure 4. Pressure pain thresholds from the most affected side.[3]

[2] Mean pressure pain thresholds assessed at the lower leg and at the forearm using a handheld pressure algometer. Group 1 (n = 26): knee OA pain and low knee pain sensitivity. Group 2 (n = 27): knee OA pain and high knee pain sensitivity. Group 3 (n = 10): pain after revision total knee arthroplasty (re-TKA) and low knee pain sensitivity. Group 4 (n = 10): pain after re-TKA and high knee pain sensitivity. Significantly lower PPTs were found in group 4 compared to PPTs in groups 1 to 3 (*, $P < 0.05$) and in groups 2 and 3 compared to group 1 ($^{\#}$, $P < 0.05$) on both sites (lower leg and forearm). Error bars indicate SEM.

[3] Mean pressure pain thresholds (PPT) measured in kPa using a handheld algometer from the knee, lower leg, and forearm. Significantly higher PPTs (*; $P < 0.05$) were found at all sites after 3 months in both the group undergoing the non-surgical treatment program (MEDIC) and the usual care group. Error bars indicate 95% confidence intervals.

Acknowledgements

First of all, I would like to thank all the patients participating in the studies, senior therapist Jan Kjærsgaard and the rest of the Department of Occupational Therapy and Physiotherapy, the orthopedic surgeons and other health care personnel from the Department of Orthopaedic Surgery, and the study funders; without their participation, engagement, and willingness to help the studies would never have been completed.

I am very grateful for the hard work that my supervisors have put into the project: orthopedic surgeon Sten Rasmussen for always being available to discuss minor and major issues, Professor Ewa Roos for her methodological and OA-related expertise that always raised the quality of the studies yet another level, Professor Lars Arendt-Nielsen for his impressive knowledge and help within the field of pain research, and orthopedic surgeon Mogens Berg Laursen for facilitating and supporting the completion of the studies.

Furthermore, I would like to thank orthopedic surgeon Ole Simonsen for his continuing spirit and enthusiasm within research and for always being there for me in all aspects of the career process, postdoc Michael Skovdal Rathleff for his commitment to the projects, biostatistician Martin Berg Johansen for statistical advice, and Professor Thomas Graven-Nielsen for support and important feedback on the design and reporting of the studies.

I would also like to acknowledge Anders Bundgaard Lind, Anders Norge Jensen, Anna Emilie Livbjerg, Dorte Rasmussen, Helle Mohr Brøcher, Henriette Duve, Janus Duus Christiansen, Josephine Nielsen, Kate Mcgirr, Lasse Lengsø, Lonneke Hjermitslev, Malene Daugaard, Maria Helena Odefey, Mette Bøgedal, Mikkel Simonsen, Niels Balslev, Rikke Elholm Jensen, and Svend Lyhne for helping with the administration, data collection, data entry, and treatment in study III.

Last but certainly not least, I would like to express my deepest gratitude toward my loving wife and son, Naja and Carl, who have had to put up with their husband and father spending so much time on research. Naja, I truly appreciate all the times you have listened and discussed study- and work-related issues and sacrificed yourself for me, and I hope that I will be able to give you the same in return in the future.

Abbreviations

ADL	Activities of Daily Living
ANOVA	ANalysis Of VAriance ANOVA
BMI	Body Mass Index
CI	Confidence Interval
CPM	Conditioned Pain Modulation
EULAR	The European League Against Rheumatism
HSD	Honest Significant Difference
IASP	The International Association for the Study of Pain
KOOS	The Knee Injury and Osteoarthritis Outcome Score
MA	Meta-Analysis
NEMEX	The NEuroMuscular EXercise training program
NSAID	Non-Steroidal Anti Inflammatory Drug
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
PPP	Persistent Post-operative Pain
PPT	Pressure Pain Threshold
PROM	Patient-Reported Outcome Measures
PTT	Pain Tolerance Threshold
QOL	Quality of Life
QST	Quantitative Sensory Testing
RCT	Randomized Controlled Trial
Re-TKA	Revision Total Knee Arthroplasty
RM	Repeated Measures
SD	Standard Deviation
SEM	Standard Error of the Mean
SMD	Standardized Mean Difference
TA	Tibialis Anterior Muscle
TENS	Transcutaneous Electrical Nerve Stimulation
TKA	Total Knee Arthroplasty
VAS	Visual Analog Scale
WOMAC	The Western Ontario and McMaster Universities Osteoarthritis Index
YLD	Years Lived with Disability

1. Background

1.1. Knee osteoarthritis (OA): magnitude and burden

OA affects 20% of the Danish population (897,000 Danes), making it the 2nd most common disease ahead of cardiovascular disease, diabetes, and cancer[1], and costs Danish society DKK 11.5 billion annually (corresponding to EUR 1.54 billion)[2]. The Global Burden of Disease study has estimated that OA is the 11th highest contributor to global disability out of a total of 291 conditions, and that the years lived with disability related to the disease are 17.1 millions[3, 4]. Due to methodological issues concerning the Global Burden of Disease study (e.g. a conservative case definition and the restriction to only include the hip and the knee) the study likely underestimated the burden of OA[4]. Additionally, knee and hip OA are associated with an increased risk of all-cause mortality, with diabetes, cardiovascular disease, cancer and walking disability as the strongest risk factors for death, potentially due to the sedentary and inactive lifestyle attributed to OA-related pain[5].

Even though OA-related pain is highly prevalent in the elderly, with over 40% of those aged 65 years or older having hip or knee pain[6], it is not only a disease of the elderly. In Denmark, OA rises abruptly from number 74 on the cause-ranking of years lived with disability (YLD) at ages 30 to 34 to number 12 at ages 45 to 49[8]. The impact of OA on those still in the labor market is further highlighted by the fact that patients with physician-diagnosed knee OA have a twofold risk of sick leave and up to a 50% increased risk of disability pension compared to the general population[7].

This underlines the major impact of OA on society and those affected by it, which is further substantiated by the fact that the prevalence of symptomatic OA has doubled in women and tripled in men during the last 20 years[8] and is expected to increase substantially in the future[9], and that OA has increased the health care expenditure by $185.5 billion per year in the US[10] in recent years.

1.2. Knee OA pathology, symptoms, and diagnosis

1.2.1. Knee OA pathology

OA is a degenerative, usually progressive, joint disease affecting synovial joints[11], most frequently the knees, hips, hands, and spine[12]. Pathologically, the disease is characterized by local areas of damaged articular cartilage, typically in load-bearing areas, changes in the subchondral bone, osteophytes at the margins of the joint, some degree of synovitis, and thickening of the joint capsule[12]. It is the results of the failed regeneration of joint damage due to stresses arising from biomechanical[13, 14], biochemical[15], and/or genetic[16] factors. The stress is initiated by abnormalities in the tissues of the joint, including the cartilage[11], subchondral bone[17-19], joint ligaments[11], menisci[20, 21], periarticular muscles[22], peripheral nerves[11], and/or synovium[23, 24]. These abnormalities are likely to differ depending on the joint affected and whether more than one compartment and joint are affected, highlighting the complexity of the disease[11].

1.2.1. Knee OA symptoms

The initial clinical characteristics of knee OA are, most often, usage-related pain and/or functional limitations[25]. Other typical symptoms and clinical features are pain worsening during the day that is relieved by rest[25], morning or inactivity stiffness[25], reduced range of motion[12], swelling[12], crepitus[12], a feeling of giving way[26], instability[27], impaired postural balance[28, 29] and, more recently identified, lack of knee confidence[30, 31]. OA symptoms are often intermittent and vary with regard to both their severity and the time it takes the disease to progress[25]. In more advanced stages of knee OA, the pain is typically more persistent at rest and at night[25]. Due to the symptoms, reduced participation in daily activities and a downward spiral with regards to fatigue, mood, sleep, and quality of life is common in knee OA[32, 33].

Encompassing all symptoms in the clinical assessment of the patient with knee OA is difficult. Recent research has emphasized that patient-reported outcome measures (PROM) should be applied to get a comprehensive overview of the individual patient and outcome from a given treatment. Instruments used for this purpose should be valid, reliable, and responsive and include disease-specific measures such as the Knee Injury and Osteoarthritis Outcome Score (KOOS)[34, 35] and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[36] and generic measures such as EQ-5D 5 Dimensional form[37] and SF-36[38, 39]. A more thorough description of the measures of symptoms is outside the scope of this thesis; please refer to overview papers such as that of Collins & Roos 2012[40].

1.2.1. Knee OA diagnosis

According to the European League Against Rheumatism (EULAR)[25], a confident diagnosis of knee OA can be given in adults above 40 years of age if the patient has:

- usage-related knee pain;
- only short-lived morning stiffness;
- functional limitation; and
- one or more typical examination findings:
    - crepitus
    - restricted movement
    - bony enlargement

However, if a patient has knee pain but does not fulfill all criteria, they can still have OA[25]. This is especially important to recognize if early treatment should be able to have an impact on the future burden of the disease[41].
This means that the diagnosis of knee OA can be made on a clinical basis, without radiographs, and is even valid if radiographs show no signs of OA[25]. However, in clinical practice radiographic examinations are often performed to support the diagnosis, despite the fact that the discrepancy between symptoms and radiographic severity is well known[42] and that as little as 0.5% of all radiographs reveal treatment changing pathology[43]. This suggests that routine radiographic

examination is outdated and only applicable if an orthopedic surgeon is considering surgery, such as osteotomy and joint replacement[12]. If the radiographic severity of the disease needs to be characterized for clinical or research purposes, several classification systems exists[44-47], with the Kellgren-Lawrence scale being the most commonly applied (0-4, from no OA to severe OA)[44, 45]. When a definite diagnosis of OA is needed, a score ≥2 is recommended, while a score of ≥1 can be used to distinguish between no OA and possible OA[48].

1.3. Pain and sensitization in Knee OA

1.3.1. Pain in knee OA

As presented in section "1.2. Knee OA pathology, symptoms, and diagnosis", knee OA symptoms are many and vary widely within and between subjects. However, the hallmark symptom of OA is pain[12, 49]. Despite an improved understanding of pain over the past decades, the pathophysiology of OA pain remains poorly understood[50]. The nociceptive input in knee OA could originate from inflammation of the synovium, stretching of the joint capsule, raised intraosseous pressure in the subchondral bone, elevation of periosteum by osteophyte growth, sensitization of the central nervous system and/or periarticular tissues[51, 52]. In contrast to the classical 16th century Cartesian understanding of pain, it is now recognized that pain is complex and multidimensional and influenced by several modulating factors from the nociceptive input to the actual sensation of pain in the brain[12, 50, 53].

When evaluating pain, several different measures that encompass the complexity of pain should be used[54]. Besides measures of function, depression, and other symptoms, such measures include the evaluation of pain intensity using a visual analog scale[55], the usage of pain medication[54], duration of pain[54], location and pattern of pain[56, 57], and spreading of pain[58]. For a thorough description of measures of pain, please refer to overview papers such as those of Dworkin et al. 2005[54] and Hawker et al. 2011[55].

1.3.2. Sensitization in knee OA

In recent years, a mechanism-based approach to pain, which includes a focus on sensitization, has gained interest and is widely accepted and recommended to improve the understanding of pain[59]. According to the International Association for the Study of Pain (IASP)[60], sensitization can be defined as "*Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs*", with peripheral sensitization defined as an increased response and reduced thresholds of nociceptive neurons in the periphery and central sensitization defined as an increased response of the nociceptive neurons to normal or subthreshold afferent input in the central nervous system. Peripheral and central sensitization are important aspects influencing the sensation of pain[12, 50, 53]. This is also the case with knee OA pain, where sensitization is known to be a prominent mechanism[59, 61], and factors outside the joint (such as sensitization and periarticular structures) seem important for the maintenance of pain[61-64].

Recent research suggests that musculoskeletal pain spreads over time, influenced by both the intensity[65] and duration[66] of the pain, due to central sensitization[59, 67]. This implies that a given pain condition or tissue damage spreads from a local area at the start (e.g. the patella tendon), to regional areas (e.g. the knee and inferior and superior parts of the leg), and ends up being chronic/persistent and widespread[59, 67]. It has been suggested that the transition of pain from acute to widespread is initiated by tissue stress (i.e. tissue damage) that leads to excitation and peripheral sensitization of the nociceptors, causing sufficient nociceptive input to the central nervous system that again leads to central sensitization of dorsal horn neurons and/or at higher brain centers[67].The central sensitization of the dorsal horn neurons is characterized by prolonged neuronal discharges, increased pain sensitivity (hyperalgesia), response to non-painful stimuli (allodynia), and expansion of the receptive field[68, 69]. Furthermore, after (or at the same time as) the sensitization of second-order neurons, a reorganization of the higher brain centers may take place, all together ultimately leading to widespread pain[59, 67].

Quantitative sensory testing (QST) represents a particular applicable method to assess sensitization in knee OA that uses a mechanism-based approach[70]. By assessing the somatosensory response evoked by applying controlled noxious or innocuous stimuli (e.g. using a pressure algometer) it is possible to quantify sensitization in a patient[67, 71]. Even though the experimental test stimulus gives a different pain experience for the patient than does the disease-related pain experience, it offers translational information on pain mechanism, with the potential to affect the management of the disease[67]. Just as the assessment of pain needs to be multidimensional, the quantification of sensitization should preferably be multidimensional by including various stimulus modalities (mechanical (e.g. by pressure), chemical (e.g. by ischemia), electrical, etc.) and assessing different pain mechanisms (hyperalgesia, temporal summation, conditioned pain modulation (CPM), the spread of sensitization, etc.)[67, 72]. Since mechanical stimuli, in particular pressure, are by far the most commonly applied modality in knee OA[70, 73], this will be the focus of the rest of this section.

In knee OA, increased pain sensitivity (hyperalgesia) has typically been evaluated using pressure pain thresholds (PPTs)[70, 73], defined as the pressure at which the patient feels the pressure change to pain[61]. Increased pain sensitivity found locally at the affected knee (and in adjacent body parts) is associated with peripheral and central sensitization, while increased pain sensitivity distantly from the knee reflects generalized central sensitization (spreading sensitization)[59]. This has previously been demonstrated in knee OA patients compared to healthy controls[61-63, 74-77]. Handheld pressure algometry has traditionally been used to evaluate PPT, but more recently cuff algometry, a method for investigating deep tissue pain sensitivity and central mechanisms that is less influenced by intertester bias than handheld pressure algometry[78], has been used in knee OA[63, 64]. Cuff algometry can also be applied to assess pain tolerance thresholds (PTT), defined as the pressure at which the pain is intolerable[64].

Temporal summation of pain, another pain mechanism, is the perceptual correlate in humans thought to mimic the initial phase of the wind-up process in dorsal horn neurons. Temporal summation can be assessed by applying ten sequential pressure stimulations at the level of the pressure pain threshold. The patients then rate their pain intensity continuously during the

sequential stimulation on an electronic VAS[64]. In chronic musculoskeletal pain such as OA and fibromyalgia, temporal summation to repetitive pressure pain stimulations has been demonstrated to be facilitated compared to healthy controls[61, 79] due to sensitized central mechanisms. In patients with chronic painful knee OA, higher clinical pain intensities and longer pain durations caused relatively more temporal summation of pain compared with patients with shorter duration and less pain[61]. Furthermore, the extent of hyperalgesia[61, 63, 64] and temporal summation[61, 64] are related to higher pain intensities. Thus, OA disease progression seems better associated with pain and sensitization than with the actual joint destruction assessed by radiological scorings[61].

Another important pain mechanism associated with sensitization is the descending inhibitory and facilitatory modulation of the peripheral nociceptive inputs in the dorsal horn neurons[59, 80]. CPM is a manifestation of this modulation which can be assessed in patients and is characterized by a changed response to a painful test-stimulus when another painful conditioning stimulus is applied[81]. CPM is impaired in chronic pain disorders such as knee and hip OA[61, 63, 82], temporomandibular joint disorders[83], and fibromyalgia[84, 85].

For a more thorough description of sensitization and measures of sensitization, please refer to overview papers such as those of Graven-Nielsen 2006[72], Arendt-Nielsen & Graven-Nielsen 2011[59], and Graven-Nielsen & Arendt-Nielsen 2010[67] and for more a comprehensive overview of sensitization in knee OA, see Suokas et al. 2012[70] and Lluch et al. 2014[73].

1.4. Treatment of knee OA

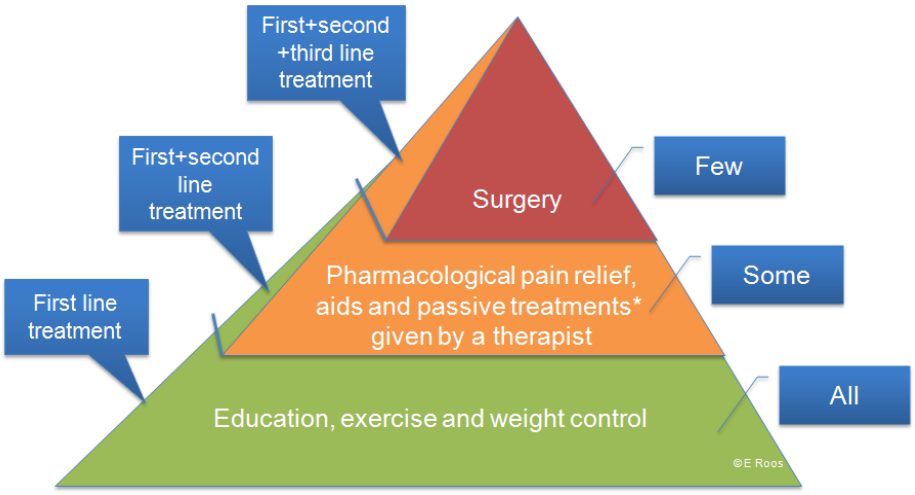


Figure 5. Osteoarthritis treatment pyramid (reprint from[86], permission to reuse has been obtained). While all patients should be offered first line treatment, only some need second line treatment, and a few will need surgery (third line treatment). *Passive treatments are manual therapy, acupuncture, and other treatments given by a therapist not requiring an active effort by the patient. Only if the lower level of the pyramid is not sufficient in controlling/reducing the symptoms should the next level be considered.

No cure exists for knee OA, which is why the treatment is aimed at improving symptoms and preventing further progression of the disease. Due to the future burden of the disease, the need for a

paradigm shift toward early treatment is evident[41]. The treatment can be divided into three overall categories (first line, second line, and third line treatment) based on the recommended order of initiation (Figure 5)[86]. As recommend by the international organizations dealing with OA, EULAR[87], and the Osteoarthritis Research Society International (OARSI)[88], the core treatment (first line treatment) that should be offered as an individualized combined treatment is education, exercise, and weight loss (if needed), while other non-surgical treatments (second line treatment) can be added if needed, and only after this should surgical treatments be considered (third line treatment). However, despite the recommendations, the combined efficacy of the recommended treatments has yet to be investigated. Figure 6 summarizes the effect sizes demonstrated in meta-analyses of randomized controlled trials (RCTs)[88, 89] for frequently applied first, second, and third line treatments.

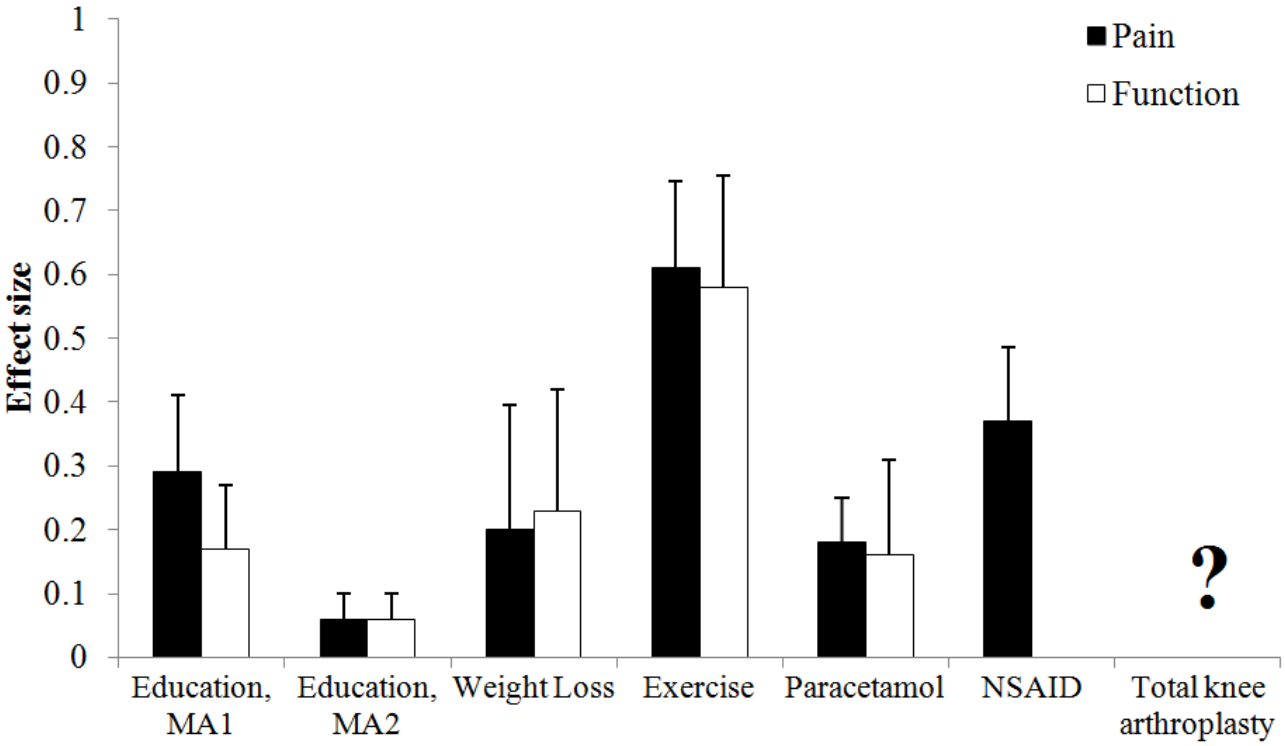


Figure 6. Effect sizes for treatment of knee osteoarthritis (based on meta-analyses (MA) of randomized controlled trials (RCT) [88, 89]). A larger effect size (SMD) indicates a larger effect. SMDs can be clinically interpreted as ≥0.2: small, ≥0.5: moderate, and ≥ 0.8: large[90]. Two MAs[91, 92] have produced different results for education, therefore both are presented. No RCTs have been conducted for total knee arthroplasty[124], which is why the SMD is not known. Error bars indicate 95% CI.

1.4.1. First line treatment of knee OA

Education/self-management is considered a core element of first line treatment of knee OA[87, 88]. Despite small to moderate effect sizes (Figure 6)[88, 91, 92], which may have arisen because the efficacy on pain and function were measured rather than the efficacy of education on anxiety, self-efficacy, adherence to exercise, etc., education is recognized as an important aspect of the treatment due to the central role of the patient in the treatment of the disease[87]. Since the two other aspects of first line treatment (exercise and weight loss) will only be beneficial if the patient is committed to the

treatment, it is important that it is delivered together with an educational aspect that teaches the patient about the disease, that pain during exercise is okay as long as it subsides, and the importance of the lifelong continuation of treatments such as exercise[93, 94]. Furthermore, long-term efficacy is dependent on the patient's adherence to the treatment after the intervention period[95]. So far, no optimal educational program has been indentified for patients with knee OA[92], but experiences from an implementation initiative in Denmark have shown promising results from a combined treatment of exercise and three 1.5-hour sessions of patient education, two led by a physiotherapist and one led by a previous participant in the treatment program. The education aims to improve the knowledge of the participants regarding OA and the treatment of it[96-98].

Obesity and knee OA are closely interrelated and often occur at the same time[99]. The effect sizes for weight loss in knee OA are small to moderate (Figure 6)[88]. Weight loss programs have typically been delivered as supervised sessions on a weekly basis for a range of 8 weeks to 2 years[100-106]. The strategies of the weight loss programs focused on how to reduce calorie intake using meal plans, reduced fat, sugar and portion sizes, meal replacements, and included behavioral modifications, self-monitoring, weight-loss goals, and maintenance of body weight when pre-defined goals were reached[100-106]. However, evidence for long-term maintenance of the weight loss achieved at short-term is sparse[87].

A recent systematic review incorporating trial sequential analysis and network meta-analysis[107] concluded that sufficient evidence had accumulated in knee OA to show significant benefit of exercise over no exercise and that future trials were unlikely to change the conclusion. The effect sizes (Figure 6) for the efficacy of exercise to improve pain and functions illustrate that this is a very potent treatment of knee OA[89]. Similar effect sizes ($p = 0.733$) have been demonstrated when aerobic exercise (SMD: 0.67, focusing on improving cardiorespiratory fitness); resistance exercise (SMD: 0.62, focusing on improving muscle force); and performance exercise (SMD: 0.48, e.g. neuromuscular exercise, focusing on improving sensorimotor control and obtaining compensatory functional stability) have been compared across all RCTs in knee OA[89]. Even though this could lead one to conclude that the type of exercise is less important, it is reasonable to believe that different subgroups of patients (phenotypes) with knee OA would benefit from different types of exercise, which would thereby have the potential to attenuate the efficacy of exercise further[108]. This is supported by two recent studies[109, 110] demonstrating that muscle strength[109] and alignment[110] mediated the outcome of different exercise interventions. While intensity, duration of individual sessions, and patient characteristics (including radiographic severity) seem less important for the effects of exercise[89], a prior meta-analysis showed that 12 or more supervised exercise sessions were approximately twice as effective as less than 12 sessions on both pain and function[111]. The importance of the number of supervised sessions for the efficacy has recently been confirmed by another meta-analysis[89]. After a supervised period, the exercise should be integrated into the daily life of the individual patient[87].

1.4.2. Second line treatment of knee OA

As illustrated in Figure 5, second line treatment includes a large variety of treatments, which is why the focus of this section will only be on some of those often applied in research and clinical practice and those relevant for this thesis. For a more comprehensive review, see McAlindon et al. 2014[88] and Fernandes et al. 2013[87].

OARSI recommends the application of biomechanical interventions if needed[88]. Two recent meta-analyses have evaluated the effects of a valgus knee brace[112] and lateral wedge insoles as a treatment for medial knee OA[113]. Moyer et al.[112] demonstrated small to moderate effect sizes for both pain (SMD (95%CI) = 0.56 (0.03 to 1.09)) and function ((SMD (95%CI) = 0.48 (0.02 to 0.95)) when a valgus brace was compared to a control group not using a brace, while the effect was small, and only significant for pain, when compared to a control group that did not use an orthosis (SMD (95%CI) = 0.33 (0.08 to 0.58)). Parkes et al.[113] found a small effect size for pain (SMD (95%CI) = 1.20 (0.30 to 2.09)) when a lateral wedge insole was compared to a control group not using a wedge, while the effect was non-significant when compared to a neutral insole. It has been suggested that the non-significant effect when comparing a lateral wedge insole to a neutral insoles is based on the lack of individualization and/or medial arch support in the existing RCTs, potentially representing a key factor in the effect of insoles in medial knee OA[114].

As presented in Figure 6, acetaminophen (paracetamol) has small effect sizes for pain and function, suggesting that it is a useful short-term treatment[88, 115]. However, the risk of adverse events associated with paracetamol, including gastrointestinal adverse events and organ failure, has also been highlighted in two systematic reviews[115, 116]. Therefore, it is recommended that paracetamol is given for only short periods of time and in reduced doses[88].

Albeit more potent than paracetamol, oral NSAIDs have also demonstrated only small effect sizes (Figure 6)[88]. Due to the increased risk of serious gastrointestinal, cardiovascular, and renal adverse events compared to placebo[117], OARSI recommends that they be used for only short periods of time and in reduced doses[88].

1.4.3. Total knee replacement (third line treatment)

If first and second line treatment fail in improving symptoms, TKA is considered an effective treatment of knee OA[118], replacing the joint surfaces with metal femoral and tibial prosthetic implants and a polyethylene insert between the two metal implants[118, 119]. The incidence of TKA in the US has increased markedly from 31.2 per 100,000 person-years in 1971–76 to 220.9 in 2005–2008[120], and is expected to increase by almost 700% by 2030[121]. Similarly, the incidence of the procedure has risen in the Scandinavian countries[122] during the last decades, even though it seems to have leveled off in Denmark during recent years[123]. There are no published RCTs assessing the efficacy of TKA (Figure 6)[124]; however, one is underway in Denmark, finishing its long-term follow-up in January 2015[125]. Based on uncontrolled studies, TKA has been shown to improve pain, function and quality of life in the patient[126, 127]. However, the procedure is associated with an increased risk of adverse events and death, even when compared to unicompartmental knee

arthroplasty[128], and imposes a large financial burden on most health care systems, e.g. $10.4 billion in the US in 2008[118]. Traditionally, survival rates of the implant or time to revision, and not PROMs, have been the most important outcome measures for TKA registered in national arthroplasty registries[118]. The survival of the implant varies, but a systematic review demonstrated that 6.2% of patients (range 4.9% to 7.8%) had undergone revision after 10 years[129], while a study from the Scandinavian countries showed that between 4% and 6% had undergone revision after 10 years[122]. However, the number of patients dissatisfied with the outcome is higher, with 8% who had not undergone revision being dissatisfied[130]. Furthermore, a systematic review has demonstrated that 20% undergoing TKA experience only small or no improvements in pain outcome[131], and more knee pain is known to be related to lower patient satisfaction[132].

1.5. Revision of total knee arthroplasty (TKA) and persistent post-operative pain

Revision TKA (re-TKA) is defined as a second surgery needed to remove, add, or exchange one or more components of the primary TKA[118]. Pain, aseptic loosening, infection, instability, and stiffness following the primary TKA account for 80–90% of all revisions[133-135]. However, re-TKA is not as effective as the primary TKA[118], the risk of re-revision being four to five times higher than the risk of revision after the primary TKA[133] and patients being less satisfied after re-TKA compared to the primary TKA[130]. As the number of revision TKAs are expected to increase by more than 600% by 2030[121], primarily because of a substantial increase in primary TKAs, the future economic burden of the procedure is evident[136] and calls for a better understanding of risk factors and characterization of the patient population.

Persistent post-operative pain (PPP) is a largely underestimated clinical problem known to affect between 5% and 85% of patients undergoing surgery depending on the type of surgery[137, 138]. PPP has previously been defined as pain after a surgical procedure lasting for at least 2 months[138]. However, this timeframe can vary depending on the type of surgery type [139]. From studies of outcome in TKA, we know that pain levels off after 3 months[140], which is why PPP in this thesis is defined as pain presenting for at least 3 months after surgery, with a change in pain characteristics following surgery, as recently recommended[141]. A systematic review pointed out that there is a wide variation in measures applied in the assessment of PPP after TKA and that many of these measures were unidimensional[142] as opposed to current recommendations of a multimodal assessment of pain[54, 143]. Furthermore, evidence is missing concerning sensitization following re-TKA, even though this could help explain the poor pain outcome in some patients following surgery[59].

1.6. Treatment of sensitization

A combination of strategies is recommended to be applied when treating sensitization in patients with persistent pain[144]. These strategies should target different mechanisms capable of desensitizing the central and peripheral nervous system using top-down (targeting the central nervous system) and bottom-up (targeting the peripheral nociceptive input) treatments[144]. Most current treatments of knee OA target the knee and adjacent structures, with little or no focus on central components of the pain (i.e. on top-down treatment)[145], despite the apparent presence of central sensitization as

demonstrated in the section " 1.3.2. Sensitization in knee OA". On the other hand, studies demonstrating normalization of sensitization after total joint replacement (bottom-up treatment) in knee[63] and hip OA[82, 146] suggest that the sensitization, at least to some extent, arises and is maintained by peripheral input[63]. This is supported by two recent RCTs demonstrating that improvements in peripheral and central sensitization can be attained through resistance exercises for the neck/shoulder in patients with neck/shoulder pain[147] and through resistance and coordination exercises in patients with knee OA[148], even though it can be questioned whether the effects of exercise are top-down (descending inhibitory mechanism) or bottom-up (the peripheral nociceptive input)[144].

Indications of modulation of sensitization in patients with knee OA have been found following a wide variety of non-surgical treatments targeting both bottom-up and top-down mechanisms[148-153]. The modulation have been found from exercise[148], manual therapy[149, 150], transcutaneous electrical nerve stimulation (TENS)[151], opioids[152], and coping skills training[153]. However, none of the studies combined the recommended treatments, and in most of the studies sample sizes were small, only small treatment effects were found, and/or patients were not randomized, questioning the validity of the findings. More research is needed regarding the investigation of the effects of non-surgical treatment on sensitization in knee OA[73].

1.7. Summary of background

As proposed in Figure 1, pain and sensitization in OA-related pain can be considered a continuum going from few symptoms and low sensitization to severe pain and widespread sensitization, with, however, considerable variations between patients and subgroups within the populations. There is substantial evidence supporting the presence of pain and sensitization in knee OA[70, 73], while the state of the nociceptive system in patients with PPP after re-TKA is unknown. Since 20% of patients undergoing a TKA have an unfavorable pain outcome[131], knowledge of mechanisms (such as sensitization) involved in PPP is needed[137, 138].

Based on the available evidence, it is recommended that the treatment of knee OA includes education, exercise, and weight loss and can be supplemented with insoles and pain medication if needed[87, 88] and that sensitization should also be treated using a multimodal approach[144]. However, little is known of the combined effects from the recommended non-surgical treatment on pain-related measures and sensitization in knee OA, even though this could potentially prevent pain and sensitization from progressing and become severe and widespread[73, 154].

1.8. Aim of the PhD project

1.8.1. General

The overall aim of this thesis was to establish evidence concerning pain sensitization in patients with PPP after re-TKA, compare this to painful knee OA and explore whether the spreading of sensitization differs within the patient populations based on local knee pain sensitivity, and, lastly,

investigate whether multimodal non-surgical treatment improves outcomes of pain and sensitization in patients with knee OA.

1.8.2. Specific

The specific aims of the individual studies were:

Study I: To compare patients with and without PPP after re-TKA utilizing a variety of experimental pain techniques for assessing 1) local sensitization, 2) widespread sensitization, 3) temporal summation, and 4) CPM.

Study II: To compare sensitization (spreading of sensitization, facilitated temporal summation) in patients with knee OA and those suffering from PPP after re-TKA and in patients with low and high knee pain sensitivity.

Study III: To investigate the combined efficacy of education, neuromuscular exercise, diet, insoles, and pain medication (the MEDIC treatment) in improving different pain-related measures and sensitization after 3 months compared to usual care (information and treatment advice) in patients with knee OA not eligible for TKA.

1.9. Hypotheses

Study I: Patients with PPP after re-TKA would have more pronounced peripheral and central sensitization than those without PPP after re-TKA.

Study II: Patients with PPP after re-TKA and patients with high local knee pain sensitivity would have a more pronounced spreading of sensitization and temporal summation than patients with knee OA pain and patients with low local knee pain sensitivity.

Study III: It was hypothesized that the MEDIC treatment would result in greater improvements in pain-related measures and sensitization than usual care at the 3-month follow-up.

2. Materials and Methods

2.1. Design

Study I and Study II were cross-sectional studies, while Study III was an ancillary report of the 3 months results from a two arm parallel group assessor-blinded RCT (1:1 treatment allocation) for which the study protocol has previously been published[155]. The ancillary report was pre-defined in the statistical analysis plan made available before unblinding the data[156].

2.2. Study populations

Study I

Patients previously diagnosed with knee OA who had undergone TKA followed by a re-TKA using standard procedures[157] with pain as one reasons for the re-TKA were invited to participate. In total, 54 were screened and 40 patients agreed to participate; 20 with PPP in the revised knee and 20 patients without pain in the revised knee matched on body mass and reasons for re-TKA (besides pain: loosening, infection, instability and stiffness). In the background, PPP was defined as pain present 3 months after surgery. However, since the pain has the potential to improve until 12 months after TKA[126], only patients with pain 12months after re-TKA were included in study I and II to ensure that possible improvements from surgery had been obtained. The participants were asked to refrain from using pain medication 24 h before the QST session. The study was conducted in accordance with the Helsinki Declaration and approved by the local ethics committee of the North Denmark Region (N-20100050). Oral and written information were provided to the participants, and written consent was obtained from all participants.

Study II

Fifty-three pain patients previously contacted regarding enrolment (some participating) in a study assessing sensitization in knee OA using QST[61] and the 20 patients with PPP after re-TKA from study I participated. Raw data from a subset of patients published previously[61] and parts from study I was included and reanalyzed according to the new protocol. The patients were divided into four groups according to the degree of their knee pain sensitivity (using PPTs) assessed at the most affected knee (see section 2.3. Procedure). The patients were asked to refrain from using any analgesics 24 h before the QST session. The study was approved by the local ethics committee of the North Denmark Region (N-20100050) and conducted in accordance with the Helsinki Declaration. Both oral and written information were provided to the patients, and written consent was obtained from all patients.

Study III

100 patients with radiographic and symptomatic knee OA found not eligible for TKA but experiencing more than mild functional limitations were enrolled. Patients were recruited from two specialized, public outpatient clinics at Aalborg University Hospital (Frederikshavn and Farsoe; 50 patients from each clinic) between the 3rd of April 2012 and the 12th of July 2013. Major exclusion criteria were above 75 in the self-report questionnaire $KOOS_4$ defined as the average score for the subscale scores for pain, symptoms, activities of daily living (ADL) and quality of life (QOL),

previous ipsilateral knee replacement and mean knee pain in the previous week greater than 60 mm on a 0-100 mm visual analogue scale (VAS). Table 1 includes the full list of inclusion and exclusion criteria. All patients gave informed consent before being enrolled and the study was conducted in accordance with the Helsinki declaration and approved by the local Ethics Committee of The North Denmark Region (N-20110085). Furthermore, the study was registered at ClinicalTrial.gov (NCT02091830).

Inclusion Criteria	**Exclusion criteria**
Referred from primary care to an orthopedic surgeon in a public hospital in The North Denmark Region for evaluation of the need for total knee arthroplasty	Previous ipsilateral knee arthroplasty
Considered ineligible for a TKA by the surgeon	Inflammatory arthritis
Diagnosed with KOA using standing, weight-bearing knee radiographs (Kellgren-Lawrence score ≥1 on the original scale[44, 45].	Mean pain the previous week >60 mm on a 100 mm Visual Analogue Scale
Aged ≥18 years	Possible pregnancy or planning pregnancy
$KOOS_4$≤75 (the average score for four of the five Knee Injury and Osteoarthritis Outcome Score subscales covering pain, symptoms, activities of daily living and quality of life)[34, 35].	Inability to comply with the protocol

Table 1. Inclusion and exclusion criteria in study III

2.3. Procedures

Study I

Prior to the QST, the participants completed a questionnaire on demographics and clinical characteristics including questions on revision knee, other reasons for revision than pain, time between primary arthroplasty and first revision, number of revisions and total number of surgeries after their primary arthroplasty, duration of pain, and mean pain intensity in the revised knee before the primary arthroplasty, before the first revision and current knee pain measured on a 100 mm VAS with the endpoint descriptors of 'no pain' and 'maximal pain', respectively. Furthermore, the participants reported pain sites on a region-divided body chart, completed the WOMAC[36], usage of pain medication, and the Knee Pain Map to evaluate their knee pain location and pattern[56]. The Knee Pain Map identifies areas of the knee that are painful and characterizes knee pain as localized (patellar, superior-medial, inferior-medial, medial joint line, superior-lateral, inferior-lateral, lateral joint line, or back of knee), regional (medial, lateral, patellar, or back of the knee), or diffuse, defined as unable to identify pain as localized or regional[56].

The participants rested in a comfortable recumbent position in a quiet, temperature-controlled room during the QST. The participants were carefully instructed in the QST methods before the experiment was initiated to make them familiar with the procedure. The data were collected by the same examiner (the author of this thesis).

Study II

Prior to the QST, the patients completed a short questionnaire on demographics and clinical characteristics including questions on duration of knee pain and peak clinical pain intensity in the affected knee in the previous 24 h measured on a 100 mm VAS with the endpoint descriptors of 'no pain' and 'maximal pain', respectively. The patients rested in a comfortable recumbent position during the QST and were carefully instructed in the QST methods and made familiar with the procedures.

Subgrouping of patients

The pressure pain sensitivity from the knee region of the most affected knee (localized sensitization/local knee pain sensitivity) was used to subgroup the patients. PPTs from the knee region were assessed using a handheld pressure algometer (Figure 7; Algometer Type II, Somedic AB, Sweden). Pressure was applied perpendicular to the skin (30 kPa/s) with a 1 cm^2 probe until the patient felt the pressure as pain and pressed a stop button attached to the handheld algometer after which the pressure was released. This defined the PPT.

Figure 7. Handheld pressure algometer

The average PPT for each patient was calculated from PPTs measured twice from eight sites in the knee region: 1) 2 cm distal to the inferior medial edge of patella; site 2) 2 cm distal to the inferior lateral edge of patella; site 3) 3 cm lateral to the midpoint on the lateral edge of patella; site 4) 2 cm proximal to the superior lateral edge of patella; site 5) 2 cm proximal to the superior edge of patella; site 6) 2 cm proximal to the superior medial edge of patella; site 7) 3 cm medial to the midpoint on the medial edge of patella; and site 8) at centre of patella[61, 64] (Figure 8).

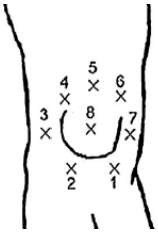


Figure 8. Sites at knee where PPT was assessed

In the OA group and re-TKA group the median knee PPT value for each group was used to subdivide into four groups based on the degree of localized sensitization: Group 1: OA patients with knee PPTs higher than the median PPT based on all OA patients. Group 2: OA patients with knee PPTs equal to or lower than the median PPT based on all OA patients. Group 3: re-TKA with knee PPTs higher than the median PPT based on all re-TKA patients. Group 4: re-TKA with knee PPTs lower than the median PPT based on all re-TKA patients.

The median PPT was chosen as the cut-off point, since this divides the groups in equally sized subgroups with distinguishable degrees of local knee pain sensitivity.

Study III

Patients in need of evaluation for TKA in The North Denmark Region are referred by their general practitioner to an orthopedic surgeon at the outpatient clinics in Frederikshavn and Farsoe, Department of Orthopaedic Surgery, who specializes in TKAs. A standardized weight-bearing anterior-posterior knee x-ray is obtained on arrival[158].

After the baseline measures were obtained, patients who agreed to participate in the RCT were assigned to one of two treatments: (i) the MEDIC-treatment, or (ii) usual care. Participants were reassessed 3 months after randomization (12-week follow-up). Both the baseline and 3-month follow-up were carried out at the Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital, Denmark by the same outcome assessor, who was specifically trained in all aspects of the assessments in particular to obtain knowledge and experience in using the handheld algometer. Additional follow-ups were conducted 6 and 12 months and 2, 5 and 10 years after randomization (not part of this thesis).

Randomization procedure and concealment of allocation
Before initiating the trial, the schedule for randomization was randomly generated in permuted blocks using a computer. To control for variation in patient characteristics between the two clinics, the randomization was stratified according to the clinic (Frederikshavn or Farsoe). The allocation numbers were put in concealed, opaque C5 envelopes to conceal the outcomes of the randomization. In blocks of eight, these envelopes were placed in consecutively numbered opaque larger envelopes (seven larger envelopes in total for each clinic). A staff member, independent of this study, prepared the envelopes. These were only accessible by one research assistant at each of the respective clinics. A smaller envelope from the numbered larger envelopes were opened by the research assistant following the informed consent and completion of the baseline measures, after which the allocation was revealed to the participant. The smaller envelopes of the second larger envelope were added, when only two smaller envelopes were left in the first of the numbered larger envelopes. The last two of the smaller envelopes were added, when there were six smaller envelopes left in the sixth of the seven numbered larger envelopes at each clinic.

Blinding
The outcome assessor were blinded to group allocation, unaffiliated with the treatment sites, and not involved in providing the interventions. Furthermore, the statistician performing the statistical analyses was also blinded. The participants, the project physiotherapist and the project dietician delivering the interventions could not be blinded.

2.4. Interventions

Only study III included interventions. The participants in study III were randomized to MEDIC treatment or usual care.

2.4.1. The MEDIC treatment

The 12-week MEDIC treatment consisted of five components: education, exercise and insoles were prescribed to everyone in the MEDIC group, with weight loss and/or pain medication prescribed if indicated. The MEDIC treatment was delivered at Aalborg University Hospital, Denmark, by physiotherapists and dieticians trained in delivering the treatment to ensure proper standardization of the treatment. As recommended[144], the aspects of the treatment targeted both bottom-up and top-down mechanisms involved in the sensitization.

Patient education

The patient education consisted of two 60-min sessions focusing on disease characteristics, treatment and assistance to support self-help by actively engaging the patients in the sessions and in the treatment of their knee OA. The education was delivered both orally and on a DVD to accommodate different learning styles among the patients and to give them the opportunity to review the information if needed. The patient education included in this study, in combination with neuromuscular exercise, has previously been tested in a similar population demonstrating feasibility and efficacy in reducing pain and improving function and quality of life[96].

Neuromuscular exercise

The NEuroMuscular EXercise training program (NEMEX), previously found feasible in patients with moderate to severe knee OA[159], was undertaken by patients twice a week for 12 weeks with each session lasting 60 min (Figure 9). Classes allowed for continuous admission to give new patients the opportunity to get support from more experienced patients. The exercise programme is based on neuromuscular and biomechanical principles and has different levels of difficulty for each exercise[159]. It aims at restoring neutral functional alignment (Figure 10) of the lower extremities by obtaining compensatory functional stability and improving sensorimotor control. Neuromuscular exercise is thus different from strength training (aimed at improving muscle force) and aerobic training (aimed at improving cardiorespiratory fitness). Each participant was monitored individually for pain intensity during the exercise session. Progression was allowed but only if the quality of the exercise could be maintained[159]. Details of the programme and individual exercises are provided elsewhere[159]. Following the 12 weeks of supervised exercise, there was a transition period of 8 weeks, where the programme was increasingly performed at home to improve long-term adherence.

Figure 9. Examples from The NEuroMuscular EXercise training program (NEMEX).

Figure 10. Appropriate position of knee over foot, i.e. joint in lower extremity well aligned.

Diet

Patients with a Body Mass Index (BMI) ≥25 at baseline underwent a 12-week dietary weight loss programme consisting of four 60-min sessions aimed at reducing the body weight by at least 5%

and sustaining this weight loss to reduce symptoms[102]. The dietary intervention was based on principles from motivational interviewing with instructions and guidance relevant to the individual participant and their readiness to change and take action[160].

Insoles
Patients in the MEDIC group received an individually fitted full-length Formthotics System insole with medial arch support (Foot Science International, Christchurch, New Zealand). Additionally, patients with a knee medial-to-foot position (the knee moves medially to the 2nd toe in three or more of five trials) using the valid and reliable single limb mini squat test[161], had a 4° lateral wedge added to their insole.

Medicine
The patients were offered pain medication if the orthopedic surgeon considered it necessary for participation in the exercise classes. If no contraindications were evident, they were prescribed 1g paracetamol four times daily, 400 mg ibuprofen three times daily, and 20 mg pantoprazol daily. In order to supervise the use and indications of the medication, the prescription was reassessed every 3 weeks. The patients were instructed to contact the physiotherapist if they questioned the continuation of the medicine during the 3-week period due to pain relief from the treatments given.

Booster sessions
After the 12-week MEDIC treatment and the following 8-week exercise transition period but prior to the 12-month follow-up, the physiotherapist contacted the patients monthly by telephone to support the continuation of exercise and physical activity, and to discuss issues and barriers against exercise that emerged after the supervised class-based exercise programme had stopped. Furthermore, patients undergoing dietary intervention received two additional 30-min telephone consultations with the dietician between the 3-month follow-up and the 12-month follow-up.

2.4.2. Usual care

Patients allocated to usual care were given two standardized information leaflets (also given to the MEDIC group). The first leaflet (four pages) holds information on knee OA with regard to etiology, symptoms, common functional limitations, recommended treatments and general advice on how to address the symptoms oneself. The second leaflet (two pages) contains information on where in The North Denmark Region you can seek advice regarding treatment and general information on how to sustain a healthy lifestyle (with focus on diet, smoking, alcohol and physical activity).

2.5. Outcomes

See Table 2 for a list of all outcomes in this thesis.

Study I

The QST procedure consisted of three different psychophysical parameters: 1) Cuff algometry at the lower leg, 2) temporal summation of cuff-induced pain, and 3) CPM. The procedure was performed bilaterally and the sequence was randomized.

Cuff Algometry for Assessment of the Pain Sensitivity

PPT and PTT were recorded by a computer-controlled cuff-algometer (Aalborg University, Denmark)[162]. A 13-cm wide tourniquet cuff (VBM, Germany) with an equal-sized proximal and distal chamber was wrapped around the lower leg at the level of the heads of the gastrocnemius muscle (Figure 11). The pressure was increased with a rate of 1 kPa/s and the maximal pressure limit was 100 kPa. The participants used an electronic VAS to rate their pressure-induced pain intensity and a button to release the pressure (Figure 12). The electronic VAS was sampled at 10 Hz. Zero and ten cm extremes on the VAS were defined as "no pain" and as "maximal pain", respectively. The participants were instructed to rate the pain intensity continuously on the electronic VAS from when the pressure was defined as pain (PPT) and to press the pressure release button when the pain was intolerable (PTT). The assessments were performed by inflation of the proximal chamber, the distal chamber, and both chambers simultaneously in a randomly generated sequence; each of the three conditions was repeated twice and a mean of the different parameters was applied in the statistical analysis.

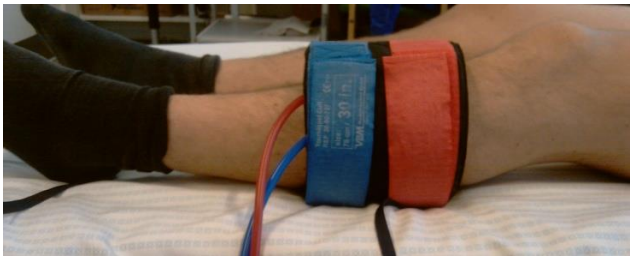


Figure 11. The tourniquet cuff wrapped around the lower leg.

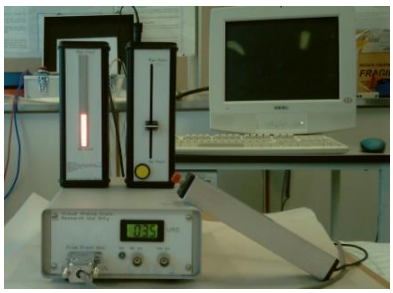


Figure 12. The electronic visual analogue scale.

Temporal Summation of Cuff-induced Pressure Pain

Temporal summation was assessed by the computer-controlled cuff-algometer (Aalborg University, Denmark)[162]. Ten cuff pressure stimuli (1s duration and 1s interstimulus interval) were delivered to the lower leg by simultaneous inflation of both cuff chambers at an intensity equivalent to the mean of the PPT and PTT recorded during the assessment of the pain sensitivity (Figure 11). In the period between stimuli a constant non-painful pressure of 5 kPa was kept ensuring that the cuff did not move. The participants rated their pain intensity continuously during the sequential stimulation on the electronic VAS without returning it to zero in-between the stimulations (Figure 12). The mean VAS scores during the 1s interstimuli interval after each of the 10 stimuli was extracted, normalized by subtraction of the mean VAS scores from the first stimulation. Two series of recordings were completed and the average was used in the statistical analysis.

Conditioned Pain Modulation

Experimental tonic pain (ischemia) was induced in the left arm by cuff-induced pain (Figure 13; conditioning stimulation), and assessment of PPTs (test-stimulus) was done before, during and 5 min. after the conditioning stimulation using handheld pressure algometry (Figure 7).

The conditioning stimulation was induced by constant cuff stimulation. A 7.5 cm wide tourniquet cuff (VBM, Germany) was wrapped around the left arm with the lower rim of the cuff placed 3 cm proximal to the cubital fossa. The

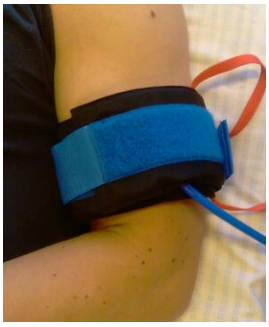


Figure 11. The tourniquet cuff used to induce tonic arm pain

computer-controlled cuff-algometer (Aalborg University, Denmark) maintained a constant pressure corresponding to a pain of 4 cm at the electronic VAS rated by the individual participant. If the cuff-induced pain did not reach 4 cm on the VAS scale, the participants were asked to do hand grip exercise until the pain intensity target was achieved. The test-stimulus (PPTs assessed using a handheld algometer) was applied, bilaterally, using the protocol described in section "2.3. Procedure", at eight test sites in the knee region (Figure 8), one site at the tibialis anterior muscle (lower leg; 5 cm distal to the tibial tuberosity), and one site at the extensor carpi radialis longus muscle (forearm; 5 cm distal to the lateral epicondyle of the humerus)[61]. The average of two PPT measurements from all eight sites in the knee region, the lower leg, and the forearm were applied in the analysis of CPM[61].

Study II

Spreading sensitization to pressure pain stimulation

Bilaterally, PPTs were measured from the lower leg and the forearm[61] using the same protocol as in study I. The PPT was measured twice at each site and the averages were used for further analysis.

Temporal summation of pressure pain

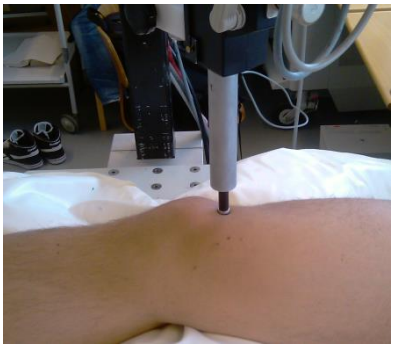


Figure 12. Computer-controlled pressure algometry

Temporal summation was assessed using a computer-controlled pressure algometer (Figure 14; Aalborg University, Aalborg, Denmark)[163]. The mechanical pressure stimuli were applied perpendicular to the skin surface using a circular aluminum footplate with a 1 cm^2 padded contact surface fixed to the tip of the piston. Using recordings of the actual force the pressure stimulation was feedback controlled. The PPT was found by increasing the pressure until the patient defined the pressure as pain. At the level of the PPT, ten sequential pressure stimuli were applied to the most sensitive site in the knee region and to the lower leg (1 s duration and 1 s inter-stimulus interval). Between the individual pressure stimuli skin contact was kept by applying a constant force of 0.1 kg, which did not evoke pain. During the sequential stimulation the patients rated their pain intensity continuously on an electronic VAS where 0 cm indicated 'no pain', and 10 cm indicated 'maximal pain'. The VAS signal for each stimulus was sampled by a computer at 200 Hz. The mean VAS scores during 1s after each stimulus were extracted and normalized by subtraction of the mean VAS score from the first stimulation. The sum of normalized VAS scores of two series of stimulations from each site was applied in the statistics (VAS sum; possible range 0-90).

Study III

Primary outcome

The primary outcome was peak knee pain intensity in the previous 24h assessed on a 100 mm VAS with terminal descriptors of 'no pain' and 'worst pain possible'. We chose peak pain intensity since it has been frequently applied in studies on sensitization in knee OA-related pain[61, 64]. The VAS is a measure of pain widely used in patients with knee OA that is valid, reliable and responsive[55].

Secondary outcomes

All secondary outcomes were declared supportive of the primary outcome.

Assessment of pain

Pain intensity during function

Knee pain intensity after 30 min of walking was assessed on a 100 mm VAS with terminal descriptors of 'no pain' and 'worst pain possible'. Pain intensity after 30 min of walking was chosen, since it can serve as an indirect measure of how the knee pain affects function.

Knee pain location and pattern

Knee pain location and pattern in the most affected knee were assessed using the reliable interviewer-administered questionnaire Knee Pain Map previously applied in knee OA patients (described in section "2.3. Procedure")[56, 57]. Since diffuse pain is indicative of a more progressed sensitization[59], the results were dichotomized (diffuse pain in the most affected knee yes/no).

Spreading of pain

The patients were asked to shade body sites with pain in the previous 24 hours on a region-divided body chart (26 sites in total). The number of pain sites was applied to classify the spreading of pain as previously suggested in a large scale study on multisite pain[58].

Functional limitations

This was evaluated using the subscale ADL (Function in daily living) from the KOOS[34, 35], which is identical to the physical function subscale from the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[36].

Usage of pain medication

This was defined as any pain medication taken on a regular basis during the last week at baseline and the 3 months follow-up. The results were dichotomized (pain medication yes/no) due to non-uniformity of the distribution of pain medication intake.

Assessment of sensitization

PPTs were measured bilaterally using the same protocol as in study I and study II at four sites at the knee (site 3, 5, 7 and 8 in Figure 8; localized/peripheral sensitization), at the lower leg (spreading/central sensitization), and at the forearm (spreading/central sensitization)[61]. One or two test assessments were performed at the dorsal aspect of the hand to ensure that the patient understood the procedure. PPTs were obtained twice at each site, and the mean of the two assessments were applied in the statistical analysis for the knee (a mean of all four sites), for the lower leg and for the forearm. The test procedure has previously been assessed in a test-retest reliability and agreement study with 20 patients with knee OA demonstrating intraclass correlation coefficients (2-way random-effects model, consistency-type) and 95% limits of agreement (95% LOA; presented as the difference between the mean difference and the upper and lower LOA) of 0.84-0.91 and 199.6-434.0 kPa[164] for the different test sites. The 95% LOA corresponds to the minimal detectable change (MDC)[165] for the assessment method.

Measure	Study I	Study II	Study III
Patient-reported			
Body sites with pain	✓		✓
Current knee pain (VAS 0-100)	✓		
Knee Pain Map (Pain location and pattern)	✓		✓
KOOS ADL[1]	✓		✓
Pain intensity after 30 min of walking (VAS 0-100)			✓
Peak pain intensity in the previous 24h (VAS 0-100)		✓	✓
Usage of pain medication	✓		✓
Duration of knee pain	✓	✓	✓
Quantitative sensory testing			
Computer-controlled algometry, temporal summation		✓	
Conditioned Pain Modulation	✓		
Cuff algometry, PPT	✓		
Cuff algometry, PTT	✓		
Cuff algometry, temporal summation	✓		
Handheld algometry, PPT at the knee		✓	✓
Handheld algometry, PPT at the lower leg		✓	✓
Handheld algometry, PPT at the forearm		✓	✓

Table 2. Overview of outcomes and other important measures in this thesis. [1]KOOS ADL in paper I was calculated from WOMAC Function using the formula 100 – (raw function score x 100)/maximum function score. VAS = Visual Analogue Scale; KOOS = The Knee Injury and Osteoarthritis Outcome Score; ADL = Activities of Daily Living; PPT = Pressure Pain Threshold; PTT = Pain Tolerance Threshold.

2.6. Statistics

Study I

Sample Size

The sample size was calculated based on the pre-defined hypothesis (Patients with PPP have more pronounced sensitization than those without pain). With a standard deviation of 4 kPa, the sample size needed to detect a 4 kPa difference between groups in PPT (cuff algometry) at the lower leg (power of 80% and significance level at 0.05 (two-sided)) was 16 in each group. To account for missing data and potential hardware issues 20 were included in each group, which was also deemed adequate to find differences between groups in the other outcomes.

Statistical analyses

Data were assumed to be normally distributed; confirmed by visual inspection of Q-Q plots. To compare demographics and clinical characteristics between the two groups Pearson's chi-square was used for gender, revision knee and pain medication, Fisher's exact test for knee pain pattern, Mann Whitney U test for total pain sites and an independent samples t-test for the other characteristics. A three-way analysis of variance (ANOVA) was used to evaluate cuff algometry and temporal summation data with factors *group (pain, no pain), side (revised, contralateral)* and *chamber (proximal, distal, both)* or *stimulation number (1-10).* A repeated measures (RM) ANOVA was used to evaluate CPM with *time (before, during, after conditioning stimulation*) as the within-subject factor and *side (revised, contralateral)* and *pressure site (knee, TA, forearm)* as the between-subject factors for both the pain group and the no pain group. Tukey HSD (for three-way ANOVA) or Bonferroni (for repeated measures ANOVA) were used as post hoc tests in cases of significant ANOVA factors or interactions. Gender and age was set as covariates in the between group ANOVA analyses to control for potential effects of these variables.

Study II

Sample Size

The sample size was calculated based on the pre-defined hypothesis (Patients with PPP have more pronounced sensitization than those with knee OA). With a standard deviation of 100 kPa, the sample size needed to detect a 100 kPa difference between groups in PPT from the forearm (power of 80% and significance level at 0.05 (two-sided)) was 16 in each group. To account for the relatively large variation previously demonstrated in sensitization in patients with knee OA[61], at least 50 patients with knee OA was needed to allow for subgroup analyses of the second pre-defined hypothesis (patients with high local knee pain sensitivity have more pronounced widespread sensitization than those with low local knee pain sensitivity). Therefore 53 patients with knee OA and 20 patients with PPP after re-TKA were included.

Statistical analyses

Confirmed by visual inspection of Q-Q plots data were normally distributed. A one-way ANOVA was used to evaluate peak clinical pain intensity in the previous 24h, PPT and temporal summation data with *group (1-4)* as a factor. Due to unequal sample size and unequal variance in the groups the adjusted F statistic, Brown Forsythe test was applied for PPT and temporal summation. Games-Howell was used as post-hoc tests in cases of a significant ANOVA except for peak clinical pain intensity in the previous 24h, where Tukey-Kramer was applied due to equal variance but unequal sample size.

Study III

Sample Size

The sample size was calculated based on the primary outcome (peak pain intensity). The sample size needed to detect a 10 point difference (standard deviation of 14) between groups in peak pain intensity was 41 patients in each group (power of 90 % and significance level at 0.05 (two-sided)). To account for possible TKA during follow-up and missing data, the drop-out rate was set to 20 % and a total of 100 patients were randomized. Due to the ancillary nature of this pre-specified

analysis the sample size was deemed adequate for the purpose of providing additional characterization of the treatment effects from the MEDIC treatment.

Statistical analyses

Since this was an ancillary analysis only patients with available data from both the baseline and 3 months follow-up, who did not undergo TKA in the follow-up period, were included in the analyses and no adjustments for multiplicity were conducted as endorsed by The European Agency for the Evaluation of Medicinal Products when exploratory analyses are declared supportive[166].

A Student's t-test was used to evaluate change in pain intensity, KOOS ADL and number of pain sites between and within groups. A three-way ANOVA was used to evaluate change in PPT from baseline to 3 months with the fixed factors *group (MEDIC, usual care)*, *site (knee, lower leg and forearm)* and *side (most affected, contralateral)*. The analysis was conducted both unadjusted and adjusted (baseline PPT, gender and age). Within-group changes from the treatment in PPTs were further assessed using repeated measures ANOVA with *time (baseline, 3 months)* as the within-subject factor and *site (knee, lower leg and forearm)* and *side (most affected, contralateral)* as the between-subject factors for both the MEDIC group and the usual care group. The assumptions of homogeneity of variance were tested using Levene's test ($P>0.05$) and the assumption of normal distribution was tested by visual inspection of Q-Q plots. In case of non-significant between-group findings a sensitivity-analysis was performed including only those participating in at least 75% of the exercise sessions. Tukey HSD was used as post hoc test in cases of significant ANOVA factors or interactions.

The relative risks for usage of pain medication and diffuse pain was estimated and compared between groups using a Poisson regression model with a robust error variance for the confidence intervals[167].

The significance level for all studies was set at $P<0.05$ and all analyses were performed in either IBM SPSS Statistics (Version 19, 20 or 22, IBM Corporation, Armonk, NY, USA) or Stata 13 (StataCorp, College Station, TX, USA).

3. Summary of results

3.1. Study I: Widespread sensitization in patients with persistent pain after revision TKA

Demographics and clinical characteristics are shown in Table 3. Figure 15 illustrates the difference in body sites with pain between groups.

Patient characteristics mean (SD) or n (%)	**Patients with pain (n=20)**	**Patients without pain (n=20)**	**P value**
Age (years)	61.5 (7.9)	65.7 (5.9)	0.06
Gender, n women	14 (70)	8 (40)	0.06
Body Mass Index (kg/m^2)	30.7 (5.5)	31.5 (4.0)	0.61
Revision knee, n right	11 (55)	6 (30)	0.11
Duration of pain before primary arthroplasty (months)	66.9 (84.8)	36.1 (41.4)	0.15
Total duration of knee pain (months)	167.0 (101.1)	64.3 (50.9)	<0.001*
Time between primary arthroplasty and first revision (months)	43.2 (52.8)	25.4 (27.3)	0.18
Knee pain before primary arthroplasty (mm)	78.3 (17.1)	81.9 (18.8)	0.53
Knee pain before first revision (mm)	64.6 (20.8)	55.9 (30.4)	0.30
Current knee pain (mm)	49.7 (26.2)	0.0 (0.0)	<0.001*
WOMAC total (arbitrary unit)	46.2 (18.9)	11.2 (9.5)	<0.001*
KOOS ADL (arbitrary unit)	52.9 (22.8)	87.4 (12.1)	<0.001*
Number of surgeries after primary arthroplasty (revisions/total)	1.4 (0.8) / 2.9 (2.5)	1.2 (0.7) / 1.4 (1.1)	0.41/0.03*
Body sites with pain	5.9 (2.7)	3.0 (3.3)	<0.001*
Knee pain pattern, n diffuse	15 (75)	0 (0)	<0.001*
Using pain medication, n	18 (90)	5 (25)	<0.001*

Table 3. Demographics of patients in study I (n = 40). *= significant differences (p<0.05).

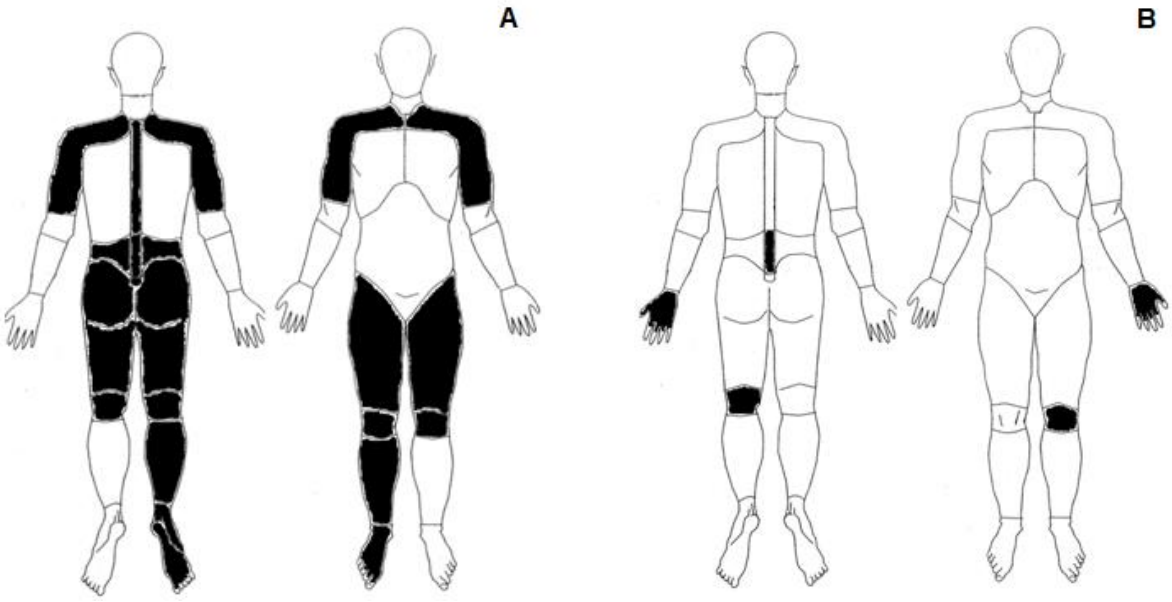


Figure 13. Body sites with pain. Sites of the body where at least 25% (n=5) of the patients with pain (A) and without pain (B) after re-TKA reported pain. The right side of the body in the figures has been set as the side with re-TKA.

Pain sensitivity

Cuff PPTs and PTTs were significantly lower in the group with pain after the re-TKA compared to the group without pain after re-TKA (ANOVA: $F(1,220) > 15.6$, $P < 0.001$; Figure 16).

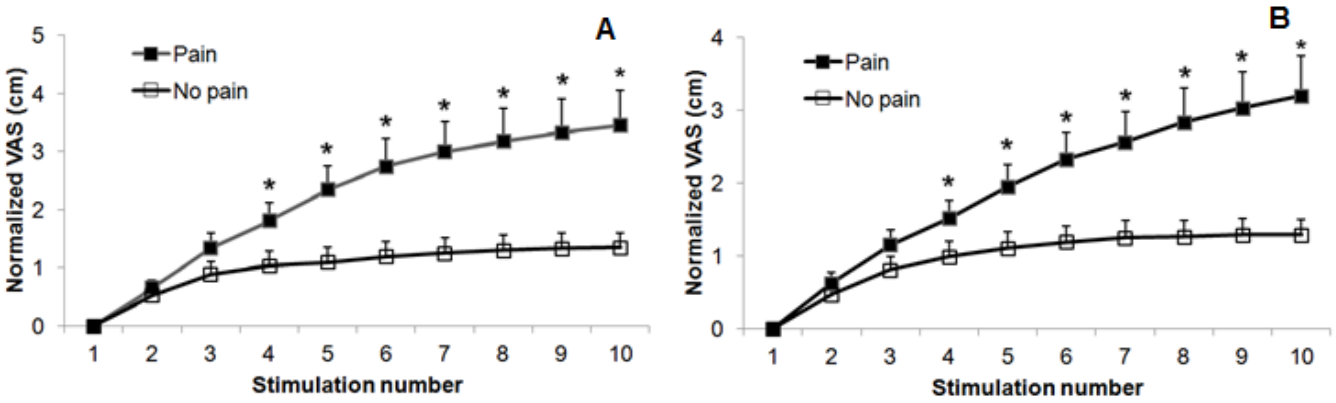


Figure 14. Cuff pressure pain thresholds and tolerances. Mean cuff pressure pain thresholds (A; PPT) and cuff pressure pain tolerances (B; PTT) in patients with (solid symbols) and without pain (open symbols) after re-TKA. PPTs and PTTs were assessed for the proximal, distal and both chambers with a cuff mounted at the lower leg of the leg with re-TKA and contralaterally. Significantly lower PPTs and PTTs were found in the pain group than in the pain free group (*, $P < 0.001$). Furthermore, significantly higher PTTs were found for the proximal chamber compared to both the distal and both chambers ($^{\#}$, $P < 0.05$). Error bars indicate SEM.

Temporal summation

An interaction between group and stimulation number showed that the normalized VAS scores to sequential stimulation were significantly higher in the pain group compared to the no pain group for stimulation 4 to 10 (ANOVA: $F(9,738) = 6.13$, $P < 0.001$; Tukey: $P < 0.05$; Figure 17).

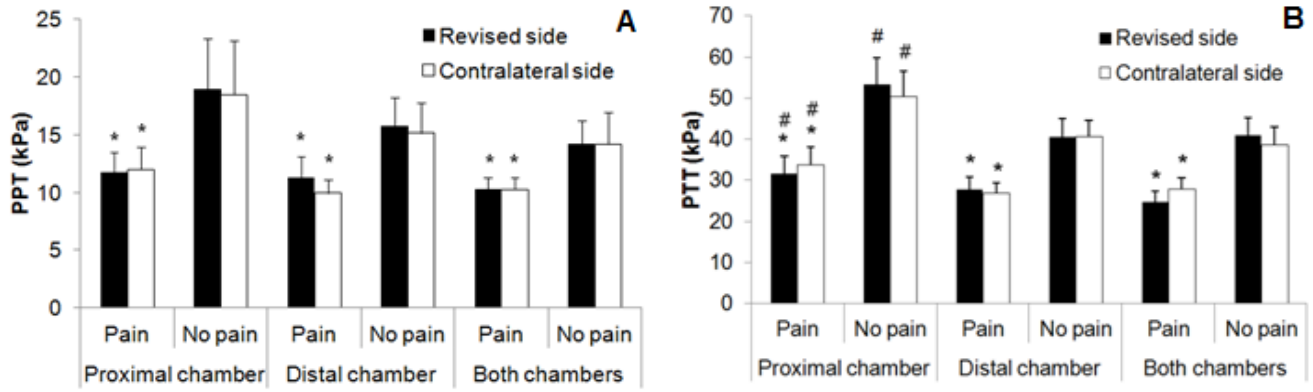


Figure 15. Temporal summation. Mean VAS scores after 10 cuff pressure pain stimulations (temporal summation) in patients with (solid symbols) and without pain (open symbols) after re-TKA. VAS scores were normalized by subtraction of the VAS scores from the first stimulation and presented for the leg with re-TKA (A) and contralaterally (B). The pain group had significantly higher VAS scores than the pain free group for stimulations 4 to 10 (*, $P < 0.05$). Error bars indicate SEM.

Conditioned pain modulation

In the pain group handheld algometry PPTs from the knee region, the TA, and the forearm were significantly reduced from baseline during the painful conditioning stimulation (ANOVA: $F(1.446, 164.830) = 8.248$, $P = 0.001$; Bonferroni: $P < 0.001$; Figure 2). In contrast, in the no pain group PPTs from all sites increased significantly from baseline during the painful conditioning stimulation (ANOVA: $F(1.575, 170.071) = 33.1$, $P < 0.001$; Bonferroni: $P < 0.001$; Figure 2).

3.2. Study II: Facilitation of sensitization in knee OA and persistent post-operative pain

Demographics and clinical characteristics are shown in Table 4. The VAS score of the peak pain intensity was not significantly different between groups (ANOVA: $F(3,72) = 0.95$, $P > 0.4$). As expected, the PPTs from the affected knee in group 1-4 were significantly different due to the subgrouping (ANOVA: $F(3,40.4) = 83.3$, $P < 0.001$; Games-Howell: $P < 0.01$).

Patient characteristics mean (SD) or n (%)	**Group 1 (n=26)**	**Group 2 (n=27)**	**Group 3 (n=10)**	**Group 4 (n=10)**
Age (years)	64.1 (7.5)	61.4 (8.5)	61.4 (9.9)	61.5 (5.7)
Gender, n women	10 (38)	15 (56)	7 (35)	7 (35)
Body Mass Index (kg/m^2)	28.9 (5.5)	28.3 (3.7)	29.3 (6.0)	32.1 (4.9)
Peak clinical pain in previous 24 h (mm)	52.1 (29.1)	62.4 (26.0)	58.0 (23.8)	65.6 (22.3)
Duration of knee pain (months)	86.6 (72.0)	89.1 (71.8)	152.2 (76.2)	181.8 (123.7)
PPT knee (kPa)	702.7 (222.8)	331.5 (99.6)	227.2 (63.7)	130.9 (18.8)

Table 4. Demographics of patients in study II (n = 73). 'PPT': Pressure Pain Thresholds measured using a handheld pressure algometer in the knee region of the affected knee. The patients were grouped according to sensitivity at the most affected knee determined using the median pressure pain thresholds (PPT) from eight test sites in the knee region. Group 1 (n=26): knee OA pain and low knee pain sensitivity. Group 2 (N=27): knee OA pain and high knee pain sensitivity. Group 3 (N=10): pain after re-TKA and low knee pain sensitivity. Group 4 (N=10): pain after re-TKA and high knee pain sensitivity.

Spreading sensitization

PPTs from the lower leg and the forearm in group 4 were significantly lower (more spreading sensitization) compared to lower leg and forearm PPTs in groups 1, 2, and 3; the lower leg and forearm PPTs in group 2 and 3 were significantly lower than the lower leg and forearm PPTs in group 1 (Lower leg: ANOVA: $F(3,81.0) = 63.3$; Forearm: ANOVA: $F(3,78.6) = 45.3$; $P < 0.001$; Games-Howell: $P < 0.05$; Figure 3).

Temporal summation

VAS sum at the knee and lower leg was significantly higher in groups 3 and 4 compared to the VAS sum in groups 1 and 2 (Knee: ANOVA: $F(3,72.3) = 10.7$; Lower leg: ANOVA: $F(3,72.7) = 11.3$, $P < 0.001$; Games-Howell: $P < 0.05$; Figure 18).

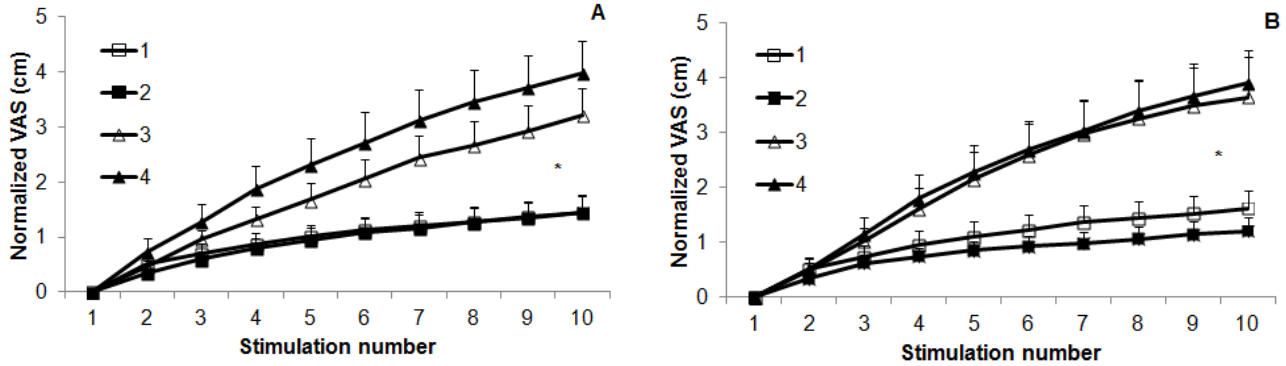


Figure 16. Temporal summation. Mean VAS scores after 10 pressure pain stimulations at the most sensitive site in the knee region (A) and at the lower leg (B). VAS scores were normalized by subtraction of the VAS scores from the first stimulation. Group 1 (n=26): knee OA pain and least knee pain sensitivity. Group 2 (N=27): knee OA pain and high knee pain sensitivity. Group 3 (N=10): pain after re-TKA and low knee pain sensitivity. Group 4 (N=10): pain after re-TKA and high knee pain sensitivity. Group 3 and 4 had significantly higher VAS sum than group 1 and 2 for both the knee and the lower leg (*, $P < 0.05$). Error bars indicate SEM.

3.3. Study III: The effects of non-surgical treatment on pain and sensitization in knee OA

The flow of patients through the study is illustrated in Figure 19. Of the 654 patients assessed for eligibility, 553 were ineligible. Of the 101 who were eligible, one did not want to be randomized. In total, 100 were randomized with 43/50 (86%) in the MEDIC group and 46/50 (92%) in the usual care group completing the 3 months follow-up and included in the analysis. Characteristics of treatment groups at baseline are presented in Table 5.

Between-group analyses

Pain intensity

There was a statistically significant difference in change (95 % CI) from baseline to 3 months of 15.4 (2.6 to 28.2) in peak pain intensity (P = 0.019) and of 32.6 (18.1 to 45.0) in pain intensity after 30 min of walking (P < 0.001) favoring the MEDIC group.

Knee pain location and pattern

There was no significant difference between treatment groups in the change in proportions with diffuse pain at 3 months compared to baseline.

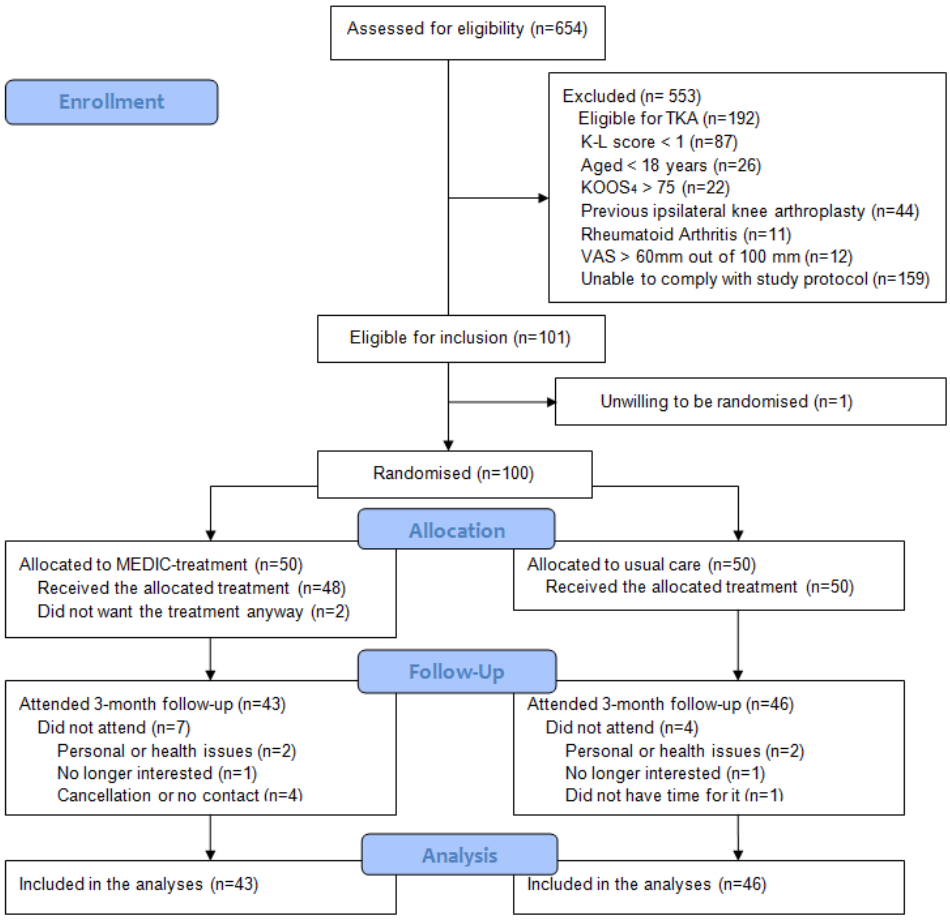


Figure 17. Flow of patients in the study. K-L score = Kellgren-Lawrence score; KOOS4 = The average score for the subscale scores for pain, symptoms, activities of daily living and quality of life from the Knee injury and Osteoarthritis Outcome Score, VAS=Visual Analogue Scale.

Patient characteristics Mean (SD) or n (%)	**MEDIC (n=50)**	**Usual Care (n=50)**
Gender, n women	26 (52)	25 (50)
Age (years)	64.8 (8.7)	67.1 (9.1)
Body Mass Index (kg/m^2)	30.6 (5.6)	29.4 (5.2)
Bilateral knee pain	18 (36)	21 (42)
Duration of knee symptoms		
0-6 months	4 (8)	2 (4)
6-12 months	9 (18)	6 (12)
1-2 years	10 (20)	5 (10)
2-5 years	11 (22)	13 (26)
5-10 years	4 (8)	8 (16)
More than 10 years	12 (24)	16 (32)
Radiographic knee OA severity (Kellgren-Lawrence)		
Grade 1	7 (14)	11 (22)
Grade 2	13 (26)	15 (30)
Grade 3	13 (26)	10 (20)
Grade 4	17 (34)	14 (28)
Peak pain intensity in the previous 24h (0-100)	60 (23)	56 (25)
Pain intensity after 30 min walking (0-100)	62 (26)	47 (24)
KOOS ADL	55.5 (17.1)	60.4 (16.4)
Using pain medication, n	32 (64)	30 (60)
Body sites with pain	3.2 (2.9)	2.8 (2.1)
Knee pain pattern, n diffuse	34 (69)	26 (55)

Table 5. Demographics of patients in study III (n = 100).

Spreading of pain

There was a statistically significant difference in change (95 % CI) from baseline to 3 months of 0.86 (0.03 to 1.70) in number of sites with pain (P = 0.042) favoring the MEDIC group.
Figure 20 illustrates the difference in body sites with pain at baseline and after 3 months in the MEDIC group and the usual care group.

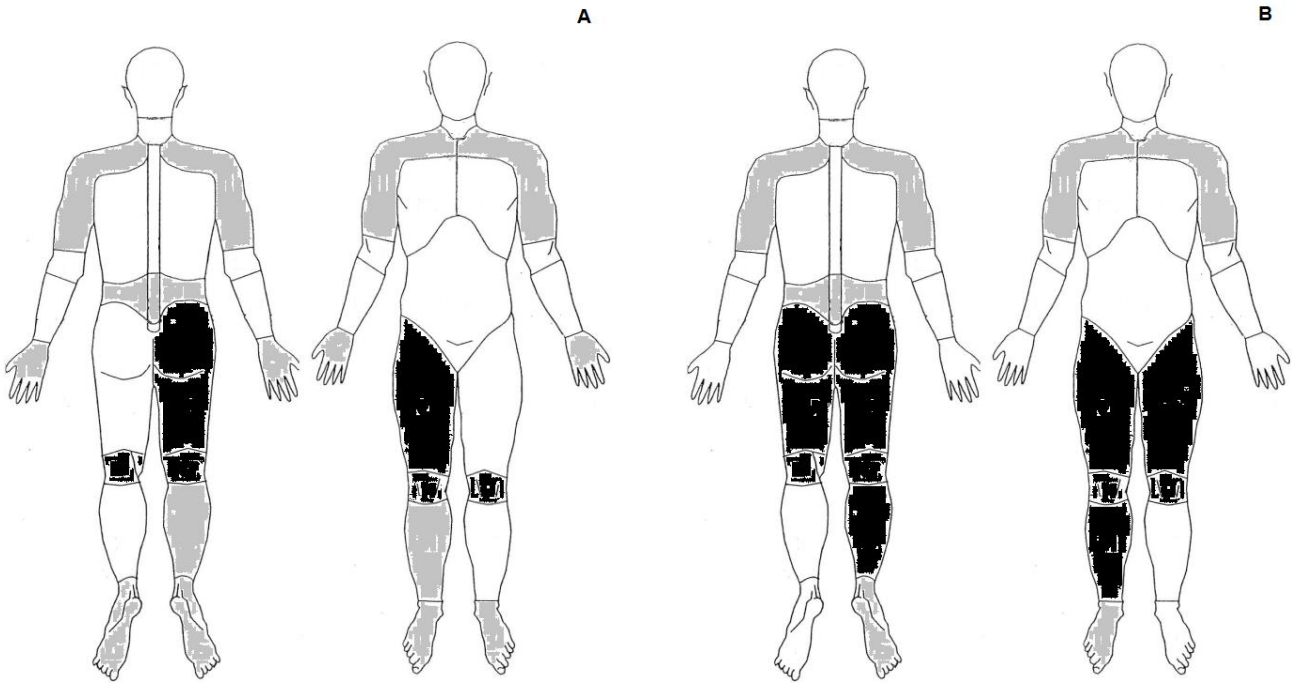


Figure 18. Pain sites. Sites of the body where at least 10% of the patients in the MEDIC group (A) and in the usual care group (B) reported pain in the previous 24 hours. A black shade indicates that at least 10% reported pain at both baseline and the 3 months follow-up, while a grey shade indicates that at least 10% reported pain at baseline, but not at the 3 months follow-up. The right side of the body in the figures has been set as the side mostly affected by knee osteoarthritis.

Functional limitations
There was a statistically significant difference in change (95% CI) from baseline to 3 months of 15.1 (7.8 to 22.5) in functional limitations ($P < 0.001$), favoring the MEDIC group.

Usage of pain medication
There was no significant difference between groups in the usage of pain medication at 3 months compared to baseline.

Sensitization
No statistically significant differences in changes in PPTs from baseline to 3 months were found between groups in the crude analysis ($F(1,468) = 0.028$, $P = 0.868$) or when adjusting for baseline PPT, age and gender ($F(1,465) = 0.015$, $P = 0.902$; Figure 4).

Within-group analyses

Within-group results are presented in Tables 3 to 5 in paper III.

4. Discussion

4.1. Main Findings

The aim of this thesis was to investigate pain and sensitization in patients with PPP after re-TKA, compare patients with PPP after re-TKA to patients with painful knee OA and explore whether the spreading of sensitization differs within the patient groups based on an evaluation of local knee pain sensitivity, and investigate whether a 3-month treatment program of education, neuromuscular exercise, weight loss, insoles, and pain medication improves pain and sensitization outcomes in patients with knee OA. Study I is the first study to investigate sensitization in patients with PPP after re-TKA, Study II is the first to compare spreading of pressure pain sensitization and temporal summation in patients with painful knee OA and patients suffering from PPP after re-TKA, and study III is the first to evaluate multiple pain-related measures, including sensitization, in a randomized setting in patients with knee OA.

The thesis demonstrated that patients with PPP after re-TKA had significantly more pain sites and more pronounced pressure pain sensitivity at the lower leg and forearm (indicators of more pronounced widespread sensitization) compared to the patients without pain after re-TKA. Furthermore, the group with PPP demonstrated facilitated temporal summation of pain and impaired descending pain modulation, highlighting the importance of central mechanisms in the process of spreading pain sensitization.

In patients with PPP after re-TKA temporal summation was more facilitated than it was in patients with knee OA with similar pain intensities. The same was found for spreading sensitization when re-TKA patients with high local knee pain sensitivity were compared to OA patients with high local knee pain sensitivity and re-TKA patients with low local knee pain sensitivity to OA patients with low local knee pain sensitivity. Furthermore, the spreading sensitization was more pronounced in patients with high local knee pain sensitivity compared to patients with low local knee pain sensitivity within the OA and re-TKA patients, respectively.

The 3-month non-surgical treatment program was associated with greater improvements in pain intensity outcomes and in measures of the spreading of bodily pain and functional limitations, but not in sensitization, knee pain pattern, and usage of pain medication after 3 months compared to information and treatment advice in patients with knee OA not eligible for TKA. These findings confirm that pain has a multitude of facets, and that treatment results may differ depending on what pain-related measures are evaluated.

4.2. Knee pain and sensitization in knee OA and persistent post-operative pain

It is generally accepted in the scientific community that a nociceptive input, including surgeries such as TKA, changes pain processing in the peripheral and central nervous systems[137, 168-174]. Even though a RCT[175] demonstrated a reduction in PPP as a result of preoperative treatment with pregabalin (a centrally acting drug) in patients with knee OA undergoing TKA, a recent review concluded that the current evidence is conflicting with regard to the efficacy of perioperative

pharmacological treatment on PPP[172]. Since 20% undergoing a TKA experience a medically unexplained unfavorable pain outcome[131], this underlines the need for a better understanding of mechanisms, such as sensitization, involved in OA-related pain[50] and PPP[137, 138] to be able to target the treatment toward those mechanisms before TKA is considered, and peri- and postoperatively to prevent and/or treat PPP. This thesis contributes significantly to this understanding.

4.2.1. Pain

Comparing the peak pain intensity in the participants in study III (mean of 58 out of 100) to that in the participants in study II (mean of 62 out of 100) and the functional limitations in the participants in study III (mean of 58 out of 100) to those in participants in study I (mean of 53 out of 100), there seemed to be small if any differences between the population with PPP after re-TKA and the population with knee OA pain. However, as described in the background, inclusion of several different measures and thereby encompassing the complexity of pain[54], also with regard to PPP[143], is recommended. Looking at the other measures related to pain, another picture emerges: body sites with pain (re-TKA: mean of 6; knee OA: mean of 3), knee pain pattern (re-TKA: 75% with diffuse pain; knee OA: 60 % with diffuse pain), duration of knee pain (re-TKA: mean of 14 years; knee OA: only 28% had had pain for more than 10 years), and pain medication usage (re-TKA: 90% were users; knee OA: 62 % were users) all indicated that the patients with PPP after re-TKA were more severely affected by the pain. Besides highlighting the importance of a multimodal pain assessment, this stresses the major clinical problem constituted by PPP after re-TKA.

4.2.2. Pain sensitivity

In persistent pain due to knee OA, localized sensitization together with widespread sensitization has been demonstrated[61-63, 74-77]. The studies in this thesis showed that similar factors are also important in patients with PPP after re-TKA and that they are more pronounced in patients with PPP as compared to patients with knee OA pain. Individuals with OA have lower PPTs in both the affected joint and at remote sites compared to pain-free participants as an indicator of spreading sensitization[70]. The studies in this thesis demonstrated that this was also the case with regard to PPP after re-TKA: pressure pain sensitivity at the lower leg was greater in both the revised and the contralateral leg than it was in pain-free patients after re-TKAs. The spreading of sensitization to the contralateral side has previously been demonstrated in knee OA using handheld pressure algometry[61, 63, 74] and cuff algometry[63]; a phenomenon for which there can be several explanations. Firstly, it is likely that some of the participants had bilateral knee OA before undergoing the primary TKA and later revision and therefore still had symptoms in the contralateral knee. Secondly, it is possible that subclinical changes exist in the contralateral knee that affect the sensitization related to the contralateral side. Lastly, the chronic pain state could result in bilateral sensitization in the central nervous system, a notion supported by data from experimental inflammatory rat OA models showing that central changes occur in addition to the localized nociceptor sensitization[176-179]. Interestingly, study II showed increased pain sensitivity distant from the affected joint in response to mechanical stimuli at the lower leg and forearm in patients who had PPP after re-TKA compared to OA pain patients, indicative of a progression of sensitization at later

stages of the disease/treatment. A recent study supports this by demonstrating increased pain sensitivity to pressure, heat, and cold at the affected knee and forearm in patients with pain 1 year after TKA, with PPTs lower than those in the patients with knee OA in studies I and II but higher than those in the patients with PPP after re-TKA[180]. This spread of sensitization could ultimately lead to a situation whereby a local pain problem develops into regional or even widespread pain[59, 63], as described in section "1.3.2. Sensitization in knee OA". The present data from patients translate previous findings from animal studies showing enhanced responses to stimuli applied to sites adjacent and distant to a joint with ongoing nociceptive activity[176]. In rats with unilateral arthritis[181] and chronic polyarthritis[182], spinal cord neurons with input from the joint become hyperexcitable, the neurons begin to display an increased responses to stimuli applied to regions adjacent to and distant from the joint, and the total receptive field can become enlarged. Secondary hyperalgesia due to joint nociception can last for several weeks, and this hypersensitivity is related to increased responses of spinal cord neurons to input from A- and C-fibers[183].

Surprisingly, the studies in this thesis also highlighted that not all patients with knee OA have increased pain sensitivity. In study III, the participants had PPTs from the knee, lower leg, and forearm (approx. 550, 590, and 400 kPa, respectively) that were significantly higher than the PPTs in patients with PPP after re-TKA in studies I/II (approx. 180, 190, and 150 kPa, respectively). However, a comparison of PPTs found in study III to those in pain-free subjects of comparable age and gender distribution from another study (approx. 600, 500, and 350 kPa, respectively)[61] illustrates that the similarities are apparent and supports the presence of subgroups with and without sensitization, potentially related to disease severity[184], within the knee OA population as recently suggested[73, 185].

4.2.3. Temporal summation and conditioned pain modulation

Temporal summation of pain has previously been demonstrated to be facilitated in patients with OA-related pain[61], but also in other chronic musculoskeletal pain conditions such as whiplash associated disorder[186] and fibromyalgia[79]. The studies in this thesis found a facilitated temporal summation of pain, mimicking the first part of the wind-up process, in patients with persistent pain after re-TKA compared to pain-free re-TKA patients and patients with symptomatic knee OA. Furthermore, a significant positive correlation (see papers I and II) between duration of knee pain and temporal summation was demonstrated. This confirms results from animals showing facilitated wind-up in experimental OA models[187]. Following strong, successive C-fiber stimulation of somatic nociceptive fibers in animals, a frequency-dependent enhancement in neuronal excitability occurs that outlasts the stimulation. In spinal cord neurons, repeated stimuli of this type result in an increase in the magnitude of the input from Aδ- and C-fibers[188], often followed by the development of an after-discharge. Another contributing factor to the enhanced excitability is the postsynaptic action of neurotransmitters, such as substance P and glutamate, released by the repeated noxious stimuli [59]. Wind-up starts and sustains central sensitization[189], and a previous study has demonstrated that wind-up increases the receptive field area of dorsal horns in rats[190]: a feature of central sensitization[59]. Combined with the fact that both the revised and the contralateral side showed enhanced temporal summation compared to pain-free re-TKA patients and patients with

symptomatic knee OA, the findings in this thesis indicate that patients with pain after re-TKA have central sensitization[191]. Furthermore, although based on a cross-sectional analysis, study II suggests a worsening in the temporal summation of pain from knee OA pain to PPP after re-TKA, which needs further attention in future studies. This notion is supported by a study by Arendt-Nielsen et al.[61] demonstrating that knee OA patients with higher pain intensities and longer pain durations had relatively more facilitated temporal summation compared to patients having lower pain intensities and shorter pain durations[61]. This is in line with the suggested spread of sensitization[59, 63], further described in the section "1.3.2. Sensitization in knee OA".

It has been suggested that a dysfunctional CPM is important for the clinical manifestations of chronic pain at the same time making the entire neuroaxis more vulnerable to pain[192]. Study I demonstrated an impaired CPM, confirming previous findings in OA patients[61, 63, 82]. It has previously been demonstrated that the change in response to stimuli is more pronounced in spinalized animals, which highlights the influence of descending pathways[193]. During the development of joint inflammation, an increase in the tonic descending inhibition of neurons with input from the inflamed joint occurs[194, 195]. Whether continuous noxious stimuli from a painful joint lead to an increase in facilitatory and/or decrease in inhibitory mechanisms remains to be explored. It is however interesting that the group of patients with pain after re-TKA demonstrated increased pain sensitivity at the knee, lower leg, and forearm during the tonic arm pain. This suggests that the descending control acted as a promoting factor. A previous study in patients with severe knee OA[63] also found an increase in pain sensitivity at the knee during tonic arm pain, but not at the lower leg. This suggests that the CPM was further impaired in patients with PPP after re-TKA in study I, further emphasizing the importance of CPM as a complex interaction between facilitatory and inhibitory mechanisms.

4.2.4. The generator of pain and sensitization in widespread sensitization

Evidence from four controlled before-and-after reports has shown a normalization of the sensitized nociceptive system in patients with OA with no residual pain after pain-relieving joint replacement [63, 82, 146, 196], suggesting that the sensitization arises and is maintained by peripheral input. In PPP after TKA and re-TKA, the environment in which the nociception can occur has changed due to the replacement of knee-related structures. However, due to the continuous pain and sensitization demonstrated in patients with PPP after re-TKA in studies I and II, it seems that there is still adequate peripheral drive to maintain the pain and sensitization. The retention of pain and sensitization after TKA and re-TKA can be related to peripheral input from non-surgically removed periarticular tissue such as adjacent muscles, connective tissue, and/or sensitization.

In study II, the four groups had similar clinical pain intensities, underlining the notion that factors other than the severity of the pain were the cause of the differences found in the spread of sensitization and temporal summation. Both patients with knee OA and patients with PPP after re-TKA with high knee pain sensitivity had more pronounced sensitization (lower PPTs distant from the affected knee and facilitated temporal summation) than those with low knee pain sensitivity. This highlights the importance of localized sensitization as an important generator of knee OA pain,

PPP, and central sensitization. This pain and sensitization could be caused and/or influenced by inflammation and neuropathic pain, e.g. due to nerve damage from surgery[197, 198]. Inflammation has recently been demonstrated to be associated with measures of sensitization in knee OA and may perhaps lead to increased pain sensitivity and pain intensity, thereby facilitating an increase in central sensitization [75], as supported by animal studies[199, 200]. Neuropathic pain has been reported in 13% of patients with PPP after TKA[201] and represents another driver of peripheral sensitization[197]. It is of course important to recognize that the ongoing pain and sensitization are probably caused and influenced by a complex interaction between several factors (other than inflammation and neuropathic pain) involved in the sensation of pain, including psychosocial and genetic factors[12, 50, 53, 137, 198].

4.3. Non-surgical treatment of pain and sensitization in knee osteoarthritis

As stated in the background, a combination of strategies should be used to treat pain and sensitization in patients with persistent pain, targeting both top-down (the central nervous system) and bottom-up (the peripheral nociceptive input) mechanisms[144]. Study III was the first study that combined treatments recommended for knee OA pain that applied both top-down and bottom-up approaches to target both pain and sensitization.

4.3.1. The efficacy of non-surgical on pain

The primary results from the RCT[202] (the origin of the data in study III) showed that the 3-month MEDIC-treatment[155] resulted in greater long-term improvements in pain, function, and quality of life compared to usual care in knee OA patients seen in a secondary care setting. These results were confirmed by the ancillary results in study III, which was a study of the short-term efficacy of the MEDIC-treatment on a range of pain-related measures (different from those of the primary report). A comparison of the short-term results from the MEDIC group in study III to those obtained in the two previous RCTs investigating the long-term efficacy of a combination of at least two of the recommended treatments as compared with usual care for knee OA[203, 204] shows some interesting differences. These two RCTs were the Enabling Self-Management and Coping of Arthritic Knee Pain Through Exercise (ESCAPE-knee pain) trial[204] , which investigated the efficacy of combining exercise and education in older adults with knee pain recruited from primary care, and the Arthritis, Diet, and Activity Promotion Trial (ADAPT)[203], which investigated the efficacy of combining exercise and weight loss in obese US community dwellers with knee OA. After 3 months, we found improvements in pain of 48% (peak pain intensity) and 56% (pain after 30min of walking) and in function of 32% in knee OA patients. These improvements are considerably larger than the short-term results from the ESCAPE knee pain study, which found improvements of approx. 23% in pain and 26% in function outcomes after 6 weeks[204], and from the ADAPT trial that demonstrated improvements of approx. 25% in pain and 24% in function outcomes after 6 months[203]. While differences in the study populations can be part of the explanation for the larger improvements found in study III in this thesis, differences in the treatment protocols are more likely to be the cause. In addition to exercise, we included both education and diet, and insoles and analgesics if needed (as opposed to the ESCAPE and ADAPT trials). This could be crucial because weight loss

is an important contributor to the improvement in pain and function outcomes[102] and the education taught the patients about the importance of the continuation of the treatment after the supervised period had ended and how to control and address OA problems on their own. Furthermore, some exercise-related causes could be an important explanation for the differences in efficacy. The ESCAPE knee pain trial comprised only 12 supervised sessions lasting 35-40 min without any transition period or booster sessions following the intervention[204], while our exercise program comprised 24 supervised exercise sessions followed by a transition period, gradually increasing exercise at home, and monthly booster sessions to improve long-term adherence. A recent meta-regression analysis demonstrated an increased efficacy with larger numbers of supervised sessions[89], and a systematic review demonstrated beneficial long-term effects of booster sessions after the intervention period in patients with knee OA[205]. The ADAPT trial included more exercise sessions than our study (3 days/week of facility-based exercise for 4–6 months; 64% adherence to exercise and diet comparable to adherence in our study), but the exercise consisted of aerobic walking without any focus on alignment[203]. Our neuromuscular exercise program aimed to restore neutral functional alignment by improving sensorimotor control and obtaining compensatory functional stability. Varus-valgus control deficits and a lack of capacity to stabilize the joint are characteristic findings in patients with knee OA, indicating that neuromuscular exercise could be more beneficial than aerobic exercise[206]. However, while the evidence concerning the efficacy of non-surgical treatment on knee OA pain is strong[87, 88], less is known about why exercise actually works[207]. Such information could help identify which patients would benefit from which type of exercise.

Study III extends these findings by adhering to recommendations on addressing other aspects of the complexity of pain than pain intensity alone[54], giving a comprehensive perspective on the effects of multimodal non-surgical treatment in patients with knee OA. The MEDIC group had a greater reduction in the number of body sites with pain compared to the usual care group. This could potentially be explained by systemic anti-inflammatory effects due to exercise[208], as well as to improvements in well-being and other psychosocial components that have been demonstrated to result from exercise[207] and/or the effects of education, i.e. teaching the patient about the etiology of pain and how to deal with it[209]. As mentioned, pain has been reported to spread over time[59], the spread being influenced by both the intensity[65] and duration[66] of the pain, and pain in other body parts is associated with PPP after joint replacement[201, 210, 211] and other surgical procedures[212-215]. The fact that knee pain increases the risk of developing persistent pain in other body parts over time further highlights the potential of multimodal non-surgical treatment for pain relief in patients with knee OA to prevent the pain from spreading.

4.3.2. The efficacy of non-surgical treatment on sensitization

Because the treatment given in the usual care group in study III closely resembles current practice in the treatment of knee OA patients not eligible for TKA, this group offered a useful standard against which to compare the efficacy of the treatment of the study population. However, while measures of localized sensitization and spreading sensitization improved in both groups, no significant differences in the efficacy of treatment on sensitization were found between the usual

care group and the MEDIC group. A recent RCT[148] and a controlled before-and-after study[76], both including a passive control group, found conflicting results with regard to the effect of exercise on sensitization in knee OA. Henriksen et al.[148] demonstrated that 12 weeks of supervised exercise reduced pressure pain sensitivity, while Kosek et al.[76] found no effects of exercise (average duration of 12 weeks) on pressure pain sensitivity. The within-group differences demonstrated in study III were not larger than the MDC for handheld algometry[164], a method also applied in the other study demonstrating no effect of exercise on sensitization, which is why measurement uncertainty could be part of the explanation for the conflicting results. On the other hand, the significant differences demonstrated by Henriksen et al.[148] were small, only borderline significant, and of questionable clinical relevance, and because the control group was asked to refrain from exercising, the results are also of little comparative relevance.

4.3.3. Treatment of sensitization – equally relevant for all?

From studies I and II and previous studies in knee OA[61-63, 74-77], it is evident that peripheral and central sensitization are important and clinically relevant problems associated with the disease. It is a puzzle why the evidence supporting the efficacy of non-surgical treatment of pain and function in knee OA is unequivocal, while the evidence for the effects on sensitization remains conflicting. Although it is important to recognize that the research area of sensitization and treatment of sensitization is still in its infancy and in need of more high quality studies, another explanation for the conflicting results could be the presence of subgroups of patients with OA with more sensitization and OA patients with less or no sensitization[73, 185]. Study II highlights that subgroups with more pronounced sensitization do exist among patients with knee OA and PPP after re-TKA, despite similar clinical pain intensities, while a recent study found that a subgroup with severe symptomatic knee OA but less severe radiographic knee OA had higher pain sensitivity than those with less severe symptomatic knee OA but severe radiographic severity[216]. Looking at studies using the questionnaire PainDETECT[217] in patients with OA[218-220], a measure used to indicate neuropathic pain, adds emphasis to the observation that the neuropathic component of OA pain is only present in some OA patients (5-50%). Albeit neuropathic pain is only an indirect indicator of sensitization[73], this suggests that sensitization is only present in some knee OA patients.

Sensitization may develop over time depending on disease severity and duration (depicted in Figure 1) [59, 67]. As presented in section "4.2.2. Pain sensitivity", the PPTs found in study III are similar to those found in pain-free subjects of comparable age and gender distribution[61], suggesting that the sensitization of the patients in study III may not yet have developed into a clinically relevant problem. This offers another explanation for the non-significant differences between groups, since it leaves little if any room for improvement in sensitization outcomes as a result of the MEDIC-treatment. If the development of sensitization over time is mediated by disease severity, this would mean that treating the knee OA pain could represent a way of preventing sensitization, if treatment was initiated at an early stage before sensitization progressed.

Regardless of whether sensitization is only found in some patients with knee OA and/or it is only present in those with more progressed symptom severity, non-surgical treatment of sensitization

should be targeted toward those actually affected by the problem, with the potential to desensitize the central nervous system by affecting both top-down and bottom-up mechanisms[144, 145]. Whether the multimodal MEDIC-treatment is efficacious in treating sensitization or should be supplemented with other treatments, such as centrally-acting drugs[144], remains to be explored in future trials.

4.4. Strengths and limitations

The obvious limitation of both study I and study II is that they are cross-sectional, implying that no conclusions can be drawn on causality or the temporal changes in pain and sensitization. However, the novel findings provide useful insight relevant for future trials and clinical practice. Another potential limitation of study I and study II could be that the QST was restricted to mechanical, and to some extent chemical by ischemia, stimulation, even though a multimodal QST consisting of several stimulus modalities is recommended[67, 72]. On the other hand, since the studies investigated several different pain mechanisms (pain sensitivity, temporal summation, CPM, etc.) and several aspects of pain (intensity, duration, spreading, pattern, etc.) as has been recommended[54, 67, 72], the outcome measures of study I and study II can actually be regarded as strengths instead of limitations.. Strength of studies I and II is their application of measures previously applied to other patient populations or with other purposes. Because of the consistency with previous results, this strengthens the validity of the findings.

The MDC of the handheld pressure algometry applied in study III was relatively high, thereby affecting the conclusions that can be drawn on the effects of the treatment on sensitization. However, due to the ancillary nature of this study, the findings are not meant to give firm conclusions, but to be hypothesis generating for future confirmatory trials. Due to the multimodal setup of the treatment program in study III, it is unknown whether all components of the treatment are required for the improvements found in pain-related measures, and at the same time it makes it impossible to identify the efficacy of the individual treatment modalities alone. However, since the treatment program adheres to current guidelines on the treatment of knee OA[87, 88] and is embedded in secondary health care, strengthening the generalizability of the findings, the strengths of the study are considered to outweigh the limitations.

5. Conclusions

This thesis established that patients with PPP after re-TKA have prominent widespread sensitization, involving similar pain mechanisms as previously demonstrated in patients with knee OA. Furthermore, it was found that the spreading of sensitization and temporal summation were more pronounced in patients with PPP after re-TKA compared to patients with knee OA, despite similar clinical pain intensities, and that subgroups of patients with high knee pain sensitivity within the population of PPP and knee OA patients are more affected by spreading sensitization than those with low knee pain sensitivity. Lastly, the thesis demonstrated that a multimodal non-surgical treatment consisting of education, neuromuscular exercise, diet, insoles, and pain medication resulted in greater improvements in pain intensity, spreading of pain, and functional limitations outcomes than did usual care in patients with knee OA not eligible for TKA, while no between-group differences were found in peripheral or central sensitization.

5.1. Implications

It is well known in the clinical setting that the pain in patients with knee OA and PPP after TKA and re-TKA becomes more and more complex if not treated successfully. The findings in this thesis support this and suggest some important clinical implications:
1) The primary TKA and subsequent revisions should only be carried out if a potential involvement of peripheral and central pain mechanisms is either treated concurrently or, at best, before even the surgical procedure is considered.
2) Furthermore, the treatment of pain and sensitization should comprise a combined, individualized early-stage treatment program addressing both peripheral and central components of the pain, with the potential to lessen pain and the spreading of pain and sensitization in those affected by the problem.

5.2. Future perspectives

The research area of sensitization, PPP after re-TKA, and treatment of sensitization in knee OA and PPP is still in its infancy, mostly consisting of cross-sectional studies and small, exploratory longitudinal studies[221]. Further large-scale prospective cohort studies identifying predictors (such as the QST applied in this thesis) of PPP and diagnostic decisions trees are needed to enhance the understanding of the area[221, 222]. Furthermore, high quality RCTs investigating the efficacy of non-surgical and surgical treatment of pain and sensitization in knee OA would support clinical guidelines and improve the treatment of the patients[124, 154], with the potential to reduce the growing burden of OA.

6. English Summary

Osteoarthritis (OA) is an increasingly prevalent disease with substantial impact on those affected by it and on society. Knee OA, one of the most prevalent of all types of OA, is characterized by failed regeneration of joint damage, resulting in pain and functional limitation for the patient. Persistent post-operative pain (PPP) is a largely underestimated clinical problem known to affect between 5% and 85% of patients undergoing surgery. The pathophysiology of OA pain and PPP remains poorly understood, but a mechanism-based understanding is widely accepted and provides a basis for the understanding of pain. Peripheral and central pain sensitization have been demonstrated as prominent mechanisms influencing the pain in knee OA, while the state of the nociceptive system in patients with PPP after revision of total knee arthroplasty (re-TKA) is unknown. Since 20% undergoing a TKA have an unfavorable pain outcome, knowledge about mechanisms, such as sensitization, involved in the PPP are needed. It is recommended that the treatment of knee OA includes education, exercise, and weight loss, supplemented with insoles and pain medication if needed, and that sensitization should also be treated using a multimodal approach. However, little is known of the combined effects from the recommended treatments on pain-related measures and sensitization in knee OA, even though this could potentially prevent pain and sensitization from progressing and become severe and widespread.

The overall aim was to investigate pain sensitization in patients with PPP after re-TKA (study I), compare this to painful knee OA and explore whether the spreading of sensitization differs within groups based on an assessment of local knee pain sensitivity (study II), and investigate whether multimodal non-surgical treatment improves pain and sensitization in knee OA (study III).

Study I, a cross-sectional study, included 40 patients who had undergone re-TKA: 20 with PPP in the revised knee and 20 patients without PPP. Pain sensitization was assessed using the following measures: spreading of pain (number of body sites with pain), pressure pain threshold (PPT) and pressure pain tolerance (PTT) at the lower leg (cuff algometry), temporal summation of pain at the lower leg (recordings of the pain intensity on a visual analog scale (VAS) during 10 repeated cuff pressure stimulations), and conditioned pain modulation (CPM: tonic arm pain by cuff pressure stimulation and assessment of PPTs at the knee, leg, and forearm using handheld pressure algometry). Participants with PPP after re-TKA compared to participants without demonstrated significantly more pain sites ($P = 0.004$), decreased cuff PPTs and PTTs at the lower leg ($P < 0.001$), facilitated temporal summation ($P < 0.001$), and impaired CPM ($P < 0.001$).

Study II, a cross-sectional study, included 53 patients with painful knee OA and the 20 patients with pain after re-TKA from study I. Median PPTs assessed at the most affected knee (localized sensitization) were used to subgroup the patients: group 1: OA and low knee pain sensitivity; group 2: OA and high knee pain sensitivity; group 3: re-TKA and low knee pain sensitivity, group 4: re-TKA and high knee pain sensitivity. Peak pain intensity in the previous 24 h was assessed using a VAS. Pain sensitization was assessed using bilateral PPTs measured from the lower leg and forearm using handheld algometry (spreading sensitization). Furthermore, the pain intensities evoked by 10 repeated pressure pain stimuli from computer-controlled pressure algometry (temporal summation)

at the knee and lower leg were assessed on an electronic VAS. The peak pain intensity was not significantly different between groups ($P > 0.40$). The PPTs from both lower leg and forearm were significantly lower in group 4 compared to groups 1, 2, and 3 and in groups 2 and 3 compared to group 1 ($P < 0.05$). Temporal summations from the knee and lower leg were significantly facilitated in groups 3 and 4 compared to groups 1 and 2 ($P < 0.05$).

Study III was an ancillary report of the 3-month results from a two-arm parallel group assessor-blinded randomized controlled trial with 100 participants that compared the efficacy of a 3-month treatment program consisting of education, neuromuscular exercise, diet, insoles, and pain medication (the MEDIC-treatment) to two leaflets with information and treatment advice (usual care) in patients with knee OA not eligible for TKA (Trial registration: clinicaltrials.gov NCT01535001). The primary outcome was peak pain intensity in the previous 24 h (VAS 0-100). Secondary outcomes included peripheral and central sensitization assessed at the knee, the lower leg and forearm (PPT from handheld pressure algometry), pain intensity after 30 min of walking (VAS 0-100), pain location and pattern (Knee Pain Map), spreading of pain (body sites with pain), and the usage of pain medication (pain medication during the last week due to knee yes/no). Furthermore, functional limitations were assessed using the subscale Activities of Daily Living from the Knee Injury and Osteoarthritis Outcome Score. The MEDIC group had a mean improvement (95% CI) in outcome with regard to peak pain intensity from baseline to 3 months that was 15.4 (2.6 to 28.2) larger ($P = 0.019$) than in the usual care group. Furthermore, the improvements in outcome were larger in the MEDIC group in pain intensity after walking, in the number of body sites with pain and functional limitations ($P < 0.05$). There was no difference in the change in sensitization from baseline to 3 months between groups ($P > 0.05$), but sensitization improved in both groups ($P < 0.05$).

This thesis established that patients with PPP after re-TKA have prominent widespread sensitization, involving pain mechanisms similar to those previously demonstrated in patients with knee OA. Furthermore, it was found that spreading sensitization and temporal summation were more pronounced in patients with PPP after re-TKA compared to patients with knee OA, despite similar clinical pain intensities, and that subgroups of patients with high knee pain sensitivity within the population of PPP and knee OA are more affected by spreading sensitization than those with low knee pain sensitivity. Lastly, the thesis demonstrated that a multimodal non-surgical treatment program consisting of neuromuscular exercise, patient education, diet, insoles, and pain medication resulted in greater improvements in outcome with regard to pain intensity, spreading of pain, and functional limitations than usual care in patients with knee OA not eligible for TKA, while no between-group differences were found with regard to change in peripheral or central sensitization. The results of the thesis suggest that:

1) Primary TKA and subsequent revisions should only be carried out if a potential involvement of peripheral and central pain mechanisms is either treated concurrently or, at best, before even considering the surgical procedure.

2) The treatment of pain and sensitization should comprise a combined, individualized early-stage treatment addressing both peripheral and central components of the pain, with the potential to lessen pain and the spreading of pain and sensitization in those affected.

7. Danish Summary

Titel: Smerte og sensitisering ved knæartrose og vedvarende smerte efter operation

Forekomsten af artrose (slidgigt) er kraftigt stigende og lidelsen har en omfattende betydning for dem, der er påvirket af den, og økonomisk for samfundet. Knæartrose, en af de hyppigst forekommende typer af artrose, er karakteriseret ved en forfejlet genopbygning af ledstrukturer medførende smerte og nedsat funktion hos patienten. Vedvarende smerte efter operation (PPP) er et meget undervurderet klinisk problem, der påvirker mellem 5% og 85% af patienter, som gennemgår operation af den ene eller anden slags. Forståelsen for patofysiologien forbundet med artrosesmerter og PPP er fortsat begrænset, men en mekanismebaseret tilgang er bredt accepteret og anbefalet for at forbedre forståelsen af smerten i fremtiden. Perifer og central smertesensitisering har vist sig at være fremtrædende mekanismer influerende på smerten hos patienter med knæartrose, mens smertesystemet tilstand hos patienter med PPP efter revision af kunstigt knæled (re-TKA) endnu ikke er kendt. Da 20% som gennemgår en KK ikke opnår en smertereduktion, er der behov for en bedre forståelse for de mekanismer, såsom sensitisering, der er involveret i PPP. Det anbefales, at behandlingen af knæartrose indeholder uddannelse, træning og vægttab, samt at denne behandling kan suppleres med såler og smertestillende medicin ved behov. På samme måde anbefales det, at sensitisering behandles med en multimodal behandling. Der mangler dog fortsat viden om den kombinerede effekt af de anbefalede behandlinger på smerterelaterede mål og sensitisering hos patienter med knæartrose, selvom det potentielt set kan forhindre smerte og sensitisering fra at forværres og spredes til andre dele af kroppen.

Det overordnede mål med denne afhandling var at undersøge sensitisering hos patienter med PPP efter re-KK (studie I), sammenligne dette med smertefuld knæartrose og undersøge om spredningen af sensitiseringen adskilte sig indenfor patientgrupperne på baggrund af smertesensitiseringen i det mest påvirkede knæ (studie II), og undersøge om multimodal ikke-kirurgisk behandling forbedrer smerte og sensitisering (studie III).

Studie I var en tværsnitsundersøgelse af 40 patienter som havde gennemgået re-TKA; 20 med PPP og 20 uden PPP. Smertesensitisering blev undersøgt med de følgende mål: spredning af smerten (antal steder i kroppen med smerte); tryksmertetærskler (PPT) og tryktolerancetærskler (PTT) på underbenet (manchetalgometri); temporal summation på underbenet (måling af smerteintensiteten på en visuel analog skala (VAS) under 10 gentagne manchettryk); og betinget smertemodulering (CPM; tonisk armsmerte fremkaldt ved manchettryk og samtidig undersøgelse af PPT på knæet, underbenet og underarmen vha. håndholdt trykalgometri). Sammenlignet med deltagere uden PPP havde deltagere med PPP: flere steder med smerte ($P = 0,004$), reducerede PPT and PTT ($P < 0,001$), faciliteret temporal summation ($P < 0,001$), og svækket CPM ($P < 0,001$).

Studie II var en tværsnitsundersøgelse med 53 patienter med knæartrose og de 20 patienter med smerte efter re-TKA fra studie I. Median PPT fra det mest påvirkede knæ (lokaliseret sensitisering) blev anvendt til at subgruppere patienterne: gruppe 1: artrose og lav smertesensitisering i knæet; gruppe 2: artrose og høj smertesensitisering i knæet, gruppe 3: re-TKA og lav smertesensitisering i knæet; gruppe 4: re-TKA og høj smertesensitisering i knæet. Maximal smerte i knæet de sidste 24

timer blev undersøgt vha. VAS. Smertesensitisering blev undersøgt vha. bilaterale PPT fra underben og underarm vha. håndholdt algometri (spredning af sensitisering). Desuden, blev smerten fremkaldt ved 10 gentagne stimulationer fra et computer-kontrolleret trykalgometer (temporal summation) på knæet og underbenet undersøgt med en elektronisk VAS. Smerteintensiteten var ikke forskellig mellem grupperne ($P > 0,40$). PPT fra underben og underarm var lavere i gruppe 4 sammenlignet med gruppe 1-3 og i gruppe 2 og 3 sammenlignet med gruppe 1 ($P < 0,05$). Temporal summation var mere faciliteret i gruppe 3 og 4 sammenlignet med gruppe 1 og 2 ($P < 0,05$).

Studie III var en analyse af resultaterne efter 3 mdr. i et parallelt, to-armet, undersøger-blindet randomiseret, kontrolleret studie med 100 deltagere, der sammenlignede effekten af 3 mdr. behandling bestående af uddannelse, neuromuskulær træning, diæt, såler og smertestillende (MEDIC-behandlingen) med to brochurer med information og behandlingsanbefalinger (standardbehandling) hos patienter med knæartrose, som ikke var kandidater til en TKA (clinicaltrials.gov NCT01535001). Primær måleparameter var maximal smerteintensitet i knæet de sidste 24 timer (VAS 0-100). Sekundære måleparametre var perifer og central smertesensitisering undersøgt på knæet, underbenet og underarmen (PPT med håndholdt trykalgometri), smerteintensitet efter 30 min. gang (VAS 0-100), smerteplacering og –mønster (Knee Pain Map), spredning af smerte (antal steder i kroppen med smerte), forbrug af smertestillende medicin pga. knæ (ja/nej) samt nedsat funktionsniveau (subskalaen Funktion i dagligdagen fra the The Knee Injury and Osteoarthritis Outcome Score). MEDIC-gruppen havde en middelforbedring (95% CI) i maximal smerte fra baseline til 3 mdr. som var 15,4 (2,6 til 28,2) større ($P = 0,019$) end gruppen, der modtog standardbehandling. Desuden havde MEDIC-gruppen større forbedringer i smerte efter gang, antal steder i kroppen med smerte og funktionsniveau ($P < 0,05$). Der var ingen forskel i ændring i sensitisering mellem grupperne ($P > 0,05$), dog forbedredes den i begge grupper ($P < 0,05$).

Denne afhandling påviste at patienter med PPP efter re-TKA har en fremtrædende udbredt sensitisering involverende tilsvarende smertemekanismer som tidligere påvist hos patienter med knæartrose. Derudover viste afhandlingen, at spredningen af sensitisering og temporal summation var mere udtalt hos patienter med PPP efter re-TKA sammenlignet med knæartrose, på trods af lignende smerteintensitet, samt at subgrupper med høj smertesensitisering i knæet er mere påvirket af spredning af smerte end dem med lav smertesensitisering. Endelig, viste afhandlingen at multimodal ikke-operativ behandling medførte større forbedringer i smerteintensitet, spredning af smerte og funktionsniveau end standardbehandling hos patienter med knæartrose, der ikke er kandidater til TKA, mens der ingen forskel var mellem grupperne i ændring i perifer og central sensitisering.
Afhandlingens resultater antyder at:
1) Den første TKA og efterfølgende revisioner skal kun udføres, hvis en involvering af perifer og central sensitisering behandles samtidig, eller, endnu bedre, før kirurgien overvejes.
2) Behandling af smerte og sensitisering bør indeholde en tidlig, individualiseret, multimodal behandling fokuserende på både perifere og centrale komponenter af smerten. Dette har potentialet til at forbedre smerte og sensitisering hos dem, der er påvirket af det.

8. References

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