Incidence of persistent pain after knee arthroplasty: A nationwide cross-sectional survey study

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The budget for the full PhD project is attached to this document (appendix 4).

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Introduction

Knee arthroplasty (KA) is an effective treatment for patients with knee osteoarthritis when non-opioid analgesics and physiotherapy cannot control their pain.[1] Generally, KA is safe and provides satisfactory results, but previous studies have found that a considerable proportion of patients suffer from persistent pain after surgery.[2,3]

Each year, more than 10,000 and 1.1 million primary KAs are performed in Denmark[4] and worldwide,[5] respectively. As these numbers increase, more and more patients will suffer from persistent postsurgical pain. Generally, chronic pain is a substantial clinical challenge because effective treatments are lacking.[6] To recognise the magnitude of the problem, but also to allow surgeons to accurately inform their patients of the long-term risks, it is important to know the incidence of persistent postsurgical pain.

We are not aware of previous assessments of long-term pain outcomes in unselected Danish patients operated with KA. The most widely used numbers originates from a systematic review published in 2012 that used data collected in various countries between 1995-2006.[2] An updated investigation is important for several reasons. First, surgical techniques and equipment have evolved over the years. Second, introduction of standard treatment with high-dose glucocorticoids should, in theory, have reduced central sensitisation, which is a key aspect of persistent postsurgical pain.[7,8] Third, implementation of early mobilisation and other enhanced recovery after surgery (ERAS) elements have reduced the mean length of hospital stay from around 10 days in 2000 to a single day in 2021.[4]

For these reasons, we aim to investigate the satisfaction and incidence of persistent pain after KA for osteoarthritis.

Methods

The study is registered at the capital region of Denmark's regional research listing (Pactius) with identifier P-2023-4, approved 4 January 2023. This protocol is registered at ClinicalTrials.gov and is currently under review. The resulting paper will be reported according to the CROSS checklist for standardised reporting of survey studies.[9] Wherever needed, a trained linguist translated questions from English to Danish and vice versa. The Danish and an English version of the questionnaire will be available in the final publication.

Study design: This study is a nationwide cross-sectional survey.

Patient involvement: A panel of KA patients helped develop the questionnaire, i.e., testing and selecting the questions.

Questionnaire: The questionnaire is composed of 22 questions, however patients answering "No" to question 3 skips questions 4-17 concerning pain in the operated knee. Only questions 3, 4, 20, and 21 are mandatory because we wanted to avoid non-respondents. The contact letter in Danish (S1) and full questionnaire in Danish (S2) and English (S3) can be found in the supplementary material. Contact information for the first author (JL) is supplied in the contact letter and the header of the questionnaire, in case the patients have difficulties with filling in the questionnaire, believe they have been contacted mistakenly etc. We used similar or identical questions to those in a survey conducted in 2004 to increase our ability to compare results (i.e., questions 3-5, 8, 10 and 18).[10]

The 1st question assesses overall satisfaction with surgery and have been translated directly from the questionnaire used by the Swedish Arthroplasty Register to enable direct comparison.[3]

Question 2 assesses willingness to repeat surgery, as described by Chestworth et al..[11]

Question 3 assesses pain frequency with the same response options as the 2004 survey.[10] This question is mandatory due to branching purposes, i.e. respondents without pain can skip questions 4-17.

Question 4 is the 11-point numerical rating scale (NRS) for knee pain, which is widely used and recommended.[12,13] To facilitate comparison with other studies, we assessed average pain in the last week.[12] This question is also mandatory because it is our primary outcome.

Question 5-9 is the pain dimension of the likert-scale version 3.1 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[14] The instrument is validated for osteoarthritis patients and specifically recommended by the International Association for the Study of Pain (IMMPACT).[13]

Question 10 assesses pain interference on everyday activities. Pain interference is often included in core outcome sets for clinical trials[13,15] and it is recommended to use disease-specific interference.[13]

Question 11-17 are the Douleur Neuropathique 4 questions (DN4) interview, which can be used to estimate the number of patients with 'possible' neuropathic pain.[16,17] We chose to the DN4 interview over other neuropathic pain measures because it is widely used and validated, short, and available in Danish (from www.mapi-trust.org).[16]

Question 18 assesses other chronic pain conditions with an open text field, which we will later categorise. We believe this is more accurate than allowing patients to categorise their pain condition from a predefined list of options.

Question 19 assesses patient-reported use of analgesics, including if the analgesics are taken for pain in the operated knee or not. Again, the type of analgesics is typed into an open text field, as to not restrict respondents to specific medications and to enable responses with typos.

Questions 20 and 21 are on the patient's current height and weight, recently found to be valid in a Danish E-survey setting.[18]

Finally, in question 22 we ask for permission to contact respondents again later.

Sample characteristics: Eligible patients are all adult (18 years or older) patients operated with primary total or medial unicompartmental KA for osteoarthritis between August 1 and November 30, 2023. Legally incompetent citizens, i.e., persons with a legal guardian, will not be asked to participate.

For total KA, we will identify patients from the Danish National Patient Register through the Danish Health Data Authority (SKS-code DM17 [knee osteoarthritis] + KNGB20, KNGB30 or KNGB40 [primary total knee arthroplasty]).

For medial unicompartmental KA, we will identify patients from the Danish National Patient Register through the Danish Health Data Authority (SKS-code DM17 [knee osteoarthritis] + KNGB01 or KNGB11 [primary medial unicompartmental knee arthroplasty]).

The sample size calculation is based on the primary outcome in total KA patients. With an estimated 16% incidence of the primary outcome[3] and a 70% response rate,[19] 3172 patients are needed to yield a 95% confidence interval of 3 percentage points (14.6-17.6). In our opinion, this level of certainty is appropriate because differences less than this, may be hard to interpret by clinicians and patients. Sampling patients that were operated during 4 months outside holiday season should yield approximately this number of identified patients.[4]

Baseline data of respondents and non-respondents are gathered from the Danish Knee Arthroplasty Register. To evaluate the generalisability of the study, we will report the respondents' baseline data and compare them to the non-respondents in Table 1.

Survey administration: In an encrypted fashion, the survey will be sent via 'Digital Post' which is linked to the unique Civil Registration (CPR) number using the Research Electronic Data Capture (REDCap) software (www.project-redcap.org). A reminder will be sent to non-respondents 14 days after the first letter. Remaining non-respondents are sent a text-message if their telephone number is registered in the electronic patient file.

For questions with an open text field option, two authors (JL, SS) will independently categorise the responses to minimise errors.

Study preparation: We will not advertise the survey and respondents are not rewarded for participation.

Ethical considerations: The local institutional review board approved the study, and the Danish Health Data Authority will provide contact information for potential respondents. Telephone numbers for non-respondents are found by searching the CPR number in the electronic patient files, but without accessing the patients' health data. According to Danish legislation, approval from the national ethics committee is neither required nor possible to obtain for survey studies (see attached 'exempt from notification' letter from the Danish national ethics committee, S5).

Because we will link survey responses with perioperative data from the Danish Knee Arthroplasty Register, responses are not anonymous. However, only the authors will have access to confidential information and data will be anonymised as soon as possible. Until then, the data are stored pseudonymised at a logged and encrypted drive.

Statistical analyses: The main outcome is the number of patients with moderate or severe persistent postsurgical pain in the operated knee, defined as patients with a numerical rating scale (NRS) score higher than 3.[20] We dichotomised the NRS score for our primary outcome because we believe this is more intuitively understood by patients and clinicians. The main outcome will be reported as percentage of all patients with 95% confidence interval, calculated with assumed binomial distribution:

$$p \pm 1.96 \sqrt{\frac{p\,(1-p)}{n}}$$

Categorical variables, including the individual questions of WOMAC pain domain and DN4 interview, will be reported directly as number of patients (percentage of all patients). The raw NRS score, height and weight are continuous variables and will be reported as median (interquartile range [IQR]) number of respondents.

The five questions in the WOMAC pain domain can be scored 0-4, where 0 is 'none' and 4 is 'extreme'. This results in an overall score of 0-20, which will be reported as median (IQR).

Each of the seven questions in the DN4 interview can be scored 0/1 (no/yes), which results in an overall score of 0-7. A score ≥3 constitutes 'possible' neuropathic pain.[16,17] Both the median (IQR) DN4 interview score and number of patients (percentage of all patients) with possible neuropathic pain will be reported.

We do expect some missing data because incomplete questionnaires may be submitted. Generally, responses will not be imputed. However, we will impute values to calculate summary scores of the WOMAC pain domain and DN4 interview as the median of the reported values within the instrument.

We do not plan to adjust for non-representativeness, but as previously mentioned, baseline characteristics (age, sex, and ASA score) and surgical details (type of anaesthesia, operation length, use of local infiltration analgesia (LIA), use of cement, and surgical complications) of respondents and non-respondents are presented in Table 1.

Data is handled in the most recent version of R (www.r-project.org).[21]

Knowledge dissemination

The survey will be fully reported in an international peer-reviewed journal. In addition, the responses from this survey will be pooled with responses from a similar survey on hip pain. The combined data will be used in two additional studies: 1) to validate the use of prescription registries on analgesic for identifying patients with persistent postsurgical pain,[22] and 2) to investigate associations between weight and weight-change and the different outcomes. Both will be published in peer-reviewed journals.

We seek to make the papers freely available (e.g., as preprint at www.medrxiv.org or through open-access publication) and to store the full dataset at the Danish national archive (www.rigsarkivet.dk). Moreover, the results will be presented at meetings and conferences, predominantly for orthopaedic surgeons, anaesthetists, pain specialists, and other health-care personnel working with this patient group.

The systematic review from 2012 that we seek to build on is widely used, even though the data may be outdated.[2] This study is necessary to avoid false assumptions regarding the contemporary risk of persistent pain after KA. We are certain that the results from this study will be used by clinicians to guide patients in their decision to undergo KA or not.

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Appendix 1 – Contact letter (Danish)

It is not possible to upload foreign language text to ClinicalTrials.gov.

Appendix 2 – Survey in Danish

It is not possible to upload foreign language text to ClinicalTrials.gov.

Appendix 3 – Survey in English

If you experience any issues responding to the survey, please contact Jens Holm Laigaard by telephone: 42 61 73 77 or email jens.holm.laigaard@regionh.dk

Satisfaction

1) How satisfied are you with the outcome of your knee replacement surgery?
   Very satisfied, Satisfied, Neither satisfied nor dissatisfied, Dissatisfied, Very dissatisfied

2) Knowing what your knee replacement surgery did for you, if you could go back in time, would you still have undergone this surgery?
   Yes, No, Uncertain

Pain in the operated knee

3) [Mandatory] Do you still have pain in the operated knee?
   Yes, constantly; Yes, daily; Yes, a few times a week; Yes, more rarely; No

4) [Mandatory if 1 ≠ "No"] Please rate your pain in the operated knee by indicating the number that best describes your pain on average during the last week.
   0 means 'No pain' and '10' means 'Pain as bad as you can imagine'.

0	1	2	3	4	5	6	7	8	9	10

What amount of knee pain have you experienced the last week during the following activities?

5) Walking on a flat surface	None	Mild	Moderate	Severe	Extreme
6) Going up or down stairs	None	Mild	Moderate	Severe	Extreme
7) At night while in bed	None	Mild	Moderate	Severe	Extreme
8) Sitting or lying	None	Mild	Moderate	Severe	Extreme
9) Standing upright	None	Mild	Moderate	Severe	Extreme

Activities of daily living

10) In total, how much does the pain in the operated knee bother you in your everyday life?
    Not at all, A little, Some, Much, Very Much

Does the pain have one or more of the following characteristics?

11) Burning	Yes	No
12) Painful cold	Yes	No
13) Electric shocks	Yes	No

Is the pain associated with one or more of the following symptoms in the same area?

14) Tingling	Yes	No
15) Pins and needles	Yes	No
16) Numbness	Yes	No
17) Itching	Yes	No

Other pain

18) Do you have chronic pain, other than from your operated knee?
Yes; No
[If yes] Please describe your pain condition: _____

Analgesic use

19) Do you take analgesic medication(s) daily or almost daily?
Yes; due to pain in the operated knee; Yes, due to other pain; No
[If yes] Which medication(s)?: _____

Please insert your height and weight

20) [Mandatory] Weight: _____ (kg)
21) [Mandatory] Height: _____ (cm)

Contact

22) Can we contact you again, e.g. regarding your responses?
Yes; No
[if yes] Please insert your contact information (telephone number, email address): _____

Thank you so much for your participation. Your responses have been saved and you can exit the site.
You are welcome to contact Jens Holm Laigaard by telephone 42 61 73 77 or email jens.holm.laigaard@regionh.dk if you have questions or comments regarding the survey.

Appendix 3 – Budget in Danish

It is not possible to upload foreign language text to ClinicalTrials.gov.

Appendix 5 – Exempt from notification

Region Hovedstaden

Center for Health

Committee on Health Research Ethics, Capital Region

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Journal no.: F-22060846

Date: 31 October 2022

F-22060846 – Notification to the Committee on Health Research Ethics

Project title: Persistent postsurgical pain after total hip arthroplasty: A nationwide cross-sectional survey study

By mail of 27 October 2022, you have requested whether above research project must be notified to the Danish Committee System on Health Research Ethics.

The study is a nationwide cross-sectional survey study aiming to investigate patients with persistent postsurgical pain, patients with possible neuropathic pain and satisfaction with surgery after total hip arthroplasty (THA) for osteoarthritis.

As defined by the "*Danish Act on Research Ethics Review of Health Research Projects*" Section 2 the project does not constitute a health research project but is considered to be a questionnaire-based study.

The project thus can be initiated without approval from The Committees on Health Research Ethics for the Capital Region of Denmark.

In Denmark, it is the responsibility of the committee system, to evaluate health research projects. Defined as: clinical trials involving live born human individuals, human gametes intended for fertilization, fertilized human eggs, embryonic cells and embryos, tissue, cells and genetic material from humans, embryos etc. or deceased persons, as well as clinical trials of medicines in humans, and clinical trials of medical devices.

Health research primarily comprises research within medical subjects, clinical and socio-medical-epidemiological research. In addition to research of somatic diseases, it also covers psychiatric and clinical-psychological diseases and conditions as well as odontological and pharmaceutical research.

Register research projects and interview- and questionnaire-based surveys are to be notified only if human biological material is included in the project.

Health research projects, solely involving anonymous human biological material, and collected in accordance with legislation at the site of collection, need only be notified to the Committee System of Ethical Research, if the project involves fertilized human **eggs and genetic material cf. Section 25 and 27 (2) in the "***Act on Artificial Insemination used for fertilization in connection with medical treatment, diagnostics and research etc.***"**

It is a requirement, that the biological material is fully anonymous. This means the material must not be individually identifiable; no code must be available for the data.

Trials, involving cell lines etc. are not to be notified, if originating from a trial regarding the collection of cells or tissue, which have obtained the required permission.

As a matter of form, our rejection to evaluate your project constitute neither an ethical nor a negative evaluation of the content of the project.

For additional inquiries, please contact the Secretariat for the Committees of the Capital Region at +45 38666395 or by e-mail: vek@regionh.dk.

Complaints procedure
Any decision concerning approval and rejection from the regional committee may be brought before the National Committee on Health Research Ethics no later than 30 days from receipt of the decision from the regional committee, cf. section 26(1) of the Committee Act
The complaint must be submitted electronically with the use of digital signature and encryption in case of confidential protocol content (confidentialities). The complaint must be justified and copy of the decision from the regional committee must be enclosed as well as the case files used for the decision. Please forward to dketik@dketik.dk

Kind regards,

Marie Skovgaard
Office administrator