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BY
PETER SKREJBORG

DISSERTATION SUBMITTED 2021

AALBORG UNIVERSITY
DENMARK

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by

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Dissertation submitted 2021

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CV

Peter trained as a physical therapist (1996-1999) and worked full-time in clinical practice until 2006. From 2006 to 2014 he worked full-time at Aalborg University Hospital with patients from the area of orthopedic surgery. From 2014 to 2016 he attended the MSc Clinical Science and Technology at Aalborg University (DK). In 2017 he was accepted as a PhD-fellow at SMI, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Denmark.

ENGLISH SUMMARY

Osteoarthritis in the knee is one of the most common pain conditions among the elderly population, and a heavy burden for both the patients and the healthcare system. Total knee replacement (TKR) is the only end-stage treatment known today. However, chronic postsurgical pain (CPSP) after TKR, a procedure conducted with the main purpose to relief the pain, occurs in one out of five TKR patients.

Despite the high number of TKR-surgeries performed all over the world little is known about how to prevent patients from developing chronic knee pain.

This PhD project consists of three studies. Study I examines if it is possible to predict which TKR patients has an increased risk of developing CPSP after surgery. Study II examines if the TKR patients developing CSP share any common characteristics. Study III examines if it is possible to reduce the number of TKR patients developing chronic knee pain by treating their postsurgical pain with a muscle relaxant drug.

Study I focuses on 493 TKR patients five years after their 2011 TKR surgery of which 29% had developed CPSP. Study I shows that Fibromyalgia, Chronic pain conditions elsewhere in the body than the knee, or if the patient has previously had cancer significantly increased the risk of developing CPSP after TKR surgery.

Study II focuses on 80 of the 493 TKR patients in Study I. The 80 TKR patients received an additional medical examination to develop a profile of TKR patients with CPSP 5 years after their surgery. Study II shows that patients with CPSP have a significantly poorer outcome measured in terms of pain, function, and satisfaction. Furthermore, patients with CPSP had significantly higher levels of low-grade inflammation.

Study III examines if treatment with the muscle relaxant "Chlorzoxazone" in the first 7 days postoperative days can reduce the acute pain and thereby reduce the proportion of TKR patients with CPSP 1 year after surgery. Using

a randomized placebo-controlled experiment with 200 patients, Study III found no significant differences in any parameters measured including pain, function, and adverse event in patients receiving “Chlorzoxazone” compared to those receiving placebo.

This PhD project can hopefully support decision makers and patients in their decision about TKR-surgery by providing knowledge about what comorbidities are important for the development of CPSP and showing that the presence of low-grade inflammation can be a driver in the patient’s development of CPSP. Furthermore, this PhD project indicates that “Chlorzoxazone” is not necessarily suitable for the treatment of acute postsurgical pain after TKR-surgery.

DANSK RESUME

Slidgigt i knæene er en af de mest hyppigt forekommende smertetilstande hos den ældre del af befolkningen, forbundet med store omkostninger for både den ældre og for sundhedsvæsenet. Indsættelse af total knæalloplastik (TKR) er i dag den eneste kendte behandlingsmulighed. Desværre opnår en ud af fem patienter ikke den forventede smertelindring efter operationen, og oplever efterfølgende kroniske smerter i knæet i form af uændrede eller øgede knæsmerter.

På trods af at der i dag foretages et højt antal TKR-operationer på verdensplan, findes der kun begrænset viden om hvordan vi kan undgå at patienterne udvikler kroniske knæsmerter.

Dette PhD-projekt, der består af tre studier, har undersøgt om det er muligt at forudsige hvilke patienter der er i øget risiko for at udvikle kroniske knæsmerter efter TKR-operation (Studie I), samt om der er nogle fælles karakteristika hos disse patienter (Studie II). Og endelig om det er muligt at reducere andelen af patienter, der udvikler kroniske knæsmerter ved at behandle patienternes postoperative smerter med et muskelafslappende medikament (Studie III).

I Studie I blev der lavet en 5-års opfølgning på 493 patienter, som fik indsat en TKR i 2011, hvor 29% af patienterne oplevede kroniske knæsmerter. Studie I viste, at Fibromyalgi, Kroniske smertetilstande andre steder i kroppen end knæet og hvis patienten tidligere har haft cancer, så er der en signifikant øget risiko for at udvikle kroniske knæsmerter efter TKR-operation.

I Studie II blev der lavet en yderligere lægeundersøgelse af 80 af patienterne fra Studie I for at lave en karakteristik af patienter med kroniske knæsmerter 5 år efter deres TKR-operation. Studie II viste, at patienterne med kroniske knæsmerter har et signifikant dårligere resultat målt på smerte-, funktions- og tilfredshedsniveau. Endvidere blev der hos patienter med kroniske

knæsmerter målt et signifikant højere niveau af low-grade inflammation i blodet.

I Studie III blev det undersøgt om behandling med det muskelafslappende middel "Klorzoxazon" de første 7 dage postoperative dage kan nedsætte de akutte smerter og derigennem nedsætte andelen af patienter med kroniske knæsmerter 1 år efter TKR-operationen. Studie III blev gennemført som et randomiseret placebo kontrolleret studie med 200 patienter, og viste at der ingen forskel er på de målt parametre hos patienter der fik "Klorzoxazon" i forhold til dem der fik placebo. Dette hverken på smerte- eller funktionsniveau eller på forekomsten af bivirkninger.

Dette PhD-projekt kan forhåbentligt være med til at understøtte beslutningstagere og patienter omkring deres valg i forhold til at få foretaget en operation med total knæalloplastik. Dette i form at viden om hvilke komorbiditeter der har betydning for resultatet og dels at tilstedeværelse low-grade inflammation kan have en indflydelse på om patienter udvikler kroniske knæsmerter. Endvidere indikerer dette PhD-projekt at "Klorzoxazon" ikke ukritisk er velegnet til at behandling akutte postoperative smerter efter TKR-operation.

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Thanks to my supervisor Prof. Lars Arendt-Nielsen at Aalborg University and to Ole Simonsen, MD at Aalborg University Hospital for giving me the opportunity. Also, a thanks to former head of the Department of Physiotherapy at Aalborg University Hospital for supporting me for so long.

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PREFACE

The project leading to this PhD-thesis was initiated in 2016 by the surgeons at the orthopedic department, Aalborg University Hospital in the North Denmark Region, as a part of their work to ensure maintenance of the high quality in their work. They wanted an overview of the patients who underwent a Total Knee Replacement surgery 5 years after the operation. How many patients still suffer from knee pain, was it possible to predict which patients who would not experience the expected pain relief, was the existing pain medication used in connection to the procedure effective and did the TKR patients share common characteristics.

TABLE OF FIGURES

CHAPTER 1. INTRODUCTION

1.1. OSTEOARTHRITIS

Osteoarthritis (OA) is the most frequent painful musculoskeletal condition in the elderly population and the most common cause of disability[1,2] in the United States[1,3] and other developed countries[1,4]. Knee OA (KOA) accounts for more than 80% of the total burden caused by OA[4,5]. KOA is a condition of failure of the joint, not only affecting cartilage, bone, and menisci, but also the synovium, ligaments, and neuromuscular tissue[6]. Evidence indicates that KOA mainly is driven by the breakdown of joint tissues from mechanical loading[7], but also from inflammation[8].

In general the definition of OA involves symptoms, physical examination of abnormalities, and radiographic criteria[7]. Table 1-1 illustrates different factors associated with pain in KOA[9]. The deeper underlying causes of the high prevalence of KOA remains unclear and insufficiently researched as the changes in pain processing and general pain sensitization have not been included in the general concepts[5].

The primary symptom of OA is pain and reduced function of the affected joints, but also reduced Quality of Life (QoL)[6].

Category	**Specific Factor**
Structural factors	Bone marrow lesions Cartilage defects Meniscal tear Effusion/synovitis
Periarticular factors	Muscle strength
Systemic factors	Obesity Inflammation Vitamin D
Central factors	Genes Depression Catastrophizing Acceptance Self-efficacy

Table 1 Factors implicated in osteoarthritis related knee pain. (Adapted from Jones G.[9])

1.2. TOTAL KNEE REPLACEMENT

Today surgery is the only end-stage treatment available, either as a total joint replacement, or as a unicondylar joint replacement.[6] Total Knee Replacement (TKR) is frequently done, effective, and produces long-lasting improvements of physical function and reduces pain for most KAO patients.[10,11]

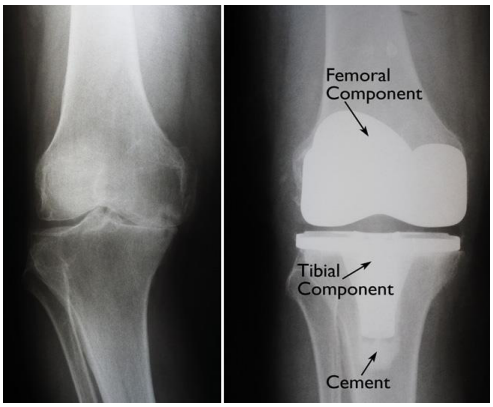


Figure 1-1 On the left: a knee with OA. On the right: a knee with a TKR. Adapted from OrthoInfo by American Academy of Orthopaedic Surgeons.

TKR was first performed in 1974, and is considered as one of the most successful procedures in all of medicine.[12] In the United States more than 670,000 knee replacements were performed in 2010.[13]

With an expected growth in the elderly population, the incidence of knee osteoarthritis (KOA) is predicted to increase in the future.[5] The incidences of total knee and hip replacements are therefore also expected to increase.[114] The demand for primary TKR is expected to increase almost 700% in the United States[14] (from 670,000 to 3.48 million) and 300% in Australia from 2010 to 2030.[15]

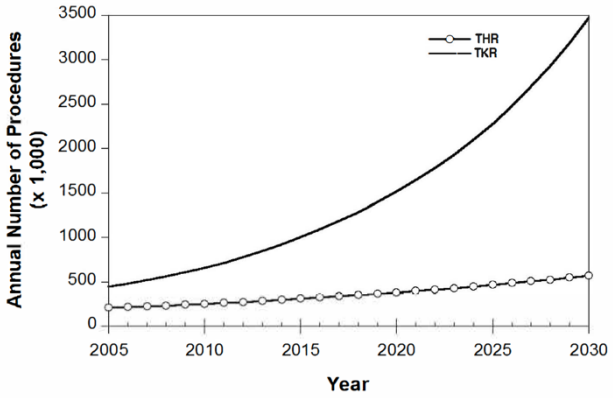


Figure 1-2 Illustration of the expected development in annual number of total knee and hip replacement in USA. (Adapted from Kurz et al 2007).

However, despite most patients being satisfied with the outcome, it is well-established that approximately 20% of TKR patients will develop chronic

postsurgical knee pain (CPSP).[10,11,16–18] CPSP causes disability, suffering, and a loss in quality of life (QoL) for TKR patients and increased use of resources for the health care system[19].

1.3. PAIN TREATMENT

Healthy joints are normally pain free, except if it they are exposed of intense pressure on the joint or movement outside the joints normal range of motion (ROM). However, if OA (or inflammation) is present in a joint, hypersensitivity of the nociceptive system can occur along with pain on palpation, movement within ROM, or at rest.[20]

So far, no treatment or drugs can prevent or modify the structural failure caused by OA in the joints.[6] Osteoarthritis Research Society International (OARSI) however, has developed "*OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis"*[21] which are patient-centered guidelines for facilitation of individualized treatment decisions of OA. The guidelines consists of both pharmacological and non-pharmacological recommandations.[21]

The pharmacological recommendations for the management of KOA pain has been investigated though several RCTs.[6] As a result, The American College of Rheumatology and the Arthritis Foundation have developed evidence-based guidelines for the comprehensive management of pain caused by KOA (table 1-2).[22]

Intervention	Recommendation for KOA
Topical nonsteroidal anti-inflammatory drugs	Strongly recommended
Oral nonsteroidal anti-inflammatory drugs	Strongly recommended
Intraarticular glucocorticoid injection	Strongly recommended
Acetaminophen	Conditionally recommended
Duloxetine	Conditionally recommended
Tramadol	Conditionally recommended
Non-tramadol opioids	Conditionally recommended
Topical capsaicin	Conditionally recommended

Table 2 Recommendations for the use of pharmacological treatment of KOA published by The American College of Rheumatology and the Arthritis Foundation.[22]

Despite the high number of TKR surgeries performed[13], and the expected increase in the future[14], no consensus about the analgesic protocols after TKR surgery exists.[23–25]

The treatment strategy of acute and chronic postsurgical pain is multimodal analgesic that involves optimizing peri- and postsurgical analgesia, reducing opioid-related adverse events, and in general limiting the causes of CPSP.[23,25–30] Ideally, sufficient analgesia should be achieved using a synergistic effect of different drugs, thus lowering the overall number of adverse events.[23]

Current treatment options for CPSP after TKR are limited because revision surgery based solely on the indication pain is not warranted.[10,31] However, the management of the acute postsurgical pain has been investigated through several studies[32–35], thus the mechanism behind the transition from acute postsurgical pain into CPSP is deficient[36,37]

1.4. AIMS OF THE PHD THESIS

The overall objective of this thesis was to examine if it is possible to predict if a patient scheduled for TKR is at risk of developing chronic postsurgical pain and to examine if modulation of the acute postsurgical pain can reduce chronic postsurgical pain after TKR.

This will be carried out through three separate studies:

Study 1: A descriptive study aimed at identifying the presurgical factors associated with developing chronic postsurgical pain 5 years after TKR surgery.

Study 2: A comparative study aim at characterizing the nature of the pain in patients with Mild-to-No or Moderate-to-Severe chronic postsurgical knee pain 5 years after TKR surgery.

Study 3: A randomized double-blind placebo-controlled trial aimed to examine if it is possible to decrease chronic postsurgical pain by modulating

the acute postsurgical pain by using Chlorzoxazone for acute pain after TKR surgery.

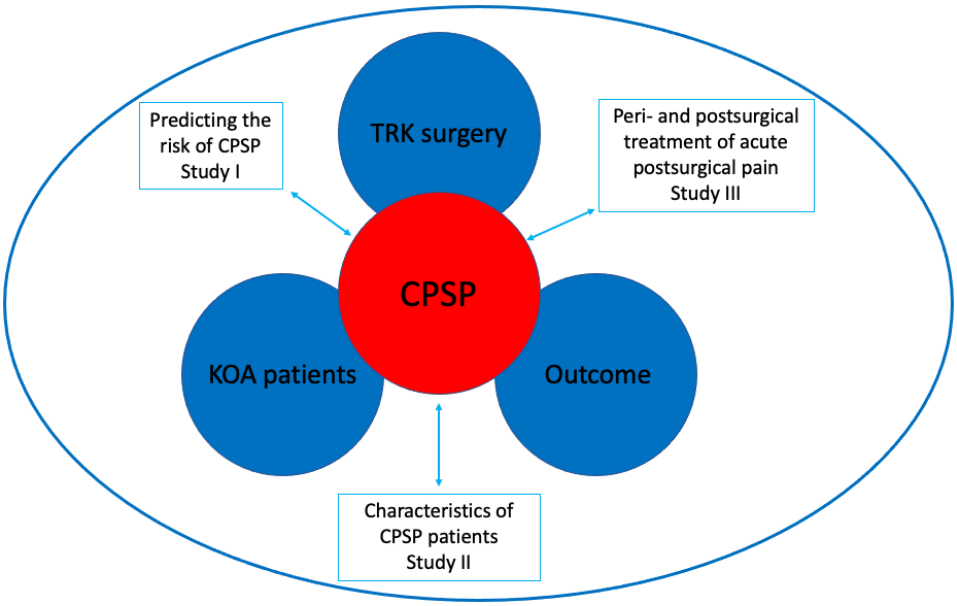


Figure 1-3 By predicting which patients in risk of developing Chronic Postsurgical Pain after TKR, and through characterization of the patients, the surgeons hopefully will be able to treat the patients' acute postsurgical pain to avoid CPSP.

1.5. OVERVIEW OF THE THESIS

The thesis is based on the results of the three studies:

Study I

Skrejborg P, Petersen KK, Kold S, Kappel A, Pedersen C, Østgaard SE, Simonsen O, Arendt-Nielsen L. *Presurgical Comorbidities as Risk Factors for Chronic Postsurgical Pain Following Total Knee Replacement.* Clin J Pain. 2019; 35 (7): 577–82.

A descriptive cohort study with a 5-year follow-up including 604 patients receiving a TKR in 2011. A screening of the patients will be conducted by a questionnaire to divide the patients into two postsurgical groups based on their *Worst pain in the last 24hours*.

Pre-surgical risk factors associated with the development of CPSP were identified, and a predictive model was established based on information about the patients at the time of surgery. The patients were described on the following parameters: Worst pain in the last 24hours, pre-surgical presence of comorbidities, and pre-surgical Knee Society Score.

Study II

Skrejborg P, Petersen KK, Kold S, Kappel A, Pedersen C, Østgaard SE, Simonsen O, Arendt-Nielsen L. *Patients with High Chronic Postoperative Knee Pain 5 years after Total Knee Replacement Demonstrate Low-grad Inflammation, Impairment of Function and High Levels of Pain Catastrophizing.* Clin J Pain. 2021; 37(3):161-167.

A descriptive comparative study in which patients with chronic postsurgical pain were offered a systematic examination by an orthopedic surgeon to clarify the cause, frequency and intensity of their pain. The patients were described on the following parameters: Worst pain in the last 24hours, PainDETECT, Pain Catastrophizing Scale, Oxford Knee Score, and Forgotten Joint Score.

Study III

Skrejborg P, Petersen KK, Beck J, Ulrich M, Simonsen O, Nielsen PT, Arendt-Nielsen L, Laursen M. *Investigating the Effect of Perioperative Chlorzoxazone on Acute Postoperative Pain after Total Hip and Knee Replacement Surgery.* Clin J Pain. 2020; 36 (5): 352–8.

A randomized double-blind placebo-controlled experiment to examine the analgesic effect of chlorzoxazone the first 7 days after total knee replacement. The patients were described on the following parameters: Pain after 5meter walk, Worst pain in the last 24hours, PainDETECT, and Oxford Knee Score.

CHAPTER 2. PREDICTING THE RISK OF CHRONIC POSTSURGICAL PAIN AFTER TKR (STUDY I)

Even though a growth in understanding of the epidemiology of CPSP, less is known about risk factors for developing CPSP or processes contributing to evolve acute pain after surgery to CPSP.[37,38] Some pre- and postsurgical risk factors have been determined for CPSP after primary TKR, such as high pre-surgical pain intensity, pre-surgical pain sensitization, high pain catastrophizing, high acute postsurgical pain, and previous surgery in the knee.[37–39]

The contributing factors to pain after TKR are several. As a directly complication after TKR there can be some mechanical issues such as loosening, malalignment and instability of the knee components. Another major complication is infection, which causes up to 45% of all failures.[17,40,41] Other reasons for development of pain are sterile synovitis, soft tissue inflammation, and referred pain from hip or back.[42]

Recent systematic reviews indicate that the number and severity of comorbidities are linked to and predictive for the prognosis of pain and physical functioning in patients with KOA[34,] and after TKR[35]. Most studies have used Charlson Comorbidity Index (CCI)[45] or Cumulative Illness Rating Scale (CIRS)[46] as measure of comorbidities when predicting prognosis of KOA. However, the main focus of these indexes is the cardiopulmonary and other systems, which is less relevant for the development of chronic postsurgical knee pain.

Although a recent study by Greene et. al (2015)[47] demonstrates that the use of standard comorbidity measures do not predict patient-reported outcome one year after total hip replacement (THR), the systematic review and meta-analysis by Lewis et. al (2015)[44] shows that comorbidities offer some help predicting CPSP after TKR. However, comorbidities are only predictive for CPSP when added in multivariate models, not as a variable in a univariate model.[44]

Common comorbidities are pain conditions such as fibromyalgia, low back pain, and chronic pain in other body parts than the knee (widespread pain), other rheumatic diseases, and diabetes.[10] However, neither of these comorbidities have been examined in a large scale study focusing on TKR.[48]

The aim of Study I is to establish knowledge about the factors associated with developing chronic postsurgical pain 5 years after TKR.

2.1. STUDY DESIGN, STUDY I

Study I was a part of the original project mentioned in "Preface" initiated by the orthopedic department at Aalborg University Hospital, Denmark. The study is a descriptive cohort study with a 5 year follow up that includes a consecutive cohort of all the patients who received a primary TKR at hospitals in the North Denmark Region.

A screening of the patients was conducted using a questionnaire to divide the patients into two post-surgical groups based on their *Worst pain in the last 24 hours*. The pain was measured on a VAS 0-10 scale, and a No-to-Mild Pain (No CPSP) Group with VAS<3 and a Moderate-to-Severe Pain (CPSP) Groups with VAS≥3 were established. The patients were also asked to assess their *Pain after 30 minutes of walk* (VAS 0-10) and their degree of satisfaction with the outcome of the TKR. The degrees of satisfaction were "very satisfied", "satisfied", and "not satisfied".

Information about pre-surgical comorbidities was obtained from the patients' medical journal. The study focuses on the following predefined set of comorbidities which have been shown to be associated with development of CPSP (reference?): OA not related to the knee scheduled for surgery, fibromyalgia, chronic pain in body parts other than the knee (widespread pain), a history of diagnosed cancer, chronic obstructive pulmonary disease (COPD), diabetes (both type I and II), lumbar issues, pacemaker, a history of diagnosed erysipelas, a history of diagnosed stroke, rheumatic diseases,

dementia, epilepsy, and gastric bypass.[48–51] Furthermore, the age and BMI at the time of surgery were retrieved through the medical journal.

Pre-surgical information regarding knee pain, knee stability, and the range of motion from a pre-surgical Knee Society Score (KSS) collected from the Danish Knee Arthroplasty Register. The KSS can be split into a knee score and a functional score. In study 1, the knee score and the functional score were used as 2 separate parameters, along with the single components in Table 3.

Presurgical KSS data were used to determine:

- *Walking distance (unlimited, >1, 0.5 to 1, <0.5 km, or housebound),*
- *Ability to walk on stairs (normal up and down, normal up and down with rail, up and down with rail, up with rail and unable down, or unable),*
- *Use of walking aids (none, the use of a cane, the use of 2 canes, the use of crutches, or the use of a walker),*
- *Range of motion (degree of flexion contracture, and degree of extension lag),*
- *Severity of presurgical pain (none, mild, or occasional, stairs only, walking and stairs, moderate occasional, moderate continual, or severe),*
- *Degree of knee instability (anteroposterior, mediolateral, and alignment.*

Table 3 The components of the Knee Society Score (KSS), a scoring system to rate the patients function of the knee before and after TKR.[126]

2.2. RESULT, STUDY I

Of the 604 patients who received a TKR in 2011, 493 patients replied to the questionnaire, 48 patients did not reply, and 63 patients were deceased. Of the 493 respondents, 352 patients provided complete data and 141 patients had missing data in the KSS.

2.2.1. CHRONIC POSTSURGICAL PAIN AT 5-YEARS FOLLOW-UP

Of the 493 patients who replied to the questionnaire, a 145 (29.4%) had CPSP 5 years post-surgical with a mean worst pain at rest of 5.24 (95%CI: 4.9-5.6). However, there is a huge difference in the knee pain outcome regarding worst pain at rest between the patients with CPSP and the patients with No

CPSP (0.38 (95% CI, 0.31-0.46)). Of the 493 responding patients, 258 (52.3%) had no pain after the surgery (Figure 2-1).

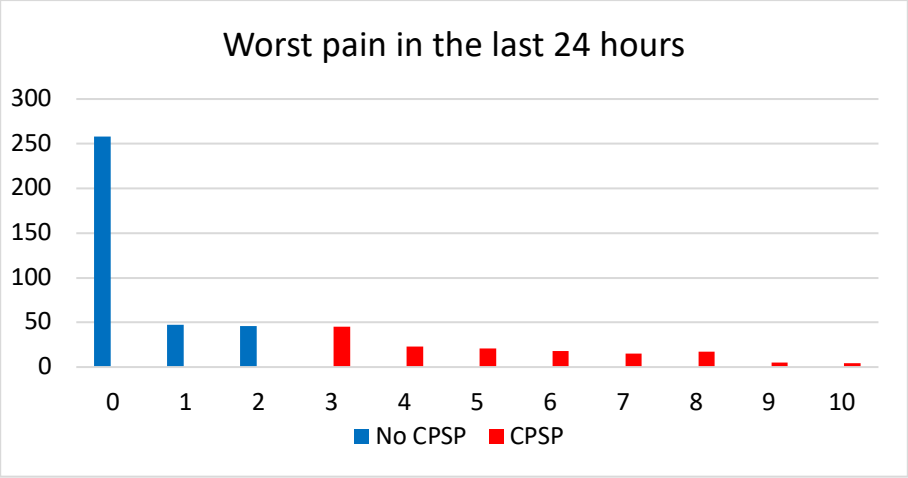


Figure 2-1 Distribution of Worst Pain in the last 24 hours in the two groups: No-to-Mild Knee Pain (No CPSP) and Moderate-to-Severe Knee Pain (CPSP).

CPSP after TKR

There is no consensus on how to assess pain, or define any cutoff, when assessing CSPS after TKR.

Despite the percentage of patients (29.4%) with CPSP being in the higher range of what has previously been demonstrated (10-34%),[16] 29.4% is still acceptable. However, there is no consensus about assessing CPSP after TKR. Frequently used questionnaire are: Western Ontario and McMaster Universities Index of Osteoarthritis (WOMAC) Pain Scale, Knee Injury and Osteoarthritis Outcome Score (KOOS), Oxford Knee Score (OKS), and Pain Visual Analogue Scales (VAS) with different cutoff points (VAS 3, 4 or 5),[16] which makes it difficult to compare different studies.

The patients with CPSP also demonstrate significantly worse functional outcome according to their *Pain after 30 minutes of walk* than the patients with No CPSP (6.09 (95%CI 5.7-6.5) versus 0.82 (95% CI 0.7-1.0), p<0.001).

Furthermore, a strong correlation between *Worst pain in the last 24 hours* and *Pain after 30 minutes of walk* is demonstrated (Pearson's correlation 0.880, p<0.001) (Figure 2-2).

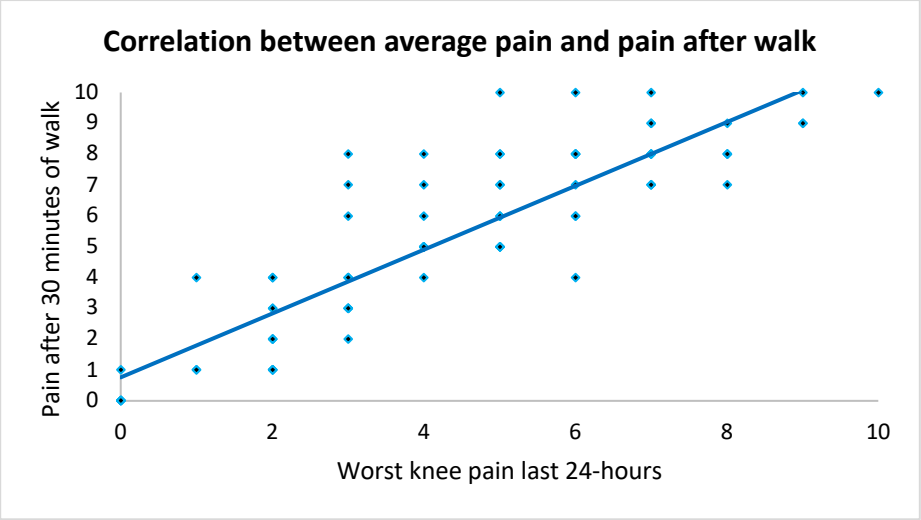


Figure 2-2 Correlation between Worst pain in the last 24 hours and Pain after 30 minutes of walk. (Pearson's correlation 0.880, p<0.001).

2.2.2. SATISFACTION WITH THE OUTCOME

Overall, the majority of the patients gain a high degree of satisfaction after TKR surgery. 435 out of the 493 responding patients (88.2%) are either "very satisfied" or "satisfied" with the outcome 5 years after TKR. Only 58 out of 493 patients (11.8%) are "not satisfied" with the outcome (Figure 2-3).

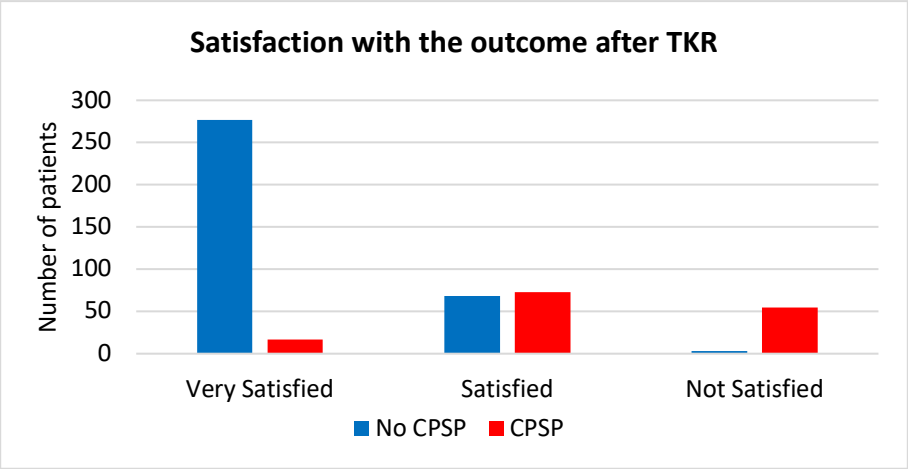


Figure 2-3 Distribution of the degree of satisfaction with the outcome after TKR.

Satisfaction

There is no consensus on how to assess the degree of satisfaction after TKR.

A systematic review by Kahlenberg et al. (2018) find that the majority of studies reporting the degree of satisfaction after TKR rates the percentage of patients being satisfied from 80-100%.[52] As for CPSP, no consensus exists about what scale to use when assessing satisfaction. However, 61.1% of the studies included in the review used a single question about the overall satisfaction with TKR and an ordinal scale comparable to the scale used in study I.[52]

2.2.3. PREDICTING THE RISK OF DEVELOPING CPSP

Several studies focusing on predicting the outcome after TKR exist.[44,53–59] Specifically, different models for predicting the post-surgical outcome based on demographic factors, pre-surgical pain scores, and different questionnaires with different success exist.[60–65] Mainly, the prediction models focus on identifying the patients at risk of not achieving a satisfying outcome with TKR. These models do not provide specific information about postsurgical pain and function, which leaves the models inadequate to guide pre-surgical interventions and expectation management.[60–65]

Non-successful outcome after TKR

There is no consensus on how to classify responders or non-responders after TKR when constructing the different prediction models for the outcome.

However, there is no consensus on how to classify responders or non-responders after TKR when constructing the different prediction models for the outcome. Most of the studies use postsurgical pain as a classifier. Previously, some studies used WOMAC for classification, either by the complete score[65] or by pain subscores[61,64], the new Knee Society Score (KSS)[63], or gait speed[62]. Furthermore, most of the studies use different methods for constructing their models. In addition, the studies found different factors predictive for the outcome after TKR, and the list of risk factors is extensive. However, all the models use pre-surgical factors and information obtained during the surgery.

The overall purpose of prediction models is to predict which TKR patients are at risk of being non-satisfied, non-responder, or having residual pain or lack of function.[44,53–59] However, due to the lack of consensus on the different aspects of the models, it is difficult to compare the different models.

Based on the available pre-surgical information (Figure 1-1) it is possible to identify 6 factors that are significantly associated with Moderate-to-Severe CPSP 5 years after primary TKR and, therefore, have some predictive value for the post-surgery outcome: Three different comorbidities diagnosed before the time of surgery, information about the pre-surgical condition of the knee, and age at the time of surgery.

Together, the 6 factors were able to correctly classify 33.6% of the patients in the CPSP group based on a binary logistic regression model and only misclassify 5.6% of the patients.

2.2.4. FACTORS ASSOCIATED WITH CPSP

In the complete cohort in Study I, 8 patients had diagnosed Fibromyalgia (FM) at the time of surgery. 6 patients had complete dataset and were included in the study. Binary logistic regression analysis shows that patients with FM have a probability of 95.4% of developing CPSP after TKR (figure 2-4). Other

studies support the finding that patients with FM report continued knee pain despite surgery.[66–68]

12 patients in the cohort (8 patients with complete data) were diagnosed with widespread pain. Widespread pain was defined in Study I as chronic pain in another body part than the knee at the time of surgery. The probability of developing CPSP after TKR when diagnosed with pre-surgical widespread pain is 87.0% (figure 2-4). Supporting this, pre-surgical widespread pain, assessed as pain sensitization, has been shown to be predictive for the development of CPSP.[56,69,70]

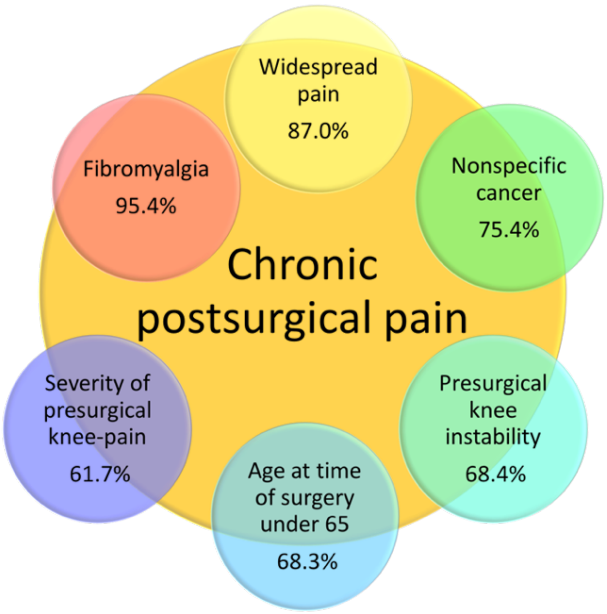


Figure 2-4 Existence of presurgical comorbidities increase the probability of developing CPSP. Study I revealed 6 different comorbidities with a probability from 61.7% to 95.4% risk of developing CPSP.

75 patients in the cohort (55 with complete data) were diagnosed with non-specific cancer. 22.1% of the patients with CPSP have a history of diagnosed cancer. Only 12.4% of the patients without CPSP have a history of diagnosed cancer (24.1% vs 11.9% of the patients with complete data). Patients with a history of cancer have a probability on 74.5% of developing CPSP after TKR (figure 2-4). However, the association between cancer and CPSP has not previously been shown. One study by Peter WF et al. (2015)[49] shows cancer to be predictive of the outcome after total hip replacement (THR), but not for TKR.

Factors with a minor probability for developing CPSP are: presurgical knee instability (68.8%), age at the time of surgery under 65 (68.3%), and severity of pre-surgical knee-pain (61.7%). These factors have all been found predictive of CPSP following TKR previously (figure 2-4).[31,33,71–73]

CHAPTER 3. THE NATURE OF CHRONIC POST-SURGICAL PAIN AFTER TKR (STUDY II)

Acute post-surgical pain is followed by CPSP in 10-50% of all patients after different kinds of surgery.[33] In most cases, these non-successful patients do not show any abnormal findings in radiology exams.[74,75] However, some alleged that CPSP is caused by ongoing inflammation or a manifestation of neuropathic pain due to surgical injury of some major peripheral nerves.[33]

Quantitative sensory testing (QST) is used to profile the sensitivity of the patients pain system.[76] It is well established, that QST can be used to profile patients with KOA, and that patients that are found pain sensitive prior to surgery are more likely to develop CPSP.[56,57,70,77–81] PainDETECT is a QST-questionnaire used to evaluate the likelihood of neuropathic pain in OA and KOA patients.[82–86]

The Pain Catastrophizing Scale (PCS) is used to assess pain catastrophizing thoughts[87], and it has been associated with CPSP shortly after TKR.[88–90] However, it is unclear if pain catastrophizing thoughts persists in patients with CPSP 5 years after TKR.[90]

The Oxford Knee Score (OKS) is used to evaluate the state of the knee before and after TKA.[91] The questionnaire is designed to assess both the functional ability and the pain from the patient's perspective.[92]

The FJS-12 is used to assess the patients awareness of artificial joints during the various activities of daily living.[93–95] It uses 5 dimensions to define the health: mobility, self-care, usual activities, pain/ discomfort, and anxiety/depression.[93]

The relationship between pain and inflammation has recently been demonstrated in patients with painful OA.[96–99] However, it is not known if the same relationships exist for patients with CPSP after TKR. Traditionally inflammation is measured by the level of C-reactive protein (CRP), which is

used in clinical practice as a rough indicator for infection, inflammatory diseases, or malignancy.[100]

CRP has been used to distinguish systemic inflammatory disorders from non-inflammatory diseases.[101] Recently, low-level elevations in CRP have been observed in diseases with a local, low-grade inflammatory component.[101] Also an association between pre-surgical increased CRP-level (low-grade inflammation) and potentially worse long-term prognosis after TKR exists.[102] However, no research has assessed the CRP-levels in patients with CPSP 5 years after TKR.

> *"In healthy persons, normal CRP levels are generally considered to be below 3 mg/L.*[100,127] *Low-grade inflammation can be defined as a CRP in the range from 3 to 10 mg/L.*[100,127] *CRP levels above 10 mg/L may suggest the presence of an underlying inflammatory disease, infection, or malignancy.*[100,127]*"*

Fact box 3-1 From Skrejborg et al. 2020. [1]

The aim was to characterize TKR patients with Moderate-to-Severe CPSP 5 years after TKR surgery.

3.1. STUDY DESIGN, STUDY II

Participants for Study II were recruited from the patients in the Study I-cohort.

The patients were divided into two post-surgical groups based on the assessment of their pain in the PainDETECT questionnaire. The PainDETECT pain assessment was chosen to have a pain score as current as possible. The pain was measured on a VAS 0-10 scale. A VAS < 3 defines the No-to-Mild Pain Group and VAS $\geq$ 3 defines the Moderate-to-Severe Pain Group.

The patients in the two groups underwent a physical examination, including having a blood sample taken, by an orthopedic surgeon at the Orthopedic Outpatient Clinic at Aalborg University Hospital, Aalborg, Denmark. The patients were also assessed using the questionnaires PainDETECT, PCS, OKS, and FJS-12 prior to the visit.

3.2. RESULT, STUDY II

Patients with CPSP 5 years after TKR experienced significantly worse outcome than patients without CPSP. Higher levels of pain decreased the range of motion of the knee, a lower level of function, and a lower degree of satisfaction with the outcome. Higher level of pain also resulted in a higher degree of pain catastrophizing thoughts, a higher awareness of the knee, and a higher risk of having a low-level inflammation.

A total of 80 patients participated in study II. 62 patients in the Moderate-to-Severe CPSP group and 18 patients in the Mild-to-No CPSP group.

No significant difference in the baseline characteristics between the two groups exists, nor between the patients in the study and the complete cohort in Study I.

3.2.1. CHRONIC PAIN AND PHYSICAL OUTCOME 5 YEARS POST-SURGERY

Patients with CPSP have significantly higher pain scores in both Pain at rest, Worst pain last 24 hours, and Pain after 30 minutes of walk ($p<0.001$) (Figure 3-1).

Despite the presence of CPSP, 29 patients (46.8%) were satisfied after TKR (Figure 3-2). Unfortunately, no data is available about the degree of pain relief or in what degree function or QoL is enhanced. However, it is well documented that satisfaction is not stable over time[103], and that the degree of pain symptoms are associated with the degree of satisfaction.[52,103–105]

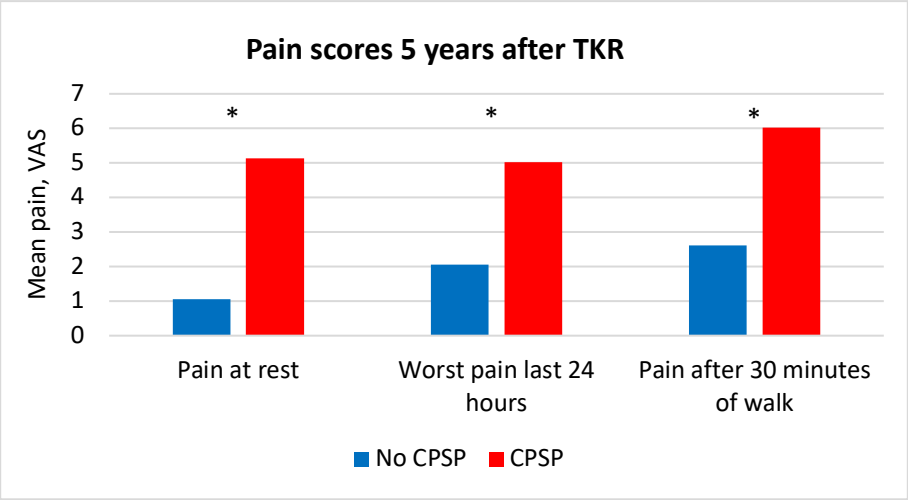


*Figure 3-1 All significant difference mean pain between patients with CPSP and without CPSP. * indicates significant difference.*

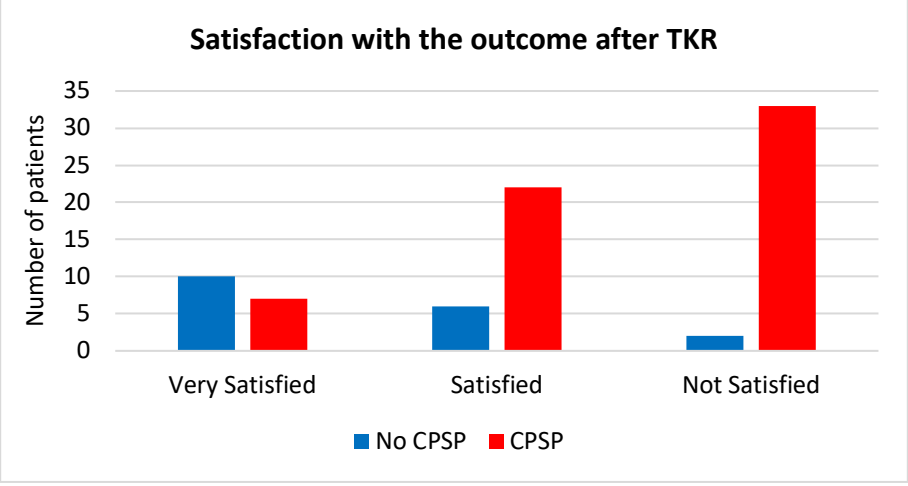


Figure 3-2 Distribution of the degree of satisfaction with the outcome after TKR, with a significant higher number of patients not satisfied with the outcome after TKR.

The patients with CPSP have a significantly higher PainDETECT score (mean: 14.8) than the patients without CPSP (mean: 6.8). Furthermore, 29% of the patients with CPSP have pain with a neuropathic component.

The Pain Catastrophizing Scale (PCS) is widely used for assessing the level of pre-surgical pain catastrophizing thoughts. The scale has been used[106–108] for predicting CPSP 1 year after TKR, with pre-surgical high level of catastrophizing being predictive for severe CPSP. However, only a few studies have evaluated the effect of pre-surgical pain catastrophizing on long-term (e.g. 5 years) outcomes.[89,90] The patients with CPSP report a significantly higher level of pain catastrophizing thoughts than the patients without CPSP 5 years after the surgery.

The significant lower OKS in both the function and the pain component shows that the patients with CPSP perceive the outcome after TKR worse than the patients without CPSP (Figure 3-3). Also, when comparing the OKS scores with the OKS scores from the patients in Study III at a 12-months follow-up, a significantly lower score is found: OKS, function (53.7 vs 78.1; $p<0.001$) and OKS, pain (49.8 vs 83.0; $p<0.001$).

The Forgotten Joint Score was assessed for the complete cohort in Study I. The result was a significant lower score in the patients with CPSP (25.8; 95% CI: 22.5-29.0) compared with the patients without CPSP (77.1; 95% CI: 75.9-79.3), $p<0.001$.

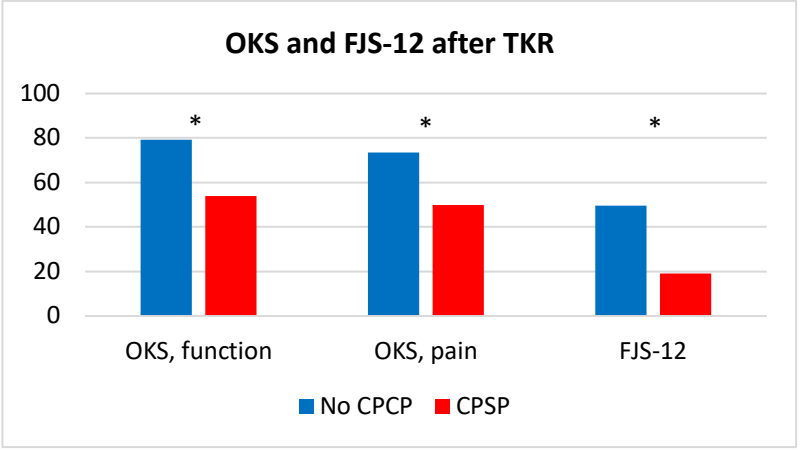


*Figure 3-3 The distribution of Oxford Knee Score, function and pain, and Forgotten Joint Score 5 years after TKR. * indicates a significant difference.*

3.2.2. LOW-GRADE INFLAMMATION AFTER TKR

Patients with CPSP 5 years after surgery have a significantly higher level of serum hs-CRP than patients without CPSP (5.0 vs 2.1), and a level of serum hs-CRP above 3 mg/L has only been registered among CPSP patients (Figure 3-4).

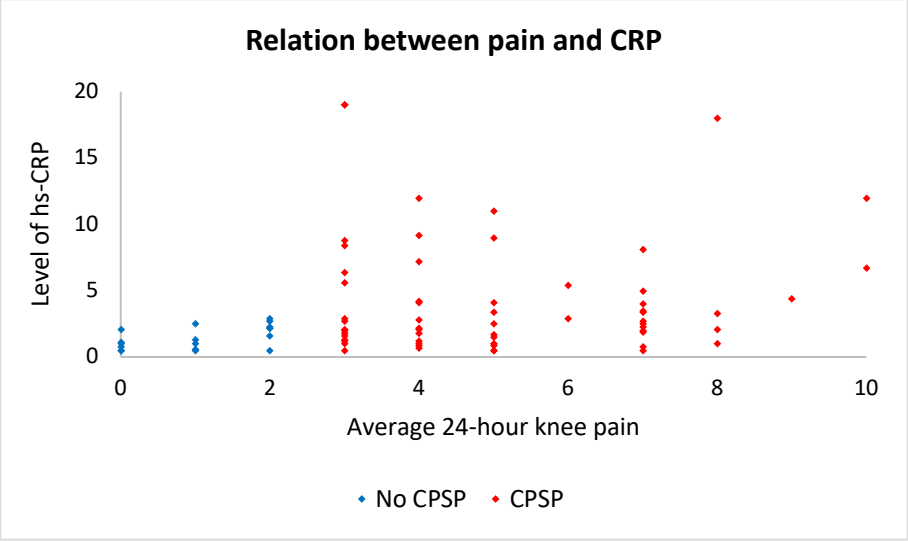


Figure 3-4 Level of serum hs-CRP in patients with and without CPSP 5 years after surgery.

There is a moderate correlation between the average 24-hour knee pain and the level of serum hs-CRP (0.325, p=0.003) (Figure 3-5).

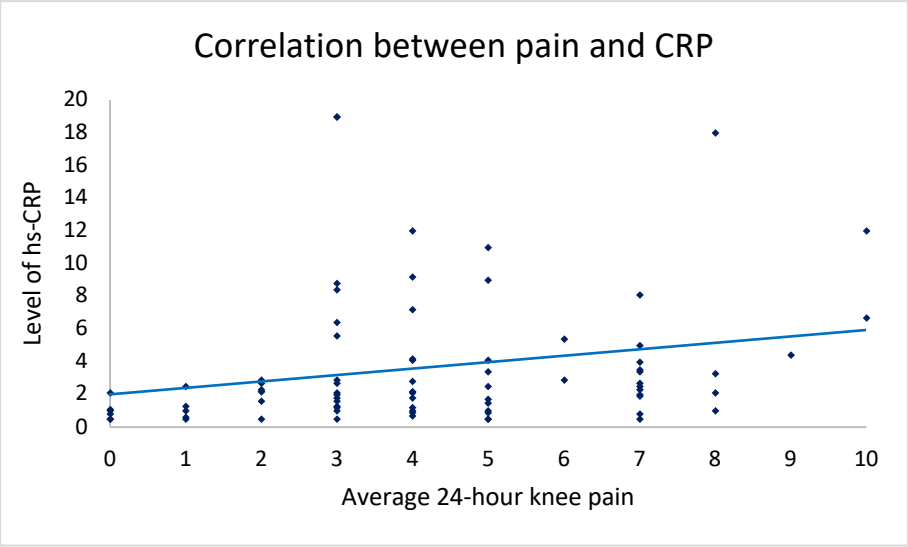


Figure 3-5 There is a significant moderate correlation of 0.325 (p=0.003) between the average 24-hour knee pain and the level of serum hs-CRP.

CHAPTER 4. MODULATION OF ACUTE POSTSURGICAL PAIN AFTER TKR (STUDY III)

Evidence has demonstrated that developing CPSP after TKR is associated with the degree of pre-surgical knee pain, and the degree of acute post-surgical pain.[33] Despite that an evidence-based guideline for the comprehensive management of osteoarthritis (OA) exists[22], there is no consensus on the analgesic protocol for treating pain after TKR.[24,25,28,29]

"Post operative pain is a unique and common form of acute pain, produces pain of moderate and severe intensity, and can result in persistent pain. In addition to emotional suffering, poorly controlled pain also causes considerable perioperative complications, delays ambulation and recovery, prolongs hospital stay, and increases perioperative cost."

Fact box 4-1 Description of Postsurgical Pain. From Xu J and Brennan TJ (2014).[128]

The analgesic strategy for treatment of acute postsurgical pain is multimodal. The strategy is to aim both the pre-, peri-, and postsurgical analgesia and focus on reducing opioid-related adverse events and minimizing causes that can lead to CPSP.[24–30]

In Denmark, Chlorzoxazone has been used as a part of the standard analgesic protocol after TKR. However, the effect of Chlorzoxazone as pain-reliever after TKR has never been investigated. Some studies have shown limited or no effect on back pain after spine surgery and questioned the continued use of Chlorzoxazone as analgesic after spine surgery.[18,35,109]

"Chlorzoxazone is a muscle relaxant that has been suggested to enhance acute postsurgical pain recovery[123], which thereby may reduce postsurgical pain.
Chlorzoxazone inhibits mono- and polysynaptic reflexes in the CNS,[109,124] but the specific mechanism of action is not clear. A study by Van Tulder et al., 2003 suggested that chlorzoxazone may partly be associated with sedative effects due to the benzodiazepine derivative structure of chlorzoxazone.[109,123]*"*

Fact box 4-2 Fact box about Chlorzoxazone. Adapted from Skrejborg P et al. (2020) [23]

The aim of study III is to examine if it is possible to decrease or eliminate CPSP by modulating the acute postsurgical pain, thereby increasing the quality of life and physical functioning, including examining the effect of Chlorzoxazone on acute pain after TKR.

4.1. STUDY DESIGN, STUDY III

Patients scheduled for elective primary TKR were recruited at a prescheduled clinical examination preceding their admission for surgery for participating in a randomized, double-blinded, placebo-controlled, parallel-group clinical experiment. Specifically, the patients were recruited to examine the effect of peri- and post-surgical administration of Chlorzoxazone on the acute postsurgical pain, and thereby on CPSP after TKR.

The patients were randomized into 2 groups receiving either Chlorzoxazone or placebo 3 times daily for the first 7 days postsurgical starting 2 hours before surgery (see Table 4 for details).

Time	Group 1	Group 2
08.00 AM	Chlorzoxazone 250mg Acetaminophen 2g Celecoxib 200mg	Placebo Acetaminophen 2g Celecoxib 200mg
04.00 PM	Chlorzoxazone 250mg	Placebo
10.00 PM	Chlorzoxazone 250mg Acetaminophen 2g Celecoxib 200mg	Placebo Acetaminophen 2g Celecoxib 200mg

Table 4 Schedule of self-administration of basic analgesic, test-drug and placebo.

The primary outcome was *Pain after 5 meters walk (VAS 0-10)* 24 hours after surgery. The secondary outcomes were *Oxford Knee Score* (OKS*), Pain at rest (VAS 0-10),* and *Worst pain in the last 24 hours (VAS 0-10)*. Appendix A provides an overview of the measure points. Opioid consumption during admission was also assessed.

The surgery consisted of a midline skin incision and medial parapatellar arthrotomy and was performed under lumbar spinal anesthesia. Post-surgical, a standard fast-track rehabilitation regime was followed, and the patients were discharged to their own homes according to usual discharge criteria.[110]

4.2. RESULT, STUDY III

185 patients participated in study III. The patients were randomized into the two groups: 94 patients in the Chlorzoxazone group and 91 patients in the Placebo group. No significant difference in the baseline characteristics existed, except a slightly better function score in OKS in the Placebo group.

4.2.1. CHLORZOXAZONE AS PAIN RELEAVER AFTER TKR

Chlorzoxazone had no significant effect on neither primary nor secondary outcomes: the Chlorzoxazone group and the Placebo group were not significantly different. Figures 4-1 to 4-4 provide an illustration of the development of pain and function from Baseline to Follow-up after TKR.

Despite no significant difference between the Chlorzoxazone and the Placebo groups, the figures illustrate a trend towards a better outcome for the Placebo group the first 14 days postsurgical. However, at follow-up after 12 months the groups are basically identical.

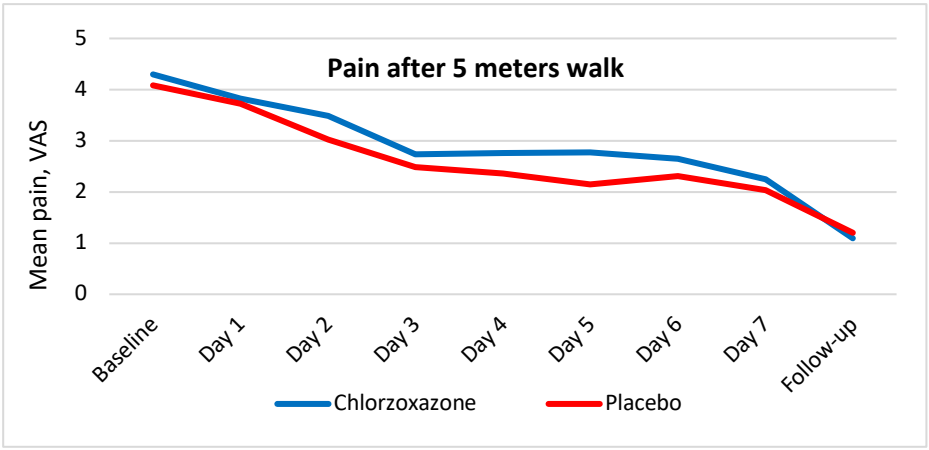


Figure 4-1 Mean Pain after 5 meters walk, from Baseline to 12 months Follow-up.

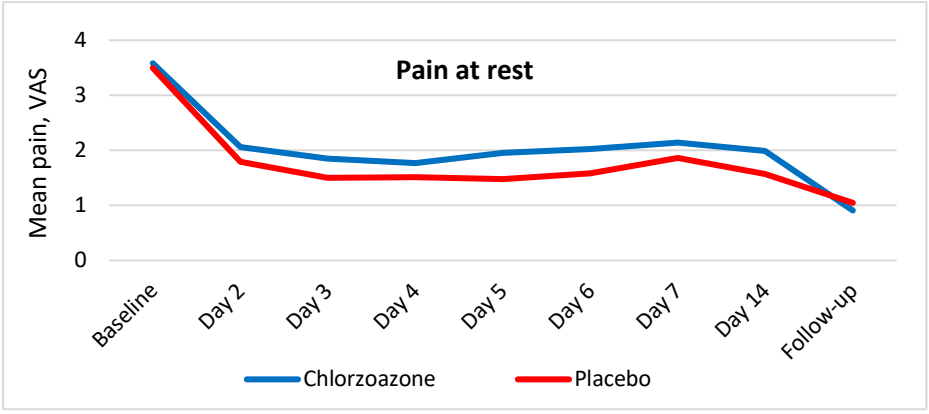


Figure 4-2 Mean Pain at rest, from Baseline to 12 months Follow-up.

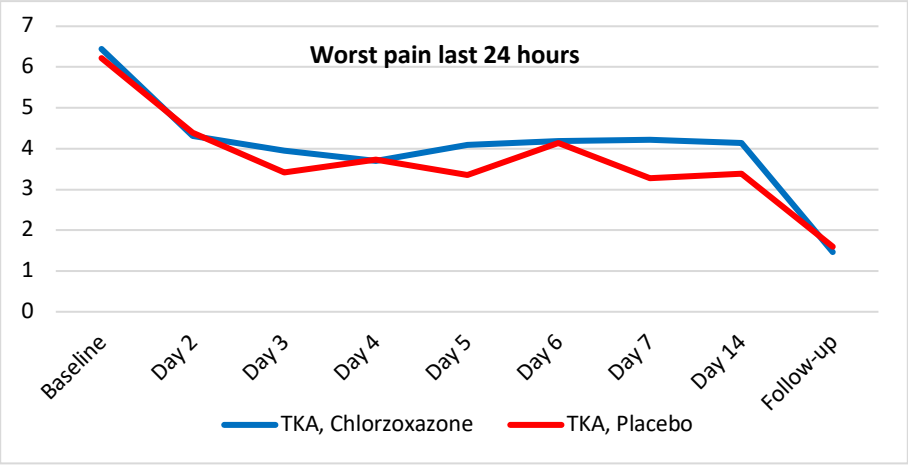


Figure 4-3 Mean Worst pain last 24 hours, from Baseline to 12 months Follow-up.

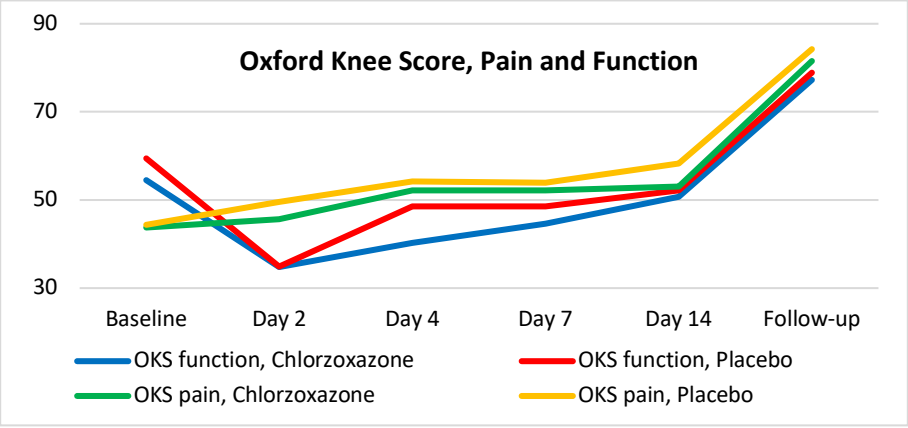


Figure 4-4 Oxford Knee Score, Pain and Function, from Baseline to 12 months Follow-up.

Furthermore, Chlorzoxazone did not reduce opioid consumption or adverse events during the first 7 days postsurgical.

When comparing Worst pain last 24 hours between the patients from Study I with the patients from Study III, no significant difference in mean pain between the two cohorts exists. This result holds whether pain is measured at the 5 years follow-up in Study I (mean: 1.81, 95% CI 1.58-2.03) or at 1-year

follow-up in Study III (mean: 1.53, 95% CI 1.19-1.87), p=1.0. However, whereas 29.4% of the patients in Study I suffer from CPSP at 5-years follow-up, only 18.2% of the patients in Study III suffer from CPSP at 1-year follow-up.

CHAPTER 5. DISCUSSION

It is always difficult to make predictions about the future, not having consensus about how to conduct the predictions makes it even more difficult.

Total knee replacement is broadly accepted to be one of the most successful orthopedic procedures. However, when reviewing the literature for knowledge about the outcome after TKR, consensus about how to define which patients respond adequately to the procedure have never been established.[111] Both the degree of post-surgical knee pain and the degree of satisfaction with the outcome after TKR are frequently used measurements to categorize responders versus non-responders. Meanwhile, there is no consensus about what questions, questionnaires, or measurements to use, nor is there consensus about what level the cutoff-points of any tools used are acceptable after TKR. The lack of consensus makes it difficult to compare the available knowledge about the outcome after TKR.

The type and design of knee replacement has been subject to minimal modifications in the last 20 years. The standard approach to implanting knee replacement has also been more or less unchanged for the last 30 years. However, in recent years there has been an increase in the number of unicompartmental knee replacements (up to 10%).[111] The benefits of this type of knee replacements are not fully understood yet, but it seems to include better functional outcome and greater cost-effectiveness.

Although there has been an increased focus on pre- and post-surgical training, and perioperative analgesic management for TKR patients, no consensus has been established. The American College of Rheumatology and the Arthritis Foundation have developed evidence-based guidelines for the comprehensive management of pain caused by osteoarthritis[22], but the evidence for analgesic management after TKR is lacking. However, some consensus that the analgesic management should be a multimodal analgesic

strategy with the aim of reducing the use of opioids has been established.[25–30]

With chronic post-surgical pain (along with poor function) as the main reason for low satisfaction after TKR, analgesic management should be considered highly important.[111]

Another way of increasing the success rate after TKR is a stratification of the patients before surgery into different categories depending on admission type: 1) outpatient surgery or same-day surgery setup, 2) fast-track surgery setup, or 3) admission with longer hospital stay. The advantage of same-day and fast track surgery is the use of minimally invasive knee replacement surgery (MIS) with reported benefits as faster recovery, reduces postsurgical pain, reduced surgical stress.[27,112,113]

Nevertheless, the continuous implementation of new knowledge should result in all aspects of the treatment of patients being optimized. From the patients who underwent surgery in 2011 (Study I) to the patients who underwent surgery in 2016/2017 (Study III), an improvement in the number of patients with chronic postsurgical knee pain exists (29% vs 18%). The improvement exists despite the surgeries being performed by the same surgeons in the same departments. Hopefully, this could be interpreted as evidence of improved management of TKR-patients, and not only a result of differences in the time of follow-up in the two studies.

5.1. PREDICTION OF NON-RESPONDERS AFTER TKR

Knowledge about the risk factors for becoming a non-responder after TKR is very useful for both decision makers, surgeons, and patients. With the expected growth in the number of procedures performed, the value of predicting which patients in risk of becoming a non-responder will increase.

It is important that the patient and surgeon make the decision about surgery on as informed basis. The risk of continued knee pain after TKR is and will continue to exist. About 20% of the patients will not obtain the expected pain

relief or satisfaction after undergoing TKR. Increased knowledge about which factors associated with increased risk of chronic knee pain after TKR will increase the ability to identify which patients require extra attention in advance. Additionally, the focus on patients at risk of developing chronic knee pain after TKR could increase satisfaction with the outcome through an increased functional performance rather than an expectation of pain relief.

Study I found a significant association between the comorbidities fibromyalgia, widespread pain, and non-specific cancer diagnosis, with a minimum 75.4% risk of developing chronic knee pain after TKR. This result can be useful when making decisions about surgery in knowing what to expect when presence of certain comorbidities.

Unfortunately, the study did not provide any information about any improvement in function, hence it would have provided valuable knowledge about which degree of improvement to expect after receiving a TKR.

5.2. LOW-GRADE INFLAMMATION IN TKR-PATIENTS

It has recently been demonstrated that low-grade inflammation has a predictive role in the progess of OA [8], with the levels of serum CRP as a bio-marker associated with local inflammation[101], knee pain and knee stiffness.[102,114,115] Smith et al.[102] demonstrated that high pre-surgical levels of serum hs-CRP in KOA patients (average higher than 7 mg/L) is associated with a high 1-year post-surgical levels of serum hs-CRP (average higher than 14 mg/L), this indicating a presence of chronic low-grade inflammation.[102] Also, it was demonstrated that a worse outcome in the Short Form health outcomes survey (SF-12) could be identified in patients with higher levels of pre-surgical serum hs-CRP 6 and 12 months after TKR.[102]

In diseases like OA, cytokines are major mediators of inflammation, and can induce and maintain the disease processes[116], with Interleukin-6 (IL-6) as a key player in systemic inflammation and OA.[117] In relation to OA, increased levels of serum hs-CRP correlate with increased IL-6 levels[101], which correlate with pain intensity.[114] It has been suggested that the level of serum hs-CRP

can be an indicator of poor outcomes after TKR[96,102], and the findings of this study can extend these suggestions to the 5 years post-surgical pain status.

5.3. CHLORZOXAZONE AS ANALGESIC AFTER TKR

Chlorzoxazone belongs to the group of muscle relaxants. There are three types of muscle relaxants: antispasmodic benzodiazepines, antispasmodic non-benzodiazepines and antispasticity drugs (Table 5).[118]

Despite the lack of scientific evidence for the use of chlorzoxazone as part of the analgesic management after TKR and THR, chlorzoxazone has been widely used in Denmark for several years.[29]

Types of muscle relaxants:
Antispasmodic benzodiazepines (alprazolam, bromazepam, chlordiazepoxide, cinolazepam, clonazepam, cloxazolam, clorazepate, diazepam, estazolam, flunitrazepam, flurazepam, flutoprazepam, halazepam, ketazolam, loprazolam, lorazepam, lormetazepam, medazepam, midazolam, nimetazepam, nitrazepam, nordazepam, oxazepam, pinazepam, prazepam, quazepam, temazepam, tetrazepam, triazolam)
Antispasmodic non-benzodiazepines (cyclobenzaprine, carisoprodol, chlorzoxazone, meprobamate, methocarbamol, metaxalone, orphenadrine, tizanidine and zopiclone)
Antispasticity drugs (baclofen and dantrolene sodium).

Table 5 Types of muscle relaxants according to Richards et al. 2012[118]

In general, muscle relaxants are used for treatment of upper motor neuron spasticity, and for treatment of pain or spasms due to peripheral musculoskeletal conditions.[109] Muscle relaxants, including chlorzoxazone, are used for treatment of low-back pain, and other musculoskeletal pain.[109,119] Despite the low level of evidence, it appears that muscle relaxants, as a group of drugs, could have a pain reducing effect on non-specific low-back pain in combination with NSAIDs or COX-2-inhibitors.[120–123] However, a recent RCT demonstrates no effect of chlorzoxazone on acute pain after spine surgery.[35]

The mechanism of action of chlorzoxazone is unclear, however it is known that chlorzoxazone inhibits mono- and polysynaptic reflexes in the central nervous system (CNS).[109,124,125] Chlorzoxazone is supposed to have an

analgesic effect due to a benzodiazepine derivative structure, which is associated with a sedative effect.[35,123]

Study III found no significant difference in pain or function, neither in the acute phase, nor at 1-year follow-up. Furthermore, no reduction in opioid consumption or adverse events was found.

5.4. PERSPECTIVE

The value of post-surgery outcome prediction is very high, however the precision of the prediction models is still not sufficiently high. Moreover, the existing prediction models are typically not comparable due to the lack of consensus. The aim must be to establish consensus about how to define responder vs non-responders after any given procedure. As an alternative, there could be both an agreement on the outcome measured as CPSP, and on the outcome measured as postsurgical function. Achieving consensus would help clarify what outcome to expect when making the decision about surgery.

This thesis also provided an indication about the presence of chronic low-level inflammation in patients with CPSP. Clinicians should take the information that inflammation can contribute to drive the pain into consideration in the pre-surgical examination.

Once consensus has been established, a large prospective study including pre-surgical measuring of pain, function, hs-CRP, and comorbidities should be conducted.

However, for a start, the result from study II should be replicated for confirmation. It could with advantage be conducted as an RCT, including treatment of any low-level inflammation present before surgery.

CHAPTER 6. CONCLUSION

The goals of PhD project were: 1) to establish knowledge about factors associated with developing chronic postsurgical pain 5 years after TKR, 2) to characterize TKR patients with Mild-to-No or Moderate-to-Severe chronic postsurgical knee pain 5 years after TKR surgery, and 3) to examine if it was possible to decrease or eliminate chronic postsurgical pain by modulating the acute postsurgical pain by investigation of the effect of Chlorzoxazone on acute pain after TKR.

Study I showed that fibromyalgia and widespread pain is highly associated with continued chronic knee pain despite a pain-relieving procedure like joint replacement. But also, that a previous diagnosis of cancer has a high association with chronic postsurgical pain after TKR.

Study II showed that patients who develop CPSP have a significantly worse outcome on both pain and function after TKR. Also, that patients with CPSP express presence of low-grade inflammation through increased levels of serum hs-CRP.

Study III showed that it cannot be recommended to use Chlorzoxazone routinely as an analgesic for the acute postsurgical pain after TKR (or THR).

During the work on the three studies, it became more and more clear that the lack of consensus within the research field of chronic postsurgical pain makes comparison between the results of the available literature difficult. However, acknowledgement of that issue can hopeful be the first step to produce the perfect model for predicting the outcome of the TKR.

LITERATURE LIST

1. Skrejborg P, Petersen KK, Kold S, et al. Patients with High Chronic Postoperative Knee Pain 5 years after Total Knee Replacement Demonstrate Low-grad Inflammation, Impairment of Function and High Levels of Pain Catastrophizing. *Clin J Pain*. 2020;37(3):161-167.

2. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis*. 2001;60(2):91-97.

3. Murray C, Atkinson C, Bhalla K, et al. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA - J Am Med Assoc*. 2013;310(6):591-608.

4. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2163-2196.

5. Wallace IJ, Worthington S, Felson DT, et al. Knee osteoarthritis has doubled in prevalence since the mid-20th century. *Proc Natl Acad Sci*. 2017;114(35):9332-9336.

6. Neogi T, Felson DT. Osteoarthritis and Rheumatoid Arthritis. In: *Textbook Of Pain*. 6th Editio. ; 2013:645-657.

7. Felson DT. Osteoarthritis as a disease of mechanics. *Osteoarthr Cartil*. 2013;21(1):10-15.

8. Robinson WH, Lepus CM, Wang Q, et al. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. *Nat Rev Rheumatol*. 2016;12(10):580-592.

9. Jones G. Mechanisms of Pain in Osteoarthritis and Rheumatoid Arthritis. In: *Musculoskeletal Pain : Basic Mechanisms and*

Implications. ; 2014:143-156.

10. Skrejborg P, Petersen KK, Kold S, et al. Presurgical Comorbidities as Risk Factors for Chronic Postsurgical Pain Following Total Knee Replacement. *Clin J Pain*. 2019;35(7):577-582.

11. Carr AJ, Robertsson O, Graves S, et al. Knee replacement. *Lancet*. 2012;379(9823):1331-1340.

12. Sale D, Rosenstock S. Discovery to Recovery. *Clin Res highlights HSS*. 2013;(Spring).

13. Kremers HM, Larson DR, Crowson CS, et al. Prevalence of total hip and knee replacement in the United States. *J Bone Jt Surg - Am Vol*. 2014;97(17):1386-1397.

14. Kurtz S, Ong K, Lau E, et al. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Jt Surg - Ser A*. 2007;89(4):780-785.

15. Ackerman IN, Bohensky MA, Zomer E, et al. The projected burden of primary total knee and hip replacement for osteoarthritis in Australia to the year 2030. *BMC Musculoskelet Disord*. 2019;20(1):1-10.

16. Beswick AD, Wylde V, Gooberman-Hill R, et al. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. *BMJ Open*. 2012;2(1):e000435.

17. Grosu I, Lavand'homme P, Thienpont E. Pain after knee arthroplasty: An unresolved issue. *Knee Surgery, Sport Traumatol Arthrosc*. 2014;22(8):1744-1758.

18. Dunbar MJ, Richardson G, Robertsson O. I can ' t get no satisfaction after my total knee replacement. Rhytmes and reasons. *Bone Jt J*. 2013;95-B(Supl 11):148-152.

19. Lavand'homme P. Transition from acute to chronic pain after surgery. *Pain*. 2017;158(2):S50-S54.

20. Schaible HG. Joint Pain: Basic Mechanisms. In: *Textbook Of Pain*. 6th Editio. ; 2013:609-619.

21. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthr Cartil*. 2019;27(11):1578-1589.

22. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Care Res*. 2020;72(2):149-162.

23. Skrejborg P, Petersen KK, Beck J, et al. Investigating the Effect of Perioperative Chlorzoxazone on Acute Postoperative Pain after Total Hip and Knee Replacement Surgery. *Clin J Pain*. 2020;36(5):352-358.

24. Karlsen APH, Wetterslev M, Hansen SE, et al. Postoperative pain treatment after total knee arthroplasty: A systematic review. *PLoS One*. 2017;12(3):8-30.

25. Terkawi AS, Mavridis D, Sessler DI, et al. Pain Management Modalities after Total Knee Arthroplasty. *Anesthesiology*. 2017;126(5):923-937.

26. Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. *Curr Opin Anaesthesiol*. 2009;22(5):588-593.

27. Kehlet H, Thienpont E. Fast-track knee arthroplasty - status and future challenges. *Knee*. 2013;20(SUPPL.1):S29-S33.

28. Young AC, Buvanendran A. Pain Management for Total Hip Arthroplasty. *J Surg Orthop Adv*. 2014;23(01):13-21.

29. Geisler A, Dahl JB, Thybo KH, et al. Pain management after total hip arthroplasty at five different Danish hospitals: A prospective, observational cohort study of 501 patients. *Acta Anaesthesiol Scand*. 2019;(March 2018):aas.13349.

30. Andersen LØ, Gaarn-Larsen L, Kristensen BB, et al. Subacute pain and function after fast-track hip and knee arthroplasty. *Anaesthesia*.

2009;64(5):508-513.

31. Petersen KK, Simonsen O, Laursen MB, et al. Chronic postoperative pain after primary and revision total knee arthroplasty. *Clin J Pain*. 2015;31(1):1-6.

32. Lunn TH, Husted H, Laursen MB, et al. Analgesic and sedative effects of perioperative gabapentin in total knee arthroplasty: A randomized, double-blind, placebo-controlled dose-finding study. *Pain*. 2015;156(12):2438-2448.

33. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367(9522):1618-1625.

34. Wu CL, Raja SN. Treatment of acute postoperative pain. *Lancet*. 2011;377(9784):2215-2225.

35. Nielsen R V., Fomsgaard JS, Siegel H, et al. The effect of chlorzoxazone on acute pain after spine surgery. A randomized, blinded trial. *Acta Anaesthesiol Scand*. 2016;60(8):1152-1160.

36. Chapman CR, Vierck CJ. The Transition of Acute Postoperative Pain to Chronic Pain: An Integrative Overview of Research on Mechanisms. *J Pain*. 2017;18(4):359.e1-359.e38.

37. Van Den Kerkhof EG, Peters ML, Bruce J. Chronic pain after surgery: Time for standardization? a framework to establish core risk factor and outcome domains for epidemiological studies. *Clin J Pain*. 2013;29(1):2-8.

38. Schug SA, Bruce J. Risk stratification for the development of chronic postsurgical pain. *PAIN Reports*. 2017;2(6):e627.

39. Petersen KK, Arendt-Nielsen L. Chronic Postoperative Pain After Joint Replacement. *Pain Clin Updat*. 2016;24(3):1-6.

40. Mortazavi SMJ, Molligan J, Austin MS, et al. Failure following revision total knee arthroplasty: infection is the major cause. *Int Orthop*. 2011;35(8):1157-1164.

41. Sharkey PF, Lichstein PM, Shen C, et al. Why are total knee arthroplasties failing today-has anything changed after 10 years? *J Arthroplasty*. 2013;29(9):1774-1778.

42. Lee Y, Malfait A-M, Neogi T. The Relation Between Structural Joint Pathology and Joint Pain. In: Graven-Nielsen T; A-NL, ed. *Musculoskeletal Pain : Basic Mechanisms and Implications*. Washington: IASP Press; 2014:xvi, 534 pages.

43. de Rooij M, van der Leeden M, Heymans MW, et al. Prognosis of Pain and Physical Functioning in Patients With Knee Osteoarthritis: A Systematic Review and Meta-Analysis. *Arthritis Care Res (Hoboken)*. 2016;68(4):481-492.

44. Lewis GN, Rice DA, McNair PJ, et al. Predictors of persistent pain after total knee arthroplasty: A systematic review and meta-analysis. *Br J Anaesth*. 2015;114(4):551-561.

45. Charlson M, Szatrowski TP, Peterson J, et al. Validation of a combined comorbidity index. *J Clin Epidemiol*. 1994;47(11):1245-1251.

46. Conwell Y, Forbes NT, Cox C, et al. Validation of a measure of physical illness burden at autopsy: the Cumulative Illness Rating Scale. *J Am Geriatr Soc*. 1993;41(1):38-41.

47. Greene ME, Rolfson O, Gordon M, et al. Standard Comorbidity Measures Do Not Predict Patient-reported Outcomes 1 Year After Total Hip Arthroplasty. *Clin Orthop Relat Res*. 2015;473(11):3370-3379.

48. Hawker GA, Badley EM, Borkhoff CM, et al. Which patients are most likely to benefit from total joint arthroplasty? *Arthritis Rheum*. 2013;65(5):1243-1252.

49. Peter WF, Dekker J, Tilbury C, et al. The association between comorbidities and pain, physical function and quality of life following hip and knee arthroplasty. *Rheumatol Int*. 2015;35(7):1233-1241.

50. Singh JA, Lewallen DG. Medical and psychological comorbidity predicts poor pain outcomes after total knee arthroplasty. *Rheumatol (United Kingdom)*. 2013;52(5):916-923.

51. Ayers DC, Li W, Oatis C, et al. Patient-Reported Outcomes After Total Knee Replacement Vary on the Basis of Preoperative Coexisting Disease in the Lumbar Spine and Other Nonoperatively Treated Joints. *J Bone Jt Surgery-American Vol*. 2013;95(20):1833-1837.

52. Kahlenberg CA, Nwachukwu BU, McLawhorn AS, et al. Patient Satisfaction After Total Knee Replacement: A Systematic Review. *HSS J*. 2018;14(2):192-201.

53. Tolk JJ, Waarsing J (Erwin) H, Janssen RPA, et al. Development of Preoperative Prediction Models for Pain and Functional Outcome After Total Knee Arthroplasty Using The Dutch Arthroplasty Register Data. *J Arthroplasty*. 2020;35(3):690-698.e2.

54. Scott CEH, Howie CR, MacDonald D, et al. Predicting dissatisfaction following total knee replacement: A PROSPECTIVE STUDY OF 1217 PATIENTS. *J Bone Jt Surg - Br Vol*. 2010;92-B(9):1253-1258.

55. Sanchez-Santos MT, Garriga C, Judge A, et al. Development and validation of a clinical prediction model for patient-reported pain and function after primary total knee replacement surgery. *Sci Rep*. 2018;8(1):3381.

56. Petersen KK, Arendt-Nielsen L, Simonsen O, et al. Presurgical assessment of temporal summation of pain predicts the development of chronic postoperative pain 12 months after total knee replacement. *Pain*. 2015;156(1):55-61.

57. Kurien T, Arendt-Nielsen L, Petersen KK, et al. Preoperative Neuropathic Pain Like Symptoms and Central Pain Mechanisms in Knee Osteoarthritis Predicts Poor Outcome 6 Months After Total Knee Replacement Surgery. *J Pain*. 2018;00(00):1329-1341.

58. Garriga C, Sanchez-Santos MT, Judge A, et al. Development of a model

predicting non-satisfaction 1 year after primary total knee replacement in the UK and transportation to Switzerland. *Sci Rep*. 2018;8(1):1-8.

59. Jiang Y, Sanchez-Santos MT, Judge AD, et al. Predictors of Patient-Reported Pain and Functional Outcomes Over 10 Years After Primary Total Knee Arthroplasty: A Prospective Cohort Study. *J Arthroplasty*. 2017;32(1):92-100.e2.

60. Barroso J, Wakaizumi K, Reckziegel D, et al. Prognostics for pain in osteoarthritis: Do clinical measures predict pain after total joint replacement? *PLoS One*. 2020;15(1):1-22.

61. Dowsey MM, Spelman T, Choong PFM. Development of a Prognostic Nomogram for Predicting the Probability of Nonresponse to Total Knee Arthroplasty 1 Year After Surgery. *J Arthroplasty*. 2015;31(8):1654-1660.

62. Pua YH, Seah FJT, Clark RA, et al. Development of a prediction model to estimate the risk of walking limitations in patients with total knee arthroplasty. *J Rheumatol*. 2016;43(2):419-426.

63. Van Onsem S, Van Der Straeten C, Arnout N, et al. A New Prediction Model for Patient Satisfaction After Total Knee Arthroplasty. *J Arthroplasty*. 2016;31(12):2660-2667.e1.

64. Riddle DL, Golladay GJ, Jiranek WA, et al. External Validation of a Prognostic Model for Predicting Nonresponse Following Knee Arthroplasty. *J Arthroplasty*. 2017;32(4):1153-1158.e1.

65. Lungu E, Desmeules F, Dionne CE, et al. Prediction of poor outcomes six months following total knee arthroplasty in patients awaiting surgery. *BMC Musculoskelet Disord*. 2014;15(1):1-11.

66. D'Apuzzo MR, Cabanela ME, Trousdale RT, et al. Primary Total Knee Arthroplasty in Patients With Fibromyalgia. *Orthopedics*. 2012;35(2):175-178.

67. Brummett CM, Urquhart AG, Hassett AL, et al. Characteristics of fibromyalgia independently predict poorer long-term analgesic outcomes following total knee and hip arthroplasty. *Arthritis Rheumatol*. 2015;67(5):1386-1394.

68. Schrepf A, Moser S, Harte SE, et al. Top down or bottom up? An observational investigation of improvement in fibromyalgia symptoms following hip and knee replacement. *Rheumatol (United Kingdom)*. 2020;59(3):594-602.

69. Johansen A, Schirmer H, Stubhaug A, et al. Persistent post-surgical pain and experimental pain sensitivity in the Tromsø study: Comorbid pain matters. *Pain*. 2014;155(2):341-348.

70. Wylde V, Sayers A, Lenguerrand E, et al. Preoperative widespread pain sensitization and chronic pain after hip and knee replacement: A cohort analysis. *Pain*. 2015;156(1):47-54.

71. Liu SS, Buvanendran A, Rathmell JP, et al. Predictors for moderate to severe acute postoperative pain after total hip and knee replacement. *Int Orthop*. 2012;36(11):2261-2267.

72. Gerbershagen HJ, Pogatzki-Zahn E, Aduckathil S, et al. Procedure-specific risk factor analysis for the development of severe postoperative pain. *Anesthesiology*. 2014;120(5):1237-1245.

73. Ip HYV, Abrishami A, Peng PWH, et al. Predictors of Postoperative Pain and Analgesic Consumption. *Anesthesiology*. 2009;111(3):657-677.

74. Wylde V, Hewlett S, Learmonth ID, et al. Persistent pain after joint replacement: Prevalence, sensory qualities, and postoperative determinants. *Pain*. 2011;152(3):566-572.

75. Pinto PR, McIntyre T, Ferrero R, et al. Persistent pain after total knee or hip arthroplasty: Differential study of prevalence, nature, and impact. *J Pain Res*. 2013;6:691-703.

76. Arendt-Nielsen L. Joint pain: more to it than just structural damage?

Pain. 2017;158:66-73.

77. Petersen KK, Graven-Nielsen T, Simonsen O, et al. Preoperative pain mechanisms assessed by cuff algometry are associated with chronic postoperative pain relief after total knee replacement. *Pain*. 2016;157(7):1400-1406.

78. Izumi M, Petersen KK, Laursen MB, et al. Facilitated temporal summation of pain correlates with clinical pain intensity after hip arthroplasty. *Pain*. 2017;158(2):323-332.

79. Vaegter HB, Handberg G, Emmeluth C, et al. Preoperative Hypoalgesia after Cold Pressor Test and Aerobic Exercise is Associated with Pain Relief 6 Months after Total Knee Replacement. *Clin J Pain*. 2017;33(6):475-484.

80. Petersen KK, Simonsen O, Laursen MB, et al. The Role of Preoperative Radiological Severity, Sensory Testing, and Temporal Summation on Chronic Postoperative Pain following Total Knee Arthroplasty. *Clin J Pain*. 2018;34(3):193-197.

81. Rice DA, Kluger MT, McNair PJ, et al. Persistent postoperative pain after total knee arthroplasty: a prospective cohort study of potential risk factors. *Br J Anaesth*. 2018;121(4):804-812.

82. Hochman JR, Gagliese L, Davis AM, et al. Neuropathic pain symptoms in a community knee OA cohort. *Osteoarthr Cartil*. 2011;19(6):647-654.

83. Hochman JR, Davis AM, Elkayam J, et al. Neuropathic pain symptoms on the modified painDETECT correlate with signs of central sensitization in knee osteoarthritis. *Osteoarthr Cartil*. 2013;21(9):1236-1242.

84. Moreton BJ, Tew V, Das Nair R, et al. Pain phenotype in patients with knee osteoarthritis: Classification and measurement properties of painDETECT and self-report leeds assessment of neuropathic symptoms and signs scale in a cross-sectional study. *Arthritis Care*

Res. 2015;67(4):519-528.

85. Moss P, Benson HAE, Will R, et al. Patients with Knee Osteoarthritis Who Score Highly on the PainDETECT Questionnaire Present with Multimodality Hyperalgesia, Increased Pain, and Impaired Physical Function. *Clin J Pain*. 2018;34(1):15-21.

86. Roubille C, Raynauld JP, Abram F, et al. The presence of meniscal lesions is a strong predictor of neuropathic pain in symptomatic knee osteoarthritis: A cross-sectional pilot study. *Arthritis Res Ther*. 2014;16(1):1-7.

87. Sullivan M, Bishop S, Pivik J. The pain catastrophizing scale: development and validation. *Psychol Assess*. 1995;7(4):524-532.

88. Wade JB, Riddle DL, Thacker LR. Is pain catastrophizing a stable trait or dynamic state in patients scheduled for knee arthroplasty? *Clin J Pain*. 2012;28(2):122-128.

89. Bierke S, Petersen W. Influence of anxiety and pain catastrophizing on the course of pain within the first year after uncomplicated total knee replacement: a prospective study. *Arch Orthop Trauma Surg*. 2017;137(12):1735-1742.

90. Bierke S, Häner M, Karpinski K, et al. Midterm Effect of Mental Factors on Pain, Function, and Patient Satisfaction 5 Years After Uncomplicated Total Knee Arthroplasty. *J Arthroplasty*. 2019;35(1):105-111.

91. Dawson J, Fitzpatrick R, Murray D, et al. Questionnaire on the perceptions of patients about total knee replacement. *J Bone Jt Surg - Ser B*. 1998;80(1):63-69.

92. Murray DW, Fitzpatrick R, Rogers K, et al. The use of the Oxford hip and knee scores. *J Bone Joint Surg Br*. 2007;89(8):1010-1014.

93. Behrend H, Giesinger K, Giesinger JM, et al. The “Forgotten Joint” as the Ultimate Goal in Joint Arthroplasty. Validation of a New Patient-

Reported Outcome Measure. *J Arthroplasty*. 2012;27(3):430-436.e1.

94. Thienpont E, Opsomer G, Koninckx A, et al. Joint awareness in different types of knee arthroplasty evaluated with the forgotten joint score. *J Arthroplasty*. 2014;29(1):48-51.

95. Thienpont E, Vanden Berghe A, Schwab PE, et al. Joint awareness in osteoarthritis of the hip and knee evaluated with the 'Forgotten Joint' Score before and after joint replacement. *Knee Surgery, Sport Traumatol Arthrosc*. 2016;24(10):3346-3351.

96. Eitner A, Pester J, Vogel F, et al. Pain sensation in human osteoarthritic knee joints is strongly enhanced by diabetes mellitus. *Pain*. 2017;158(9):1743-1753.

97. De Lange-Brokaar BJE, Ioan-Facsinay A, Yusuf E, et al. Association of pain in knee osteoarthritis with distinct patterns of synovitis. *Arthritis Rheumatol*. 2015;67(3):733-740.

98. Neogi T, Guermazi A, Roemer F, et al. Association of Joint Inflammation with Pain Sensitization in Knee Osteoarthritis: The Multicenter Osteoarthritis Study. *Arthritis Rheumatol*. 2016;68(3):654-661.

99. Yusup A, Kaneko H, Liu L, et al. Bone marrow lesions, subchondral bone cysts and subchondral bone attrition are associated with histological synovitis in patients with end-stage knee osteoarthritis: A cross-sectional study. *Osteoarthr Cartil*. 2015;23(11):1858-1864.

100. Windgassen EB, Funtowicz L, Lunsford TN, et al. C-reactive protein and high-sensitivity C-reactive protein: An update for clinicians. *Postgrad Med*. 2011;123(1):114-119.

101. Pearle AD, Scanzello CR, George S, et al. Elevated high-sensitivity C-reactive protein levels are associated with local inflammatory findings in patients with osteoarthritis. *Osteoarthr Cartil*. 2007;15(5):516-523.

102. Smith JW, Martins TB, Gopez E, et al. Significance of C-reactive protein

in osteoarthritis and total knee arthroplasty outcomes. *Ther Adv Musculoskelet Dis*. 2012;4(5):315-325.

103. Clement ND, Bardgett M, Weir D, et al. Three groups of dissatisfied patients exist after total knee arthroplasty: Early, persistent, and late. *Bone Jt J*. 2018;100B(2):161-169.

104. Shannak O, Palan J, Esler C. A regional registry study of 216 patients investigating if patient satisfaction after total knee arthroplasty changes over a time period of five to 20 years. *Knee*. 2017;24(4):824-828.

105. Loth FL, Giesinger JM, Giesinger K, et al. Single-item satisfaction scores mask large variations in pain, function and joint awareness in patients following total joint arthroplasty. *Eur J Orthop Surg Traumatol*. 2019;30:267-274(2020).

106. Riddle DL, Wade JB, Jiranek WA, et al. Preoperative pain catastrophizing predicts pain outcome after knee arthroplasty. *Clin Orthop Relat Res*. 2010;468(3):798-806.

107. Riddle DL, Keefe FJ, Ang DC, et al. Pain coping skills training for patients who catastrophize about pain prior to knee arthroplasty: A multisite randomized clinical trial. *J Bone Jt Surg - Am Vol*. 2019;101(3):218-227.

108. Birch S, Stilling M, Mechlenburg I, et al. No effect of cognitive behavioral patient education for patients with pain catastrophizing before total knee arthroplasty: a randomized controlled trial. *Acta Orthop*. 2020;91(1):98-103.

109. Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: A systematic review. *J Pain Symptom Manage*. 2004;28(2):140-175.

110. Husted H, Lunn TH, Troelsen A, et al. Why still in hospital after fast-track hip and knee arthroplasty? *Acta Orthop*. 2011;82(6):679-684.

111. Price AJ, Alvand A, Troelsen A, et al. Knee replacement. *Lancet*. 2018;392(10158):1672-1682.

112. Lloyd JM, Wainwright T, Middleton RG. What is the role of minimally invasive surgery in a fast track hip and knee replacement pathway? *Ann R Coll Surg Engl*. 2012;94(3):18-21.

113. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg*. 2008;248(2):189-198.

114. Stürmer T, Brenner H, Koenig W, et al. Severity and extent of osteoarthritis and low grade systemic inflammation as assessed by high sensitivity C reactive protein. *Ann Rheum Dis*. 2004;63(2):200-205.

115. Takahashi M, Naito K, Abe M, et al. Relationship between radiographic grading of osteoarthritis and the biochemical markers for arthritis in knee osteoarthritis. *Arthritis Res Ther*. 2004;6(3):208-212.

116. Schaible HG. Nociceptive neurons detect cytokines in arthritis. *Arthritis Res Ther*. 2014;16(5):470.

117. Fonseca JE, Santos MJ, Canhão H, et al. Interleukin-6 as a key player in systemic inflammation and joint destruction. *Autoimmun Rev*. 2009;8(7):538-542.

118. Richards BL, Whittle SL, Buchbinder R. Muscle relaxants for pain management in rheumatoid arthritis. *Cochrane Database Syst Rev*. 2012.

119. Hadlandsmyth K, Vander Weg MW, McCoy KD, et al. Risk for Prolonged Opioid Use Following Total Knee Arthroplasty in Veterans. *J Arthroplasty*. 2018;33(1):119-123.

120. Richards BL, Whittle SL, Buchbinder R. Neuromodulators for pain management in rheumatoid arthritis. *Cochrane database Syst Rev*. 2012;1(1):CD008921.

121. Beebe FA, Barkin RL, Barkin S. A clinical and pharmacologic review of skeletal muscle relaxants for musculoskeletal conditions. *Am J Ther*. 2005;12(2):151-171.

122. Patel HD, Uppin RB, Naidu AR, et al. Efficacy and Safety of Combination of NSAIDs and Muscle Relaxants in the Management of Acute Low Back Pain. *Pain Ther*. 2019;8(1):121-132.

123. Van Tulder MW, Touray T, Furlan a D, et al. Muscle relaxants for nonspecific low back pain: A systematic review within the framework of the Cochrane Collaboration. *Spine (Phila Pa 1976)*. 2003;28(17):1978-1992.

124. Desiraju RK, Renzi Jr. NL, Nayak RK, et al. Pharmacokinetics of chlorzoxazone in humans. *J Pharm Sci*. 1983;72(9):991-994.

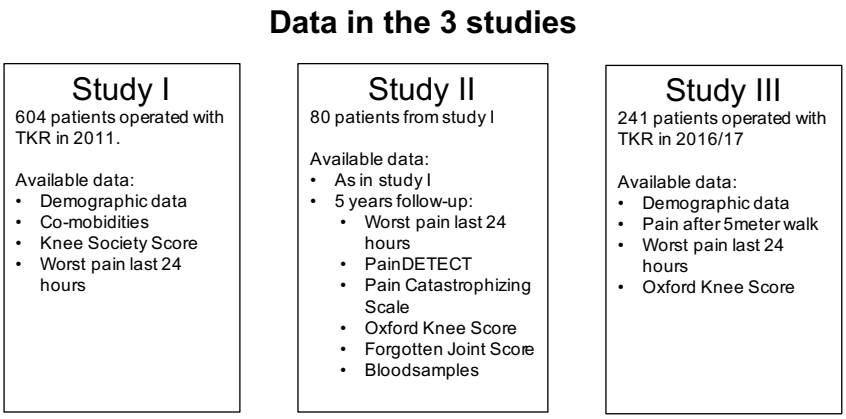
125. Liu YC, Lo YK, Wu SN. Stimulatory effects of chlorzoxazone, a centrally acting muscle relaxant, on large conductance calcium-activated potassium channels in pituitary GH3cells. *Brain Res*. 2003;959(1):86-97.

126. Noble PC, Scuderi GR, Brekke AC, et al. Development of a new knee society scoring system. *Clin Orthop Relat Res*. 2012;470(1):20-32.

127. Tao Q, Ang TFA, DeCarli C, et al. Association of Chronic Low-grade Inflammation With Risk of Alzheimer Disease in ApoE4 Carriers. *JAMA Netw open*. 2018;1(6):e183597.

128. Xu J, Brennan TJ. Incision-Induced Nociceptive Effects in Deep Tissue. In: *Musculoskeletal Pain : Basic Mechanisms and Implications*. Washington: IASP Press; 2014:xvi, 534 pages.

Appendix A. **Overview of data in the three studies**



Overview of the available data in the 3 studies.

Appendix B. **Overview of measure points in Study III**

Timepoint	**Measure**
Baseline	Pain after 5meters walk Baseline characteristics Pain at rest Worst pain last 24 hours Oxford Knee Score
4 hours postsurgical	Pain after 5meters walk Pain at rest
6 hours postsurgical	Pain after 5meters walk Pain at rest
24 hours postsurgical	Pain after 5meters walk Pain at rest
32 hours postsurgical	Pain after 5meters walk Pain at rest
48 hours postsurgical	Pain after 5meters walk Pain at rest
Day 2 postsurgical	Pain at rest Worst pain last 24 hours Oxford Knee Score
Day 3 postsurgical	Pain at rest Worst pain last 24 hours
Day 4 postsurgical	Pain at rest Worst pain last 24 hours Oxford Knee Score
Day 5 postsurgical	Pain at rest Worst pain last 24 hours
Day 6 postsurgical	Pain at rest Worst pain last 24 hours
Day 7 postsurgical	Pain at rest Worst pain last 24 hours Oxford Knee Score
Day 14 postsurgical	Pain at rest Worst pain last 24 hours Oxford Knee Score
12 months follow-up	Pain after 5meters walk Pain at rest Worst pain last 24 hours Oxford Knee Score

Table 6 Timetable of available measure points in Study III

Appendix C. **Presentation of the three studies**

Study I

ORIGINAL ARTICLES

Presurgical Comorbidities as Risk Factors For Chronic Postsurgical Pain Following Total Knee Replacement

Skrejborg, Peter MSc*,†; Petersen, Kristian K. PhD*,‡; Kold, Søren MD, PhD†,§; Kappel, Andreas MD†,§; Pedersen, Christian MD†; Østgaard, Svend E. MD, PhD†; Simonsen, Ole MD, Dr. Med†; Arendt-Nielsen, Lars Dr. Med, PhD* **Author Information**

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doi: 10.1097/AJP.0000000000000714

ORIGINAL ARTICLES

Patients With High Chronic Postoperative Knee Pain 5 Years After Total Knee Replacement Demonstrate Low-grad Inflammation, Impairment of Function, and High Levels of Pain Catastrophizing

Skrejborg, Peter MSc[*,†,‡]; Petersen, Kristian K. PhD[*,§]; Kold, Søren MD, PhD[†,‖]; Kappel, Andreas MD[†,‖]; Pedersen, Christian MD[†]; Østgaard, Svend E. MD, PhD[†,‖]; Simonsen, Ole MD[†,‖]; Arendt-Nielsen, Lars PhD[*,§] **Author Information**

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ORIGINAL ARTICLES

Investigating the Effect of Perioperative Chlorzoxazone on Acute Postoperative Pain After Total Hip and Knee Replacement Surgery

Skrejborg, Peter MSc[*,†,‡]; Petersen, Kristian K. PhD[*,§]; Beck, Jacob MD[†]; Ulrich, Michael MD, PhD, DMSc[†,‖]; Simonsen, Ole MD, DMSc[†,‖]; Nielsen, Poul T. MD[†,‖]; Arendt-Nielsen, Lars PhD, DMSc[*]; Laursen, Mogens MD, PhD[†,‖] **Author Information**

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