Center for Sensory-Motor Interaction

Chronic Pain after Total Knee Replacement

Doctor of Philosophy Thesis by
Kristian Kjær Petersen

River Publishers

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Kristian Kjær Petersen

21 August 2014, Aalborg, Denmark

Preface

This PhD is in part based on three studies, referred to in the text as study I-III. The studies have been conducted in the period 2011-2014 at the Center for Sensory Motor Interaction, Aalborg University, Denmark. Please find appendix 1 for a quick glance at the methods applied, findings and conclusions from the three studies.

Study I: Petersen KK, Simonsen O, Laursen MB, Nielsen TA, Rasmussen S, Arendt-Nielsen L (2014). Chronic Postoperative Pain Following Primary and Revision Total Knee Arthroplasty. *Clinical Journal of Pain*, *in pre*ss.

Study II: Petersen KK, Arendt-Nielsen L, Simonsen O, Wilder-Smith O, Laursen MB. Pre-surgical assessment of temporal summation of pain predicts the development of chronic postoperative pain 12 months after total knee replacement. *Submitted to Pain.*

Study III: Petersen KK, Siebuhr AS, Graven-Nielsen T, Simonsen O, Karsdal M, Bay-Jensen AC, Arendt-Nielsen L. Sensitization and serological biomarkers in knee osteoarthritis patients with different degrees of synovitis and pain. *Submitted to Osteoarthritis and Cartilage, under revision*.

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Abbreviations

BLOKS - The Boston-Leeds OA Knee Score
CPM – Conditioning pain modulation
HsCRP – High-sensitive C-reactive protein
IASP – The International Association for the Study of Pain
KL – Kellgren & Lawrence scale
KOA – Knee osteoarthritis
KSS – The Knee Society Score questionnaire
MMPs – Matrix metalloproteinases
MRI – Magnetic Resonance Imaging
OA – Osteoarthritis
PPT – Pressure pain threshold
QST – Quantitative sensory testing
Re-TKR – Revision Total Knee Replacement
THR – Total hip replacement
TKR – Total knee replacement
VAS – Visual analog scale
WORMS - The Whole-Organ MRI Score
QoL – Quality of life

Introduction

An estimated 500 million working days are lost in Europe each year due to chronic pain, of which 1 million workdays are lost in Denmark. This corresponds to an economic loss of at least 252 billion DKK. In US the loss is estimated to be between 560 and 635 billion $ per year. In addition, many patients end up on social welfare as a consequence of lost or reduced ability to work. Higher demand for more efficient drugs and medical devices for pain treatment thus continue to drive the pain management market. Therefore, technology enabling an improved diagnosis and as a result a more efficient and personalized treatment of chronic pain patients will have great perspectives.

It seems evident that preoperative sensitization of the nervous system holds prognostic information to if patients develop chronic postoperative pain. Chronic postoperative pain is defined by the International Association for the Study of Pain (IASP) as persistent pain six months after surgery. This thesis will focus on the prevalence of chronic postoperative pain after total knee replacement (TKR) surgery in knee osteoarthritis (KOA) patients and to subgroup KOA patients using quantitative sensory testing (QST), which is systematically method for quantifying alterations in the nervous systems sensory function. This thesis aims to describe 1) the prevalence of chronic postoperative pain after TKR surgery and 2) the connection between preoperative QST and postoperative chronic pain.

Current perspectives on osteoarthritis

Taxonomy

Osteoarthritis (OA) is considered a degenerative disease and is associated with pain, stiffness and decreased function of the joint. For over 50 years, radiological findings have been the most widely used method to characterize the presence of osteoarthritis, where the degeneration of the joint is often confirmed using X-ray imaging by applying the Ahlback[1] or Kellgren & Lawrence (KL)[2] system. The Ahlbeck method is generally used for severe KOA where the Kellgren & Lawrence method is more general for all KOA patients (table 1 for comparison). Most widely used in OA studies is the Kellgren & Lawrance system.

Interestingly, little association is found between radiological findings of the knee and pain intensities[3-6], as some subjects have radiological KOA but no pain and vice versa[7].

Ahlbäck grade	Ahlbäck definition	Kellgren & Lawrence grade	Kellgren & Lawrence definition
		Grade 0 "Non"	Non
		Grade 1 "Doubtful"	Minute osteophyte, doubtful significance
		Grade 2 "Mild"	Definite osteophyte, unimpaired joint space
Grade I	Joint space narrowing (joint space < 3mm)	**Grade 3 "Moderate"**	Moderate dimunition of joint space
Grade II	Joint space obliteration	**Grade 4 "Severe"**	Joint space greatly impaired with sclerosis of subchondral bone
Grade III	Minor bone attrition (0-5 mm)	**Grade 4 "Severe"**	Joint space greatly impaired with sclerosis of subchondral bone
Grade IV	Moderate bone attrition (5-10 mm)	**Grade 4 "Severe"**	Joint space greatly impaired with sclerosis of subchondral bone
Grade V	Severe bone attrition (10>mm)	Grade 4 "Severe"	Joint space greatly impaired with sclerosis of subchondral bone

Table 1: Radiological grading of knee osteoarthritis - comparing the Ahlbäck and the Kellgren and Lawrence grading systems. Modified from Petersson et al., 1997[8].

Prevalence of osteoarthritis

OA is the most frequent musculoskeletal diagnosis in the elderly population and the most common cause of disability[9] where 40% of females and 25% of males aged 60-70 years are diagnosed with OA[10]. With the expected global growth in the elderly population and concomitant rise in sedentary lifestyle choices, the incidence of OA is predicted to increase in the coming years[11-13].

Treatment of knee osteoarthritis

Several pharmacological and non-pharmacological treatments are available in the early stages of KOA[14] and weight loss and moderate exercise seems to give the patients pain relief[15]. The current treatment of severe KOA is total knee replacement (TKR) surgery. An interesting and novel protocol claims that exercise is as good as TKR surgery[16]; however, only the protocol and not any results have been published at this time point. In 2011 more than 8000 TKR surgeries were performed in Denmark[17] and nearly half a million in the United States and believed to increase to almost 3.5 million in 2030[18].

Even though TKR have a low rate of technical errors, 20% of the patients are render into chronic postoperative pain[19]. For total hip replacement (THR) the number is 10%[20]. Only a few attempts have been made to subgroup KOA patients; however, these subgroups have shown different degeneration of the joint[21] and pain profiles[22]. With the rising number of patients to treat and the risk of developing chronic postoperative pain – the industry, the researchers and the healthcare sector must develop new preoperative prediction methods for individual treatment to comply with this alarming problem.

Pain in osteoarthritis

OA is recognized as a disease involving all joint tissues[23]. The specific pain mechanisms in OA are largely unknown although many studies have shown that sensitization of the pain system contributes[22,24-27].

The diagnosis of knee osteoarthritis (KOA) is based on a combination of symptomatic pain and stiffness and radiographic assessments such as the KL score[2]. Interestingly for the individual patient there is little correlation between the pain intensity in KOA and the KL score[6], suggesting that other factors than joint damage is involved. The pain from KOA can arise from different structures, such as subchondral bone, periosteum, tendons and the synovium[4,28], why inflammation of the synovium, synovitis, has been highly researched in the recent years. Interestingly, KOA is often diagnosed using radiological assessment of the degeneration of cartilage; however, no nociceptive fibers are located in the cartilage, why pain cannot arise from this structure[4,28]. Inflammation leads to sensitization of peripheral nociceptors[29,30], why synovitis (inflammation of the synovial membrane)[31,32] could sensitize the peripheral nociceptors in KOA[4].

Sensitization of the nervous system

When a pain signal arises from the peripheral nervous system it is transmitted through the dorsal horn to the central nervous system. Presumably, chronic pain disorders arise from an initial peripheral nociceptive input, which can alter central nociceptive pathways[33]. Wilder-Smith proposed that three key central aspects are important for targeting chronic pain; (1) is central sensitivity altered and is spreading hyperalgesia present, (2) is the descending central pain modulation limited, and (3) is the sensitivity related to a peripheral drive. Therapeutically, central sensitization should be considered as contributing factor to the pain, since studies have shown that once established, the sensitization respond poorly to opioid and peripheral nerve blockade treatment but requires special targeted treatment, such as special targeted neuropathic medical treatment[34]. Pain related pathways in the peripheral and central nervous system can be altered by neurotransmitters, peptide hormones, neurosteroids and cytokines released in the synaptic or non-synaptic terminals, neighboring neurons or glia cells and can alter the neuronal excitability in the pain matrix[35-38]. At the central nervous system level, this is reflected as alterations in excitability and inhibitory mechanisms[39-42].

Excitability in the nervous system

In animal models, excitatory neuroplasticity (sensitization) is explained from activation (acute changes) through modulation (sub-acute changes) to modification (chronic changes)[43]. Activation of transduction (peripheral nociceptors) and transmission (central processing) is considered a reversible process[43]. Modulation is expressed as peripheral and central sensitization due to phosphorylation of receptors and ionophores and is a slowly revisable process. Modification is expressed as chronic pain due to altered regulation, cell connectivity and cell death, which affect the inhibitory system[43].

Inhibition in the nervous system

In the healthy organism, excitability in the nervous system should be countered by inhibition[44]. An inhibitory response, a complex modulation of the excitatory nociceptive transmission from the peripheral to the central nervous system[45,46], can be both spinal and supraspinal. Descending inhibition originates in the medulla and midbrain and is closely related to parallel descending facilitatory systems[45-48]. The loss of the ability to produce an inhibitory response is considered an important factor for the development of chronic pain[49,50].

Pain measurements

The pain experienced by patients is complex and several attempts and options are available when assessing pain. This chapter is dedicated to different relevant measurements of pain.

Quantitative measurements of pain mechanisms

In 1990's and early 2000's it became apparent that methods for sensory testing were available[51-61]; however, there was no general agreement on standard procedures. Rolke and colleagues proposed a quantitative sensory testing (QST) platform in 2006, composed of 13 different sensory modalities, to diagnose sensitization in neuropathic pain[62], including mechanical and thermal stimulations. QST is an assessment tool to diagnose peripheral and central sensitization in patients with musculoskeletal pain[63] and a tool for monitoring and diagnosing pain processing and its alterations in patients[53,60]. The concept of QST is to use standardized defined stimuli to the patient under standardized conditions, while the patient rates the stimulus regarding the subjects experienced pain. QST provides information about the subjects pain sensitivity. The subject is asked to rate the stimulus regarding the experienced pain. The use of multiple stimulus modalities with different intensities or one prolonged stimuli with increasing intensity makes it possible to construct stimulus-response relationships, which characterize the subjects pain sensitivity. Increasing pain sensitivity can objectively be quantified by a leftwards shift compared to a healthy control subject (figure 1)[64].

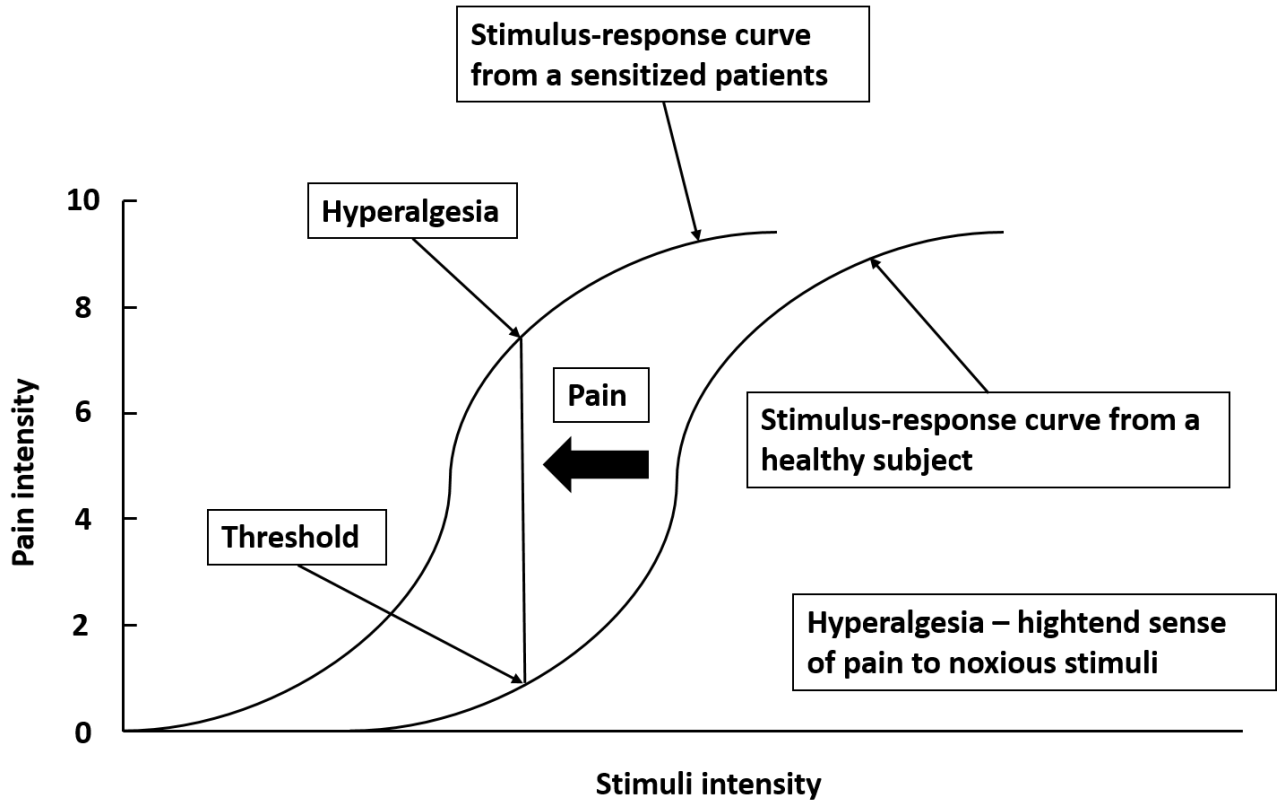

Figure 1: Stimulus-response curves for a sensitized patient and a healthy subject. The stimulus-response curve for the sensitized patient is shifted leftwards by the nociceptive input accompanying pain, which can cause hyperalgesia. Modified from Wilder-Smith, 2013[33].

QST aims to give a deeper insight into the pain mechanisms compared e.g. to the simple visual analogue scale (VAS); however, QST is time consuming and requires that the subject is trained in rating pain stimuli accurately and reliably[64]. Combining different stimulation techniques allows for a more "complete" quantification of the state of the nervous system[65,66].

Sensitization in osteoarthritis

Pain can arise from several structures in the joint e.g. the subchondral bone, the periosteum or the synovial membrane[4,28]. Each structure needs to be examined to understand the origin of pain in OA. Several studies have shown that increased pain is associated with increased sensitization[22,26,67-69] but fewer studies have focused on the association between pain from specific tissues and sensitization.

Recent reviews by Sukoas et al., 2012[70] and Lluch et al., 2014[71] concludes that central sensitization is highly involved in the pain in OA (see appendix 2 for an overview).

OA is associated with local and widespread hyperalgesia compared to controls[24,26,67,69,72-74], which is improved after joint replacement surgery[24,72,75]. Higher degree of general sensitization (i.e.

around the knee) have been shown to be related to higher levels of pain[22,26,67-69], disability and poorer quality of life[69], poorer outcome after TKR surgery[76] and higher concentration of pro-inflammatory cytokines[73]. In addition, allodynia, both widespread[72] and locally[74,77], has been documented in OA patients compared to controls. Furthermore, increased facilitated temporal summation applied by either thermal[78] or mechanical stimuli[24,26] has been documented in OA patients compared with controls. Dysfunctional endogenous nociceptive inhibition, measured as impaired conditioning pain modulation (CPM), has been documented in patients with OA[24,26,49], which is restored after joint replacement[24,49].

Increased excitability of the nociceptive flexion reflex (a measure of central nociceptive processes) has been documented in patients with severe KOA compared to controls[79].

KOA patients demonstrating more than one location of pain often express pain symptoms being more diffuse and spreading to larger areas[80], supporting the notion that spreading sensitization may be present in these patients[81]. Pain intensity and duration of KOA have been found to be associated with the degree of sensitization[26]. Pressure pain thresholds (PPTs) have been shown to be decreased in patients with KOA before TKR surgery[26] and normalized after TKR surgery[24]. CPM has been shown to be low in KOA patients before surgery compared to controls; however, increased after surgery. Pre and post TKR treatment with pregabalin seems to inhibit the development of chronic postoperative neuropathic pain[82], which may indicate that sensitization plays a key role in determining the outcome of TKR.

Sensitization seems to be normalized in the general KOA population when comparing pre- and postoperative QST measurements[24,49]; however, 20% of KOA patients report chronic postoperative pain after TKR surgery[20], indicating that these patients could have different preoperative sensitization profiles. Patients with ongoing pain after primary TKR surgery can be offered revision TKA surgery (re-TKA) but re-TKR is involved with high risk of a poor outcome. Patients with pain after re-TKR surgery show widespread hyperalgesia, facilitated temporal summation and lower CPM compared with patients with no pain after re-TKR surgery[25]. Facilitated temporal summation is more predominant in patients with widespread hyperalgesia after re-TKR surgery compared to KOA patients before primary TKR surgery[83], which indicates that re-TKR surgery should be considered with care.

Mechanical stimulations have been the main focus of understanding sensitization in OA patients, where pressure pain thresholds (PPTs), temporal summation and CPM are the most widely used[12,24-26,74]. In addition, Neziri et al., 2012[84] ranked QST measures according to their association with chronic pain in low back pain patients and found PPTs and mechanical temporal summation as high-ranking measurements.

Pressure pain threshold

PPTs are used to understand deep-tissue hyperalgesia and to determine local and spreading sensitization[85,86]. PPTs are often assessed using a pressure algometry and applying standardized

protocols. Pressure algometry activates the nociceptors in the deeper tissues (muscle and a) through the skin[86-88].

Tenderness of damaged muscle is most likely due to peripheral sensitization of deep-tissue nociceptors[85]. In widespread pain conditions, the involvement of peripheral sensitization is most likely supplemented by central sensitization phenomenon.

Local and widespread hyperalgesia have been documented in numerous musculoskeletal disorders, such as OA[24,26] and patellofemoral pain syndrome[89].

Temporal summation

Temporal summation is a measure for central integrative mechanisms induced by sequence of stimuli with the same intensity, where a progressive increase in pain occurs[85]. Temporal summation mimics the initial phase of the wind-up process, which has been measured in the dorsal horn in animal studies[90]. Healthy controls will feel the 10th stimuli as slightly more painful compared to the 1st stimuli, whereas sensitized patients will feel a large pain difference[26], as seen in figure 2 below.

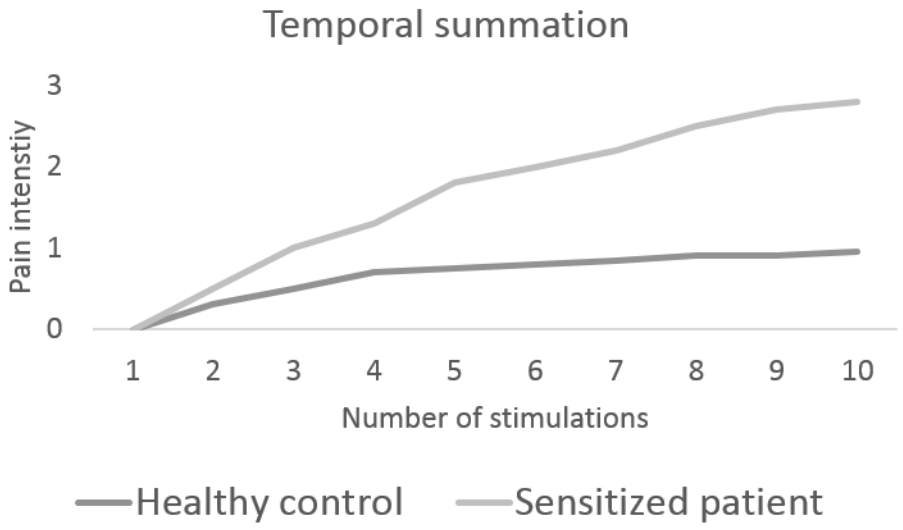

Figure 2: An example of temporal summation from a healthy control and a sensitized KOA patient. The patient has facilitated temporal summation and repeated stimuli with the same intensity are experienced as increasingly painful.

Temporal summation can be applied using e.g. electrical[91] or pressure[26] stimuli. In central sensitization, the central integrative mechanisms are unregulated resulting in facilitated temporal summation, which is seen in e.g. KOA[24-26], fibromyalgia[92] and in chronic pain patients with multiple sclerosis. Enhanced temporal summation of pain involves e.g. the neurotransmitter N-methyl-D-aspartate (NMDA)[93,94] and administration of ketamine, an NMDA antagonist, reduces clinical pain and temporal summation in fibromyalgia patients[95]. Temporal summation have been shown to

predict the development of acute postoperative pain in patients undergoing thoracotomy[96], which is a precursor for the development of chronic postoperative pain[97].

Conditioning pain modulation

Descending inhibitory inhibition and facilitation modulation of the peripheral nociceptive inputs in the dorsal horn neurons are important pain mechanisms which can cause spreadingsensitization[90]. CPM is a measure of the net effect of the facilitating and the inhibitory system[90] and can been induced by e.g. cold pressor test[98] or ischemic pain[26]. Less efficient CPM has been shown in e.g. patients with temporomandibular disorder[99], fibromyalgia[100,101], OA[24,26,49] and chronic tension-type headache[102]. The major neurotransmitters involved in descending inhibition are serotonin and norepinephrine and agents which boost these neurotransmitters will further inhibit pain perception[103]. Such an agent could be duloxetine, which reduces knee pain in patients with KOA[104,105].

Preoperative CPM can predict the risk for development of postoperative chronic pain in patients undergoing thoracotomy[106], and shown to be a reliable bedside measurement in women with chronic pain[107].

Qualitative measurements of pain

Several qualitative measurements of pain have been established. The most famous measurements must be the visual analog scale (VAS) and the numerical rating scale (NRS). Pain reported using both scales have shown to be consistent[108]. VAS has been shown useful in clinical research[109]. While a simple measure of subjective pain intensity might be beneficial, several questionnaires to company pain ratings and/or QST has been developed. Listed in table 2 are four questionnaires that have been widely used in KOA research and focuses on symptoms, stiffness of the knee, pain, function and quality of life.

Reference	Questionnaire
Insall et al., 1989[110]	Knee Society Score (KSS)
Bellamy et al., 1986[111]	Western Ontario and McMaster Universities Arthritis Index (WOMAC)
Roos et al., 1998[112]	Knee Injury and Osteoarthritis Outcome score (KOOS)
Hawker et al., 2008[113]	Osteoarthritis Research Society International (OARSI)

Table 2: Four questionnaires widely used in KOA research.

The KSS questionnaire was developed focusing on pain and mobility of the knee. The KOOS was developed as an extension of the WOMAC to evaluate short- and long-term symptoms and function in subjects with knee injury or osteoarthritis[114]. Moderate-to-strong correlations have been found between the KSS and the WOMAC's function and pain subscores[115] and the KOOS have been shown to have increased validity and at least as responsive as the WOMAC[116]. The OARSI is a

combination of the WOMAC and KOOS and have strong correlations to both WOMAC and KOOS[113].

Pain after surgery

Acute postoperative pain

Svensson et al., 2000[117] showed that 43%, 27% and 16% of patients reported moderate to severe pain (VAS≥40) at rest and 88%, 81% and 72% reported moderate to severe pain at some point in the first, second, and third postoperative day respectively, after elective orthopedic, urological, upper gastrointestinal or endocrinological surgery. The severity of acute postoperative pain has been shown to correlate to the development of chronic postoperative pain[118]. Several guidelines to acute pain treatment have been introduced over the last decade[117,119-121] but with limited results.

Pain after the acute postoperative phase

Thirty to fifty percent of patients undergoing amputation, mastectomy, thoracotomy or sternotomy still show persistent pain 3-6 months after surgery and 5-10% report severe pain[97,118]. Approx. 9% and 5% of patients have been shown to report pain 3 and 6 months (not defined as chronic postoperative pain by IASP guidelines) after TKR surgery[82], respectively. Inadequate acute postoperative pain may lead to the development of chronic postoperative pain[118].

Chronic postoperative pain

Chronic pain is defined by IASP as present pain six months after surgery. Kehlet and colleagues summarized in 2006, that the prevalence of chronic postoperative pain for major surgeries, such as amputation, breast surgery, thoracotomy, coronary artery bypass and caesarean section, was as high as 50%[118]. There is an ongoing debate regarding the prevalence of chronic postoperative pain after TKR- and THR surgery but Beswich et al. 2012[20] concluded in a large meta-analysis that the overall proportion of chronic postoperative pain after TKR surgery was approx. 20% and 10% after THR surgery. Currently there is no definitive explanation to why some patients develop chronic postoperative pain while others have a pain free recovery. The transition from acute to chronic postoperative pain is not completely understood.

Risk factors of the development of chronic postoperative pain

Low age is linked with a more vigorous neoplastic response and gender differences have been shown in regards to pain modulation[97,118,122-127], why these are classified as risk factors for postoperative pain.

Kehlet et al., 2006[118] concluded that surgical techniques that avoid nerve damage should be applied whenever possible, and that the intensity of acute postoperative pain correlated to the development of chronic postoperative pain. In addition, preoperative pain, higher analgesia consumption in the acute-operative phase and widespread hyperalgesia have been shown to be risk factors[44,97,118,124-127]. Amputees with severe phantom limb pain have more often had intense and enduring preamputation pain than amputees with less intense phantom pain[128,129], and preoperative pain intensity before TKR has been shown to be a clinical predictor for development of chronic pain[130].

Catastrophizing is described as a maladaptive cognitive style employed by patients anxiety and depression disorders (negative forecast of future events)[131] and preoperative catastrophizing have been shown to be a risk factor for chronic postoperative pain[132-136].

A recent study showed that pre and post TKR treatment with pregabalin seem to inhibit the development of chronic postoperative chronic neuropathic pain[82] indicating that preoperative sensitization of the nerve system might be connected to the development of postoperative chronic pain. Preoperative central acting pain mechanisms have been shown to predict the development of chronic postoperative pain in patients undergoing e.g. thoracotomy[96,106]. It seems evident that the nervous system becomes more sensitive if exposed to pain for a longer duration as KOA patients with higher pain and longer disease duration show spreading sensitization compared to healthy controls[26].

Pain after revision surgery

While most patients will have a pain free recovery, some patients develop chronic postoperative pain. 80-90% of re-TKR surgery in KOA patients are performed due to the assumption of pain, aseptic loosing, infection, instability and stiffness[11,137,138]. Re-TKR surgery has a lower chance of success compared with primary TKR surgery[139] and is associated with a high risk of multiple re-TKR surgeries[11]. Patients with pain after re-TKR surgery show widespread hyperalgesia, facilitated temporal summation and lower CPM compared with patients with no pain after re-TKR surgery[25]. Facilitated temporal summation is more predominant in patients with widespread hyperalgesia after re-TKR surgery compared to KOA patients before primary TKR surgery[83]. This indicates a continued nociceptive drive, despite the removal of the OA affected joint, further indicating that sensitization could play a key role in the chronification of postoperative pain and suggests that sensitization should be considered before re-TKR surgery.

Aim and overview of the PhD project

This PhD project aimed to 1) increase the understanding of the prevalence of chronic postoperative after primary and revision TKR surgery, 2) link preoperative sensitization to chronic postoperative pain and 3) describe the influence of synovitis on sensitization. Three main scientific questions were asked in the initial phase of the PhD project:

1. What is the incidence of chronic postoperative pain after primary/revision TKR surgery (study I)?
2. Can preoperative parameters describe postoperative outcomes (study II)?
3. What influence do synovitis in the knee have on sensitization (study III)?

To answer these questions, three clinical studies were initiated. Figure 3 illustrates the connection between the three studies.

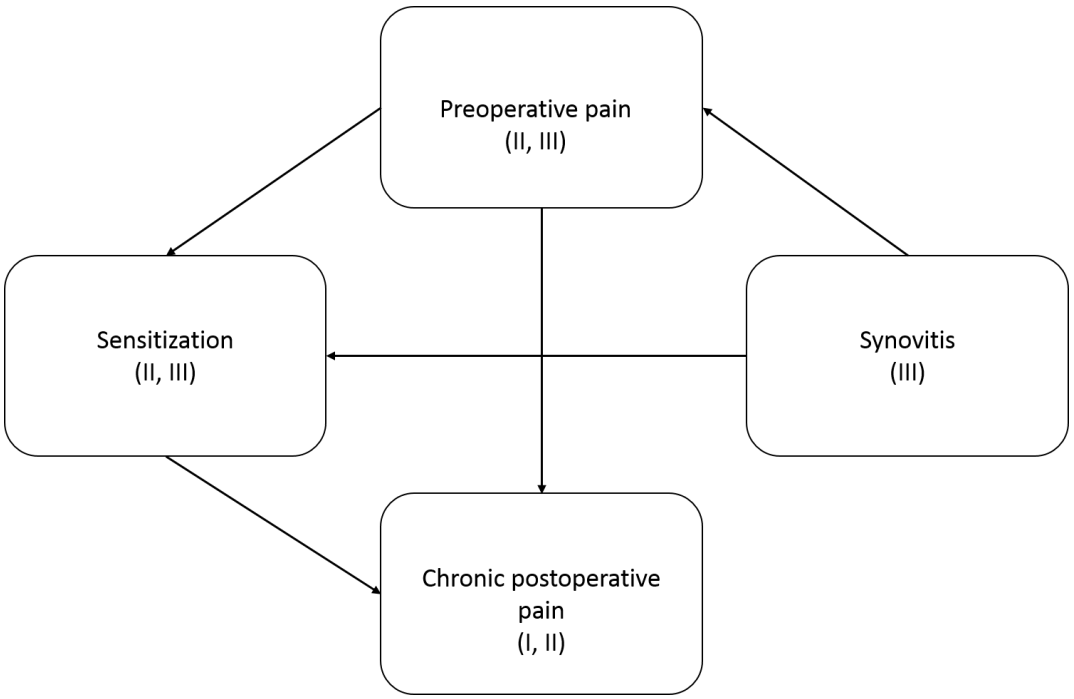

Figure 3: This PhD thesis is derived from three studies including the prevalence of chronic postoperative pain (study I and II), preoperative sensitization (study II and III), the influence of synovitis on sensitization (study III) and the link between preoperative sensitization and development of chronic postoperative pain.

Methodological considerations

The following chapter will describe the methods applied in the 3 studies and argumentation for why the specific methods were chosen.

Protocols

Table 3 gives an overview of the different protocols, which were applied in this PhD project

	Protocol	Subjects
Study I	KSS function score OARSI QoL score Categorical pain rating VAS	- 215 KOA patients pre- and post-primary TKR surgery - 90 KOA patients pre- and post-revision TKR surgery
Study II	PPTs CPM Temporal summation VAS	- 77 KOA patients pre- and post-primary TKR surgery
Study III	PPTs MRI (BLOKS) Serological biomarkers VAS	- 58 KOA patients pre-primary TKR surgery. - 33 controls

Table 3: An overview the protocols and the subjects enrolled for the three studies for the PhD project.

Sample size calculation and statistical reflections

Statistical analysis were performed in IBM SPSS Statistics, version 19.

Study I

Study I aimed to obtain a broad perspective of the incidence of chronic postoperative pain after primary and revision TKA, why a cohort design was chosen. All patients undergoing primary or revision TKR surgery during 2004-2005 in the Northern Region of Denmark were invited to join the study. No sample size calculation was applied in this study, due to nature of a cohort design.

Data were normally distributed, why Pearson correlations and t-tests were applied in the data analysis. The data contained several categorical measures (from the questionnaires) where binary logistic regressions were applied.

Study II

Graven-Nielsen et al., 2010[24] showed that patients after TKR surgery had a mean VAS of 2.6 (SD: 0.5). The study aimed to detect a change of at least 30%, with a power of 80% and a significant level at 0.05. Based on a power calculation a total number of patients needed were calculated to 10 patients (rounded off from 9.2 patients). Based on the data available at the study start, Harden et al., 2003[19] showed that the risk of chronic pain after TKR surgery was 13%, why the total amount of patients needed for examination was at least 77 patients (rounded off from 76.9).

Data were normally distributed, why t-test, Pearson correlations and analysis of variance (ANOVA) were applied.

Study III

A pilot study was performed prior to the study and found that TKR patients had an average PPT around the knee of 418 (SD: 180). The study aimed to detect a change of at least 25%, with a power of 80% and a significant level at 0.05. Based on our power equation, a total of 59.3 patients were needed, why we invited 60 patients to join the study. Two patients did not complete all examinations and were excluded from the data analysis.

The serological biomarkers were not normally distributed, why these were log transformed to achieve normally distribution. Pearson correlations and repeated measure ANOVAs were applied.

Questionnaires

KSS questionnaire was developed by Insall et al.[110] in 1989. While the KSS gives a limited insight into the patient's pain, the questionnaire was chosen since this is used in the Danish Knee Arthroplasty Registry and thus every patients undergoing TKR surgery in Denmark since 1997 will have data from this score. Study I used this registry combined with the OARSI questionnaire for quality of life (QoL) to give insights into the prevalence for chronic pain after primary and revision TKR surgery. Moderate-to-strong correlations have been found between the KSS and the WOMAC function and pain subscores[115]. While the KOOS has been shown to be as good or even superior to the WOMAC[116] and should be applied when feasible, the current study was limited to the KSS due to the reason described above.

Pain

For an easy overall pain intensity rating, the visual analog scale (VAS) was applied (study I, II and III), zero on the 100 mm line was anchored as "no pain" whereas the high end was anchored as "worst pain imaginable". The scale has been proven useful in clinical trials and in experimental pain conditions[109]. Correlations have been shown between categorical pain ratings (e.g. none, mild, moderate and severe) and the VAS[140,141] and an attempt to define moderate pain have been shown to be above 30 mm and severe pain to be above 54 mm on the 100 mm VAS[142].

Correlations between the worst pain within the last 24 hours and sensitivity profiles of patients with KOA have previously been reported[24,26], why this was chosen for the current project (study I, II and III). In addition, categorical measures of pain as mild, moderate, severe or unbearable was applied in study I.

Quantitative sensory testing

QST is a relevant assessment tool for patients with musculoskeletal pain[63] and PPT (study II and III), CPM (study II) and temporal summation (study II) have been widely used in research of underlying pain mechanisms in KOA[12,24-26,74]. While comparison with the previous literature is

essential, preoperative QST parameters have shown to have a prognostic value for the outcome after surgery[96,106,143].

Arendt-Nielsen et al., 2010[26] defined eight test sites in the peripatellar region for PPT, which have been applied (excluding the test site at the center of patella) using a standardized handheld pressure algometry (Somedic Algometer, Sweden).

Temporal summation can be applied using electrical[144], computerized algometers[24-26] or a modified Von Frey filament[145]. Stimulations should be applied with an inter-stimuli interval of at least 0.3 Hz[146,147]. A modified Von Frey filament (Aalborg University, Denmark) was used in this project, due to the easy clinical instruction and application. The modified Von Frey filament is a newly developed device, why only a single study in KOA patients have been published so far[148].

CPM is based around the concept of "pain inhibits pain" and can be induced by e.g. the cold pressor test[98] or ischemic pain[26] to a remote site (conditioning pain stimulus) from the actual pain site e.g. the painful knee in knee OA. The cold pressor test was chosen for the tonic painful conditioning stimulus as it is very painful, simply to apply and validated in the literature[149-152]. The conditioning pain was applied to the upper extremities (the hand). For test stimulus before and after cold pressor test, the pressure pain threshold was applied.

Alternatives to the applied measures for the current study could be electrical or thermal stimuli. Electrical stimuli have been used to study modifications of the synaptic strength (synaptic long-term potential), believed to be involved in the transformation from acute to chronic pain[43,153-155]. In addition, electrical stimulations can be used to study the lower limb reflex, which has been studied in humans and is believed to be an objective measure of nociceptive processing in the central nervous system[156]. The method can detect central sensitization in patients compared to controls[157,158] and a prediction model, based on statistical properties of the EMG signal, has shown promising results to further instigation of the difference in the central sensitization between controls and patients[159]. Patients with hip OA have shown thermal sensory abnormalities when comparing before and after THA surgery[72] and when comparing patients with different neuropathic pain syndroms[160]. Recently, a study showed thermal and mechanical hyperalgesia in KOA patients with high pain and low radiological OA (K&L2) compared to patients with low pain and high radiological OA[22].

Synovitis

Synovitis can be diagnosed both with and without the use of contrast-enhanced magnetic resonance imaging (MRI)[161]. Seventy-three present of KOA patients have been reported to have synovitis[162]. Synovitis is defined as inflammation of the synovial membrane and is believed to contribute to the pain experience by KOA patients[163]. The synovial membrane is filled with nociceptive fibers, hence inflammation of this tissue is considered to be painful[31,32]. Two standardized MRI protocols for assessing symptomatic KOA is The Boston-Leeds OA Knee Score (BLOKS)[164] and the Whole-Organ MRI Score (WORMS)[165] without the use of contrast-enhanced

MRI. When comparing the two systems, BLOKS identifies meniscal abnormalities best[166], while WORMS is better for bone marrow lesions[166] but detection of synovitis is similar for both methods[166,167]. The progression in synovitis thickening has been reported to be correlated with increasing pain[168] and KOA patients who report knee pain have more severe synovitis compared to patients without knee pain, which further indicates that synovitis could contribute to KOA pain[163].

Understanding the underlying mechanisms of pain in KOA is crucial to improve the diagnostic options for KOA patients. Study III focused on the contribution of pain arising from the synovial membrane in the corpus Hoffa area, however, several future studies should investigate the pain contribution from e.g. subchondral bone, periosteum or fat pad, since these structures do include nociceptive fibers[4,28] and hence could contribute to the pain experienced by KOA patients.

Serological biomarkers

Synovitis and bone remodeling biomarkers have been established, as contributors to the joint pain[169].

The synovial membrane consists of type I and III collagen[170,171]. During inflammation, the synovial membrane undergoes fibrogenesis, why markers of type I or III collagen turnover could reflect the severity of synovitis. Several studies have shown increased levels of matrix metalloproteinase (MMP) derived degradation products of type I and type III collagen (C1M and C3M) in rheumatoid arthritis[172-174] and C1M is increased in patients with end-stage OA[21]. C1M is not a biomarker of bone degradation as the fragment generated by MMPs is further degraded by cathepsin K, the most abundant protease in bone.

The synovial membrane is densely packed with nociceptive fibers[4,28] and it is believed that inflammation and degeneration could alter pain perception from the joint[31,32]. A MMP-derived fragment of type II collagen, C2M, reflects cartilage degradation and is elevated in patients with radiographic KOA[175], ankylosing spondylitis[172] and rheumatoid arthritis[172,173]. Biomarkers of inflammation is currently used to assess the extent of inflammation and furthermore diagnose chronic inflammatory diseases, such as rheumatoid arthritis. A recent study showed that C-reactive protein (CRP) was elevated in KOA patient and CRP correlated with PPTs[73], indicating that inflammation could play a role in sensitization. High sensitive CRP (hsCRP) is elevated in the later stages of OA compared to earlier stages[21] and is a sensitive biomarker of acute and systemic inflammation[176], whereas the MMP-derived fragment of CRP (CRPM) seems to be a sensitive marker of local tissue inflammation[177]. Hence, CRPM could be a more disease related measure of chronic inflammation than hsCRP and could reflect synovitis.

Arendt-Nielsen et al., 2013[178] showed associations between sensitization paradigms and serological biomarkers showing that CPM and temporal summation was associated with local and systemic inflammation. QST is dependent on expert knowledge for interpretation and is highly time consuming. Blood samples is often used in the clinical to give a fast insight to patient specific diseases, why this correlations between sensitization and serological biomarkers are highly

interesting. Study III aimed to investigate if serological biomarkers could substitute CPM and temporal summation in patients with synovitis, known to contribute to the OA pain[163], why these serological biomarkers were chosen.

Knee osteoarthritis as a model for the development of chronic postoperative pain

While the sensitization profiles and the associated incidence of chronic postoperative after TKR surgery is an important factor to consider for KOA patients, the OA model including the sensitization profiles and outcomes after surgery have the potential to be translated into other musculoskeletal pain conditions. Commonly KOA is associated with many comorbidities[179-183], why each of these should be investigated to understand the underlying pain mechanisms. While the sensory profiles KOA patients cannot be directly translated into other specific diseases, this gives an insight to the neuroplasticity of the human.

Pre- and postoperative pain in knee osteoarthritis

The following chapter focuses on the results of the PhD project. Please refer to appendix 1 for a quick insight to the key results.

Prevalence of postoperative pain

The current PhD project has provided insight to the pain pre- (study II and III) and postoperatively (study I and II) in patients with severe KOA undergoing primary and revision TKR surgery.

Combining the three studies, an overall primary preoperative pain (study II and III, N=136) intensity of VAS=7.1 (95% CI: 6.6-7.5) and an overall postoperative pain intensity (study I and II, N=293) of VAS=1.4 (95% CI: 0.8-1.9) was found.

Twelve months after primary TKR surgery, 22% of the patients report VAS>3 (study II), indicating at least moderate pain[142] and three years after primary TKR surgery, 19% of patients report severe to unbearable on a categorical pain scale. Beswich et al., 2012[20] concluded in a meta-analysis that the risk of chronic postoperative pain after TKR surgery was approx. 20%, ranging from 10% to 34%, and approx. 10%, ranging from 7% to 23%, for THR surgery. The definition of intensity of chronic postoperative pain is vague, why different outcome can be seen after surgery depending on the intensity of the postoperative pain. Table 4 summarizes chronic postoperative pain from study I and II (N=293) as mild or higher (VAS>10), moderate or higher (VAS>40), severe or higher (VAS>60) and unbearable (VAS=100). Several very different clinical conclusions can be drawn from table 4, which either promotes or hampers the postoperative chronic pain problem, why a standardized measure for postoperative chronic pain should be applied.

	Prevalence	
Postoperative pain category	**2 months after surgery***	**1-3 years after surgery****
Mild or higher (VAS>10)	56.2 %	49.1 %
Moderate or higher (VAS>40)	26.7 %	29.4 %
Severe or higher (VAS>60)	9.5 %	10.9 %
Unbearable (VAS=100)	1.0 %	0 %

*Table 4: Postoperative pain categorized as mild, moderate, severe or unbearable. * Sample size from study II (N=78). ** Sample size from study I and II (N=293).*

When re-TKR surgery is performed, almost 50% of the patients will experience severe to unbearable pain (study I) and these patients have widespread hyperalgesia, facilitated temporal summation and lower CPM compared with patients with no pain after re-TKR surgery[25]. In

addition, re-TKR surgery is associated with postoperative decrease in mobility and quality of life compared with primary TKR surgery (study I), indicating that a careful selection of patients for revision surgery should be implemented.

Sensitization

Knee osteoarthritis patients in general

The following results in this section are from pooling all patient data from study II. These results have not been published but are shown here to emphasize the importance of subgrouping KOA patients.

Pooling data from study II showed that in general KOA patients have lower preoperative PPTs at the knee, lower leg and arm compared to postoperative (figure 4) indicating preoperative widespread hyperalgesia and normalization after joint replacement, which is consisting with previous literature[24]. General conditioning pain modulation shows that KOA patients have a pre- and postoperative functional inhibitory system (figure 5) comparing baseline PPTs to PPTs after the cold pressor test ($P<0.05$), challenging the current literature on preoperative dysfunctional inhibitory pain modulation[24,72]. General temporal summation shows no significant difference between time points (figure 6), again challenging the current literature[24]; however, revealed large standard deviations, which could suggest that some patients have high and some have low facilitated temporal summation.

Subdivision of knee osteoarthritis patients

Dividing patients in study II into groups of patients with low and high postoperative pain 12 months after TKR surgery showed that patients who have low pain after surgery have an increased PPTs post TKR surgery compared to pre TKR surgery indicating normalization, which was not true for patients who have high pain 12 months after TKR surgery (study II). Patients with high pain after surgery had a dysfunctional inhibitory pain system, whereas patients with low pain after surgery had a pre- and postoperatively functional inhibitory pain system (study II). Patients with high pain after TKR surgery had facilitated temporal summation pre- and 12 months post TKR surgery compared to patients who have low pain after TKR surgery (study II).

Graven-Nielsen and Arendt-Nielsen, 2010[85] hypothesized that central sensitization is initial sustained by a peripheral drive (the pain from KOA) and if removed the central sensitization would perish. The findings in the current project indicates that the majority of patients (the low pain group from study II) will have a normal recovery phase and the removal of the peripheral drive will normalize the sensitization. Subgrouping of patients revealed that approx. 22% (the high pain group from study II) of the patients did not have normalization of widespread hyperalgesia or decrease in facilitated temporal summation 12 months after TKR surgery (study II). The high pain group has had the peripheral drive removed but demonstrated postoperative central sensitization, indicating that other factors are involved in maintaining the sensitization. The current findings

underline the importance of subgrouping of KOA patients before TKR surgery and suggests a multimodal treatment approach.

Subdividing patients according to the presents of synovitis showed that patients without synovitis compared to patients with moderate-to-severe degree of synovitis showed similar preoperative PPTs, which were lower compared to controls (study III).

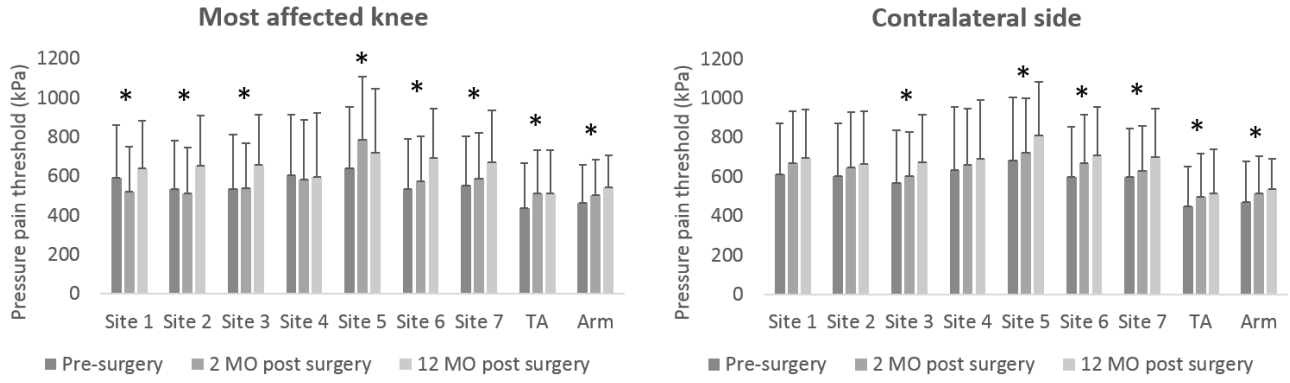

*Figure 4: Knee osteoarthritis patients have decreased preoperative PPTs compared to 12 months after surgery, indicating a normalization. * indicates P<0.05. Data from study II before subgrouping of patients.*

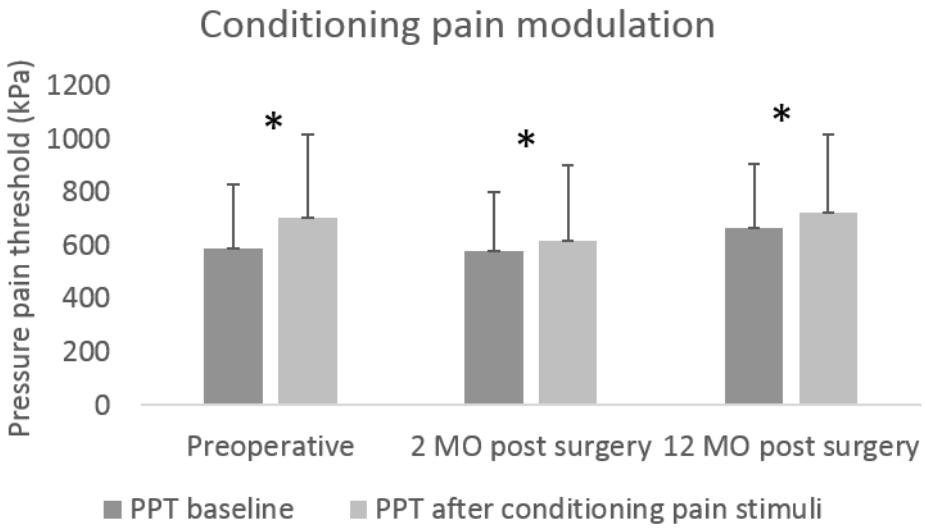

*Figure 5: Knee osteoarthritis patients have functional inhibitory pain system. * indicates P<0.05. Data from study II before subgrouping of patients.*

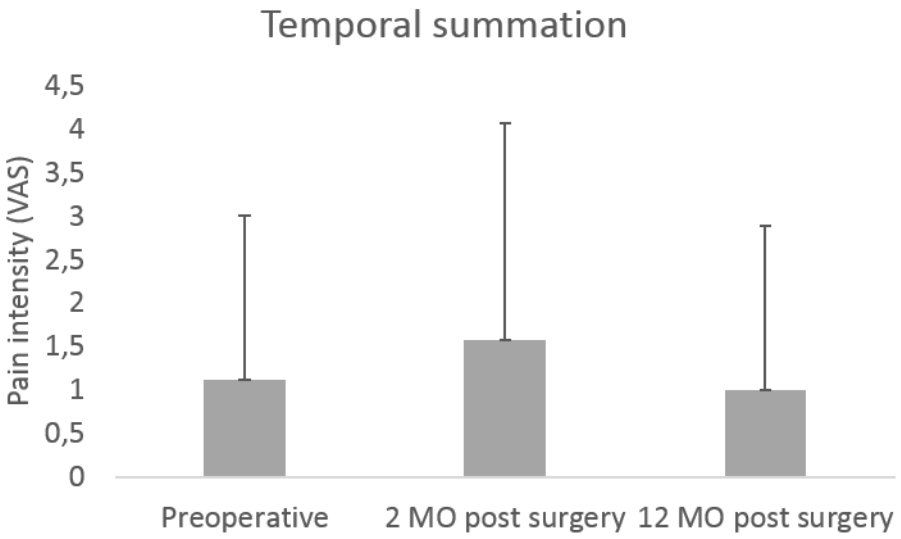

Figure 6: Facilitated temporal summation does not change comparing pre- and postoperatively in knee osteoarthritis patients. Data from study II before subgrouping of patients.

Link between preoperative sensitization and postoperative chronic pain

Administration of preoperative and postoperative pregabalin reduces the development of chronic postoperative neuropathic pain[82] and preoperative administration of duloxetine decreases the acute postoperative pain after TKR surgery[105], indicating that sensitization of the nervous system is involved in the development of postoperative pain. Preoperative CPM has been shown to predict the risk for development of postoperative chronic pain[106] and the effect of duloxetine[184]. Temporal summation have shown to predict the acute postoperative pain[96] in patients undergoing thoracotomy, which furthermore indicates that sensitization of the nervous system is linked to the development of postoperative pain.

The current PhD project showed a correlation between preoperative temporal summation and postoperative pain 12 months after surgery (study II), which furthermore links preoperative sensitization to the development of postoperative chronic pain.

Synovitis and osteoarthritis

The synovial membrane and the corpus Hoffa fat pad are densely packed with nociceptive fibers[4,28], why inflammation of these structures is believed to be associated with pain[185]. In KOA patients, 73% of the population is reported to be diagnosed with synovitis[162], why synovitis has been of interest in the recent years. There is an ongoing debate in the literature regarding if synovitis increases the pain perception in KOA patients. Synovitis can be assessed by either contrast or non-contrast enhanced MRI[161]. Hill et al., 2007[168] using non-contrast enhanced MRI, found no correlations between synovitis and pain but found a weak correlation between the progression of synovitis and pain. Baker et al., 2010[163] using contrast enhanced MRI, showed that patients with synovitis have increased pain compared to patients without synovitis. Finally, Yusuf et al., 2011[185] concluded in a review, that synovitis is associated with pain in KOA patients. These inconsistent results could be due to the different MRI scanning techniques.

The current project, did not find any associations between pain intensity and the degree of synovitis using the BLOKS for the corpus Hoffa fat pad (study III). Pain in KOA can arise from several structures, such as the subchondral bone or the periosteum[4,28], why these could be the focus of future research.

Study III focused on synovitis of the corpus Hoffa fat pad, as an estimate for synovitis of the whole knee joint, which could limit the results and the interpretation of this study. In addition, controls for study III were not MRI scanned, since these were believed to be synovitis free. A recent population study showed that 37% of subjects without diagnosed KOA have MRI categorized synovitis, which further limits the results of study III.

Serological biomarkers in osteoarthritis

The current project used five serological biomarkers; C1M, C2M, C3M, hsCRP and CRPM. Serological biomarkers for degeneration of collagen type I, II and III and inflammation and pain sensitization have been associated recently[178]. This thesis showed that patients with moderate-to-high grade of synovitis are more sensitized than controls and that these patients have increased C1M, C2M and hsCRP compared to controls, which further indicates that KOA is linked to both sensitization and changes in serological biomarkers, however, a significant correlation could not be demonstrated in the current project (study III).

Type I collagen - C1M

Bone type I collagen is mainly resorbed by cathepsin K resulting in the release of bone-specific neo-epitopes, such as CTX-I and NTX-I[186]. In contrast to CTX-I, the C1M neo-epitope is generated by MMP, but destroyed by cathepsin K[187], why the C1M is a marker of connective tissues other than calcified bone. High C1M levels are associated with reduced PPTs assessed from the knee (localized joint hyperalgesia)[178]. In addition, C1M is elevated in arthritic animal models[173] and in patients with rheumatoid arthritis[174], which is also reported in the current project (study III).

Type II collagen - C2M

Degradation of type II collagen and cartilage destruction are well established in OA[188]. C2M is found to be significantly elevated in OA patients with late stage OA (KL3-4) compared with patients with early stage OA (KL1-2) and controls[175]. In the present study none of the experimental pain parameters were associated with C2M (study III).

An ongoing debate in the recent literature focuses on synovitis' influence on increase of cartilage loss. Synovitis is assumed to be associated with increased risk of fast cartilage degeneration[189]; however, no C2M increase was found in patients with different degrees of KOA[178] and Hill *et al*., 2007[168] reported that synovitis was associated with pain but not loss in cartilage. Study III found that patients with and without synovitis of the corpus Hoffa fat pad had increased degeneration of cartilage (increased levels of C2M) compared to controls, which could indicate that synovitis and increased cartilage degeneration are not connected.

Type III collagen – C3M

Synovitis plays a role in OA pain and worsening of synovitis and effusions are associated with increased pain[190]. The synovial membrane is mainly composed of type III collagen. A combination of elevated expression and the presence of MMPs leads to the release of MMP generated fragments of type III collagen[173]. A recent study found that elevated C3M and CRPM levels are associated with impaired descending modulation and spreading sensitization[178]. C3M and CRPM correlated strongly, possibly due to the increased tissue turnover driven by local inflammation as synovitis[191]. Study III did not find an increased C3M level comparing patients with or without synovitis, but showed higher C3M levels to be higher in controls. An increased fibrogenesis of the synovial membrane is part of the synovitis; hence in the thickening of the synovial membrane is

the result of an overexpression type III collagen shifting the turnover balance toward formation instead of degradation, which partly could explain the findings from study III.

Inflammation – hsCRP and CRPM

CRP as an indicator for acute inflammatory[192] has limited value in monitoring inflammation in OA[193]. The hsCRP is a marker for low grade systemic inflammation, which correlates with pain severity in OA when assessed on a VAS[194]. Recently, an association between hsCRP levels and localized and spreading sensitization was documented in KOA patients[178]. Study III found that hsCRP levels were increased in both KOA with and without synovitis although not correlated with pain intensity. In addition, there was a trend for higher levels of hsCRP in patients with moderate-to-severe grades of synovitis.

CRP could indirectly reflect synovitis in OA[191]. Degraded cartilage fragments cause the synovial cells to produce inflammatory mediators, which further increases the synthesis of inflammatory cytokines and MMPs by the synovial cells[195]. When CRP binds to its receptors, it will gradually be degraded by proteolytical enzymes and released as fragments into the surrounding fluids (initially to e.g. the synovial fluid and later to the blood)[196] and can be measured by CRPM[177].

CRPM is suggested as a measure of chronic inflammation in contrast to the acute inflammation of circulating CRP, which could act as a reflection of longer lasting chronic inflammatory stage in OA. A recent study showed CRPM to be elevated in the patients with facilitated temporal summation and decreased pain modulation[178]. Study III showed a non-significant trend towards increased levels of CRPM in KOA patients with and without synovitis compared to controls.

Limitation of systemic biomarkers

Life style changing parameters gender, BMI and age can have an influence on serological biomarkers, especially inflammation biomarkers[197,198], why analysis should be adjusted for these, as in study III. Some of the literature reviewed in this thesis, regarding serological biomarkers, is unadjusted for life style parameters, why interpretation of these studies should be cautious.

Systemic biomarkers, as these applied in this PhD project, is often criticized due to the problematic source of tissue degeneration. The currently applied serological biomarkers seems not to be sufficient specific or sensitive to be used in phenotyping OA patients with or without synovitis. OA is often localized and affecting only one joint, why Felson, 2014[199] suggested that biomarkers from synovial fluid could contain more diagnostic information regarding the joint of interest.

Recommendations for clinical implications

Several risk factors for chronic postoperative pain have been identified, as listed in the introduction section. The current chapter will focus on a clinical review for preoperative evaluations, which could lead to a decrease of patients developing chronic postoperative pain after TKR surgery.

Preoperative screening of sensory profile

Several studies suggest that KOA patients are sensitized before TKR surgery[12,24-26,74] and normalized after TKR surgery[24]. The data presented in this PhD project suggests that KOA patients cannot be diagnosed as one patient group but should be subdivided. This is supported by several recent studies[21,22], yielding a large percentage of the KOA patients with a normal recovery phase and a smaller percentage who have continued widespread hyperalgesia, facilitated temporal summation and decreased pain inhibition, which could explain why these patients have continued pain 12 months after surgery (study II).

As described earlier, drugs designed to block the NMDA receptors have shown decrease facilitated temporal summation[93,94] and drugs who promote the reuptake serotonin and norepinephrine have shown to increase descending pain inhibition[103], which reduces knee pain in patients with KOA[104,105]. While these drugs are available, the current selection of drugs is limited, which could explain why central sensitized pain syndromes are often difficult to treat[103]. Preoperative QST screen would enable an easier selection for which patients should be offered drug therapies.

Opioids can combat pain immediately but there is no evidence for these to have an effect on the central pain states; however, some evidence suggest that patients can develop opioid-induced hyperalgesia, which can worsen the patient[103]. Ketamine and pregabalin/gabapentin have been used to combat central sensitization. Ketamine is used to decrease facilitated temporal summation[95], preoperative temporal summation has shown to predict the postoperative outcome of pregablin[143] and preoperative pregabalin has been shown to reduce the incidence of chronic postoperative pain the KOA patients after TKR surgery[82]. In addition, CPM has shown to predict the outcome of duloxetine[184], which if administrated preoperatively will decrease the acute postoperative pain in KOA patients[104]. KOA patients are often presented with a combination of both facilitating and inhibitory problems, why a combination of drugs, based on preoperative QST screening, should be applied in this patient group. Preoperative selection of patients for drug therapy is important, since some drugs are linked to severe side effects.

Opioid treatment often associated with several adverse events and long time use can lead to addiction and opioid craving[200], which is associated with pain catastrophizing[201]. Some studies have documented that rapid opioid escalation can lead to hyperalgesia[202,203]. Ketamine has been shown to combat facilitated temporal summation; however, prescription of ketamine is associated with several adverse events[204,205]. Pregabalin is presented with minor adverse events and well tolerated in patients[206]. A recent study suggested that duloxetine can reduce knee pain and the

treatment is related with minor adverse events[105]. Based on the patients preoperative sensory profile a combination of drugs could be administrated to counter the sensory abnormalities, which could lead to a lower incidence of chronic postoperative pain. Pregabalin and duloxetine have shown to have the least amount of severe adverse events, why these are recommended for clinical use. It is hypothesized, that pre-emptive administration decreases postoperative pain intensities, decreases hyperalgesia and prevents central sensitization compared to drugs administrated after surgery[207,208], why pre-emptive administration is recommended. In addition, duloxetine is an antidepressant drug[209] and pain catastrophizing and depression are listed as preoperative risk factors for the development of postoperative pain[132-136], why duloxetine could improve both the sensory and the depression aspects of the pain.

Patients who develop chronic postoperative pain after primary TKR surgery, should carefully be selected for revision TKR surgery, since these patients have a high risk of continued pain, poor quality of life, widespread hyperalgesia and facilitated temporal summation[25,83] (study III). Revision TKR surgery on the indication of pain alone, is not recommended.

Conclusive remarks

The work presented in this thesis highlights the severity of chronic pain after primary total knee replacement. While most patients will have a pain free postoperative recovery, this thesis showed that approx. 10-50% of patients, depending on the intensity of pain, will experience pain one year after surgery. As shown in other patient groups e.g. patients undergoing thoracotomy, preoperative sensitization of the nervous system can be linked to chronic postoperative pain. This thesis focused on preoperative subgrouping of patients to minimize the risk of development of chronic postoperative pain. The work presented in this thesis, found associations between preoperative sensitization and postoperative chronic pain in patients with knee osteoarthritis before total knee replacement. Patients who develop chronic postoperative pain after primary TKR surgery have a high risk of poor outcome after revision total knee replacement, why revision surgery should be performed with care.

With the increasing number of patients to treat with TKA, the demand for more surgical procedures and the high risk of development of chronic postoperative pain, the focus of future research should aim to identify preoperative measures for which patients are in risk of developing chronic postoperative pain. An unimodal diagnoses approach only involving a simple pain rating and an X-ray image and treating patients uniformly, will cause a continuum in the of the chronic postoperative pain problem. A multimodal approach, involving preoperative QST screening to subdivide patients, is recommended.

Today, QST is only utilized in smaller research focused studies, which some scientific results. An approach to combat and accelerate the knowledge of postoperative pain, which will lead to better diagnosis, is to agree upon a clinical consensus of implementing preoperative screening for sensitization in patients with severe knee osteoarthritis. Based on the literature reviewed for this thesis, several other surgical procedures would also benefit from implementation of preoperative QST screening.

Dansk sammenfatning

Denne afhandling understreger vigtigheden i det voksende problem med kroniske smerter efter total knæ alloplastik. Størstedelen af patienter vil have et smertefrit postoperativt forløb, dog har denne afhandling vist at ca. 10-50% af patienter, afhængig af smerteintensitet, vil opleve kroniske smerte et år efter operation. Tidligere studier har vist præ-operative sensibilisering af nervesystemet kan forudse hvilke patienter som er i risiko for at udvikle postoperative smerter f.eks. hos patienter som gennemgår thorakotomi. Denne afhandling fokuserede på præ-operative sub-gruppering af patienter, for at minimere udviklingen af kroniske postoperative smerter. Denne afhandling fandt en sammenhæng mellem præ-operativ sensibilisering af nervesystemet og udviklingen af kroniske postoperative smerter for patienter som gennemgik total knæ alloplastik. Endvidere, viste resultaterne at patienter som udvikler kroniske smerter efter primær total knæ alloplastik har en høj risiko for et dårligt resultat, hvis disse tilbydes revisionsoperation, hvorfor revisionspatienter skal udvælges med omhyggelighed.

Det anbefales at den fremtidige forskning fokuserer på, at udvikle metoder til at forudsige hvilke patienter der har højere risiko for at udvikle kroniske postoperative smerter, grundet at antallet af knæ alloplastik operationer vil stige i de kommende år, samt den høje risiko for udvikling af kroniske smerter efter operation. Forsættes den traditionelle simple unimodal diagnose, kun indeholdende røntgen og en smerte score, vil det kroniske postoperative smerte problem fortsætte. Det anbefales at indføre en multimodal screening diagnostik, indeholdende kvantitativ sensorisk målediagnostik, for at imødekomme problemet.

I dag anvendes kvantitativ sensoriske målediagnostik kun i begrænsede forskningsstudier, med begrænsede resultater. Det anbefales at der indgås en klinisk konsensus for indførelsen af kvantitativ sensorisk målediagnostik som rutine for at øge viden omkring præ-operative screening og postoperative smerter, hvilket vil føre til bedre behandlinger og dermed mindske risikoen for kroniske postoperative smerter for patienter som gennemgår total knæ alloplastik. Baseret på litteraturen som danner grundlag for denne afhandling, antages det at flere andre operative indgreb vil drage fordel af samme tilgang.

English summery

An estimated 500 million working days are lost in Europe each year due to chronic pain, of which 1 million workdays are lost in Denmark. Higher demand for more efficient drugs and medical devices for pain treatment thus continue to drive the pain management market. Therefore, technology enabling an improved diagnosis and as a result a more efficient and personalized treatment of chronic pain patients will have great perspectives.

It seems evident that preoperative sensitization of the nervous system holds prognostic information to if patients develop chronic postoperative pain. This thesis focused on the prevalence of chronic postoperative pain after total knee replacement (TKR) surgery in knee osteoarthritis (KOA) patients and to subgroup KOA patients using quantitative sensory testing (QST).

The work presented in this thesis highlights the severity of chronic pain after primary total knee replacement. While most patients will have a pain free postoperative recovery, this thesis showed that approx. 10-50% of patients, depending on the pain intensity, will experience pain one year after surgery. As shown in other patient groups e.g. patients undergoing thoracotomy, preoperative sensitization of the nervous system can be linked to chronic postoperative pain. This thesis focused on preoperative subgrouping of patients to minimize the risk of development of chronic postoperative pain. The work presented in this thesis, found associations between preoperative sensitization and postoperative chronic pain in patients with KOA before TKR. Patients who develop chronic postoperative pain after primary TKR surgery have a high risk of poor outcome after revision total knee replacement, why revision surgery should be performed with care.

Appendix 1: the PhD project at a glance

	Aim	Methods	Main outcome
Study I	Prevalence of chronic postoperative pain in patients scheduled for primary and revision TKR surgery.	Description of pain three years after TKR surgery.	19% of patients after primary and 47% of patients after revision TKR surgery experience severe to unbearable pain.
Study II	Link between preoperative QST parameters and chronic postoperative pain.	Preoperative, 2 months and 12 months postoperative PPTs, temporal summation, CPM and VAS measurements.	Patients who develop chronic postoperative pain have a different preoperative sensory profiles compared with patients who are pain free or have mild postoperative pain 12 months after TKR surgery.
Study III	Preoperative sensitization and serological biomarker profiles of patients with or without synovitis.	Preoperative blood sampling and PPTs. MRI scans of patients to obtain status on synovitis.	Different sensory and biomarker profiles can be descripted when dividing patients based on their synovitis status compared with controls.

Appendix 2: Literature review of QST measurements used in OA research

Study	Study population	Findings
O'Driscoll et al., 1974[75]	Hip OA Patients: N=55 Controls: N=21	Mechanical hyperalgesia detected in hip OA patients compared to controls.
Farrell et al., 2000[67]	Hand OA Patients: N=24	Provocation of movement pain is associated with a decrease in mechanical pain threshold in hand OA.
Kosek et al., 2000[72]	Hip OA Patient: N=12	Increase in warmth detection, decreased in pressure pain, decrease cold pain thresholds are decreased before surgery and normalized after surgery in hip OA patients.
Kosek et al., 2000[49]	Hip OA Patients: N=15 Controls: N=15	No preoperative change in pressure pain threshold comparing before and after heterotopic noxious conditioning stimulation but an increase after total hip replacement surgery, indicating a preoperative dysfunctional inhibitory system.
Wilder-Smith et al., 2001[68]	Hip and knee OA Patients: N=61	Patients electrical pain tolerance threshold is increased postoperatively compared too preoperatively.
Hendiani et al., 2003[77]	Mixed OA Patients: N=28 Controls: N=27	Increased innocuous mechanical sensation and decreased mechanical pain thresholds in patients with OA compared to controls.
France et al., 2004[211]	Knee OA Patients: N=132 (74 women)	Comparing post-menopausal women (with and without hormone treatment) and aged matched men showed no difference in pain ratings or electrical threshold or tolerance.
Moss et al., 2007[212]	Knee OA Patients: N=38	Patients with KOA have local and widespread hyperalgesia. Joint mobilization decreased the local and widespread hyperalgesia.
Imamura et al. 2008[69]	Knee OA Patients: N=62 Only women	Once central sensitization is present, the pain treatment should target the nervous system structures instead of anti-inflammatory agents only. Patients should be evaluated using PPT before surgery.
Lundblad et al., 2008[76]	Knee OA Patients: N=69	The combination of preoperative high pain intensity and low electrical pain threshold does not preclude surgery but patients should be given information regarding risk of chronic postoperative pain.
Gwilym et al. 2010[213]	Hip OA Patients: N=20 Controls: N=20	Increased activity with the periaqueductal gray matter (commonly associated with pain experience) is associated with cutaneous stimuli in referred pain areas.

Arendt-Nielsen et al., 2010[26]	Knee OA Patients: N=48 Controls: N=24	Patients with severe knee OA have lower pressure pain thresholds and increased facilitated temporal summation compared with controls. Pain intensities correlated to the degree widespread hyperalgesia.
Lee et al., 2011[73]	Knee OA Patients: N=26 Controls: N=33	Patients have widespread hyperalgesia compared with controls. CRP levels was correlated to widespread hyperalgesia, indicating an inflammatory response in knee OA patients may play a role in sensitivity.
Graven-Nielsen et al., 2012[24]	Knee OA Patients: N=48 Controls: N=21	Widespread hyperalgesia, facilitated temporal summation and loss of CPM is present in preoperative knee OA patients compared to controls. These pain mechanisms are normalized after TKR surgery implying that these mechanisms are maintained due to a peripheral drive.
Kavchak et al. 2012[74]	Knee OA Patients: N=16 Controls: N=16	Decrease PPTs, increased mechanical detection threshold and increased vibration thresholds was reported in patients compared to controls. Self-reported instability was associated with vibration thresholds suggesting that perceived instability may be a pain mediated in knee OA.
Vance et al., 2012[214]	Knee OA Patients: N=75	PPT increased in patients with knee OA after transcutaneous electrical nerve stimulation (TENS). Sensory cutaneous pain mechanisms were unaffected.
Finan et al., 2013[22]	Knee OA Patients: N=113	Central sensitization is predominant in knee OA patients with high pain intensity and absence of moderate-to-severe radiological OA.
Skou et al., 2013[25]	Knee OA Patients: N=40	Patients with pain after re-TKR surgery have widespread hyperalgesia, facilitated temporal summation and impaired CPM compared to patients no pain after re-TKR surgery.
Skou et al., 2014[83]	Knee OA Patients: N=73	Widespread hyperalgesia is more predominant in patients with high local knee hyperalgesia. Facilitated temporal summation is higher in re-TKR patients with pain compared to knee OA patients.

An overview of the important literature covering OA and sensitization of the nervous system.

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