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Presurgical comorbidities as risk factors for chronic postsurgical pain following total knee replacement

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Abstract

Objectives Chronic postsurgical knee-pain (CPSP) is a burden for approx. 20% of the patients following total knee replacement (TKR). Presurgical pain intensities have consistently been found associated with CPSP and it is suggested that e.g. comorbidities are likewise important for development of CPSP. This study aimed to identify presurgical risk factors for development of CPSP 5 years after TKR based on medical records containing information regarding comorbidities.

Methods Patients undergoing primary TKR surgery were contacted 5 years after TKR. Presurgical Knee Society Score and comorbidities were evaluated. Postsurgical knee-pain at 5-years follow-up was assessed on a numeric rating scale (NRS, 0-10). Logistic regression models were utilized to identify patients with moderate-to-severe (NRS≥3) and mild-to-no (NRS<3) CPSP at 5-year follow-up. An odds ratio (OR) for significant factors were calculated.

Results A total of 604 patients were contacted, 493 patients responded, 352 patients provided a complete questionnaire. A total of 107 patients reported NRS≥3 at follow-up.

Significant presurgical factors associated with CPSP were fibromyalgia (OR 20.66, p=0.024), chronic pain in other body parts than the knee (OR 6.70, p=0.033), previous diagnosis of cancer (OR 3.06, p=0.001), knee instability (OR 2.16, p=0.021), age (OR 2.15, p=0.007), and presurgical knee-pain (OR 1.61, p=0.044). Regression analysis identified 36 out of 107 (33.6%) patients with CPSP based on presurgical factors, and 231 patients (94.3%) without CPSP were classified correct.

Discussion The current study found that a variety of presurgical clinical factors can correctly classify 33.6% of patients at risk for developing CPSP 5 years following TKR.

Key words: Prediction model, chronic postsurgical pain, total knee replacement, Presurgical risk factors, osteoarthritis

Introduction

Total knee replacement (TKR) is effective and produces long-lasting improvements of physical function and reduces pain for most knee OA patients (1), but chronic postsurgical knee-pain (CPSP) is a well-established burden for about 20% of the patients after TKR (2–4). CPSP causes disability and suffering, and are associated with loss in quality of life and increases use of resources for health care (5). Current treatment options for CPSP are limited as revision surgery based solely on the indication pain is not warranted (6) and clinical trials on alternative non-surgical treatments are lacking.

Despite improvements in knowledge and awareness about the epidemiology of CPSP, less is known about risk factors for developing chronic knee pain or processes contributing to the transition from acute to chronic pain or continuation of chronic knee pain (7,8). Some pre- and postsurgical risk factors have been identified for CPSP after primary TKR, such as high preoperative pain intensity, preoperative pain sensitization, high pain catastrophizing, and previous surgery in the knee (7–9). Preoperative risk stratification aim to determine the risk of developing CPSP, thereby guide presurgical interventions and acute-postsurgical care and guide the communication to patients (7). Recent systematic reviews have indicated that the number and severity of comorbidities are associated with and predictive for the development of CPSP after TKR (10,11). Common comorbidities are pain conditions such as fibromyalgia, low back pain, and chronic pain in other body parts than the knee, other rheumatic diseases and diabetes but these have not be investigated in a large scale study on primary TKR (12). However the association of some comorbidities and CPSP among 240 TKR and 281 total hip replacement patients have been studied (13). In addition, several studies focus on the number of comorbidities and report that increased number of presurgical comorbidities are associated with CPSP after TKR but diseases such as previous diagnosed cancer, diabetes and chronic obstructive pulmonary disease (COPD) are less studied (13–17).

The aims of the present study were 1) to identify presurgical risk factors for development of CPSP 5-years after TKR based on accessible data from the medical records and 2) to establish a predictive model for the development or continuation of CPSP based on presurgical recorded data.

Materials and Methods

Protocol

A consecutive cohort of patients undergoing TKR surgery in 2011 in the Northern Region of Denmark were contacted by letter 5 years after primary TKR surgery and were invited to participate in the study. A questionnaire was sent to the patients if the patients accepted the invitation. Patients were excluded if they did not understand Danish.

The study was approved by the local ethics committee (N-20170072), by the Danish Data Protection Agency and followed the rules of the Declaration of Helsinki. All patients signed an information consent prior to enrollment.

Presurgical Knee Society Score

The Knee Society Score (KSS) consists of 9 questions focusing on pain, stability and range of motion of the knee and have been validated for use in knee OA patients (18). Presurgical KSS data were used to determine walking distance, (unlimited, >1km, 0.5-1km, <0.5km, or housebound), the 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 two 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 (non, mild or occasional, stairs only, walking and stairs, moderate occasional, moderate continual, or severe), and degree of knee instability (anteroposterior, mediolateral, and alignment). The KSS was collected from the Danish Knee Arthroplasty Register and the information was added by the surgeons prior to TKA.

The knee score and the functional score are scored on a scale from 0-100, where a knee score of 100 points will be obtained by a well-aligned knee with no pain, free range of motion, and negligible instability. A functional score of 100 points will be obtained by a patient with unlimited walking distance and who can go up and down stairs normally (19). In this study the knee score and the functional score were used as two separate parameters, as well as the single components.

Presurgical Presence of Comorbidities

Information about comorbidities was obtained by reviewing the patients´ medical journal retrospectively. A set of predefined comorbidities were investigated and only comorbidities present prior to or at the time of surgery and noted in the medical journal were collected. The following comorbidities were examined: osteoarthritis elsewhere than the knee scheduled for surgery, fibromyalgia, chronic pain in other body parts than the knee, previous diagnosis of cancer, chronic obstructive pulmonary disease (COPD), diabetes, lumbar issues, pacemaker, history of erysipelas, stroke, rheumatic diseases, dementia, epilepsy and gastric bypass, which are parameters found associated with the development of CRPS (12,13,20,21).

Furthermore the total count of comorbidities with and without OA was used to investigate the importance of OA in other joints than the knee scheduled for surgery.

Postsurgical Pain

The patients were contacted 5 years postsurgical by letter and pain were asked to score their mean average 24 hours pain intensity of the index knee pain on a numeric rating scale (NRS 0 to 10 scale). Two groups were defined: a mild-to-no pain group with NRS<3, and a moderate-to-severe pain group with NRS≥3. (22)

Data Analysis

Statistical analyses were performed in IBM SPSS Statistics (ver. 25, IBM Corporation, New York, USA) and the data is presented as mean and standard deviations unless otherwise stated. $P<0.05$ was considered significant.

Initially, chi-square tests were used to compare gender and presence of comorbidities, and t-tests were used to investigate difference in preoperative age, BMI, and the average pain in the last 24 hours between the patients responding and not responding to the 5 years postsurgical questionnaire. Pearson Chi-Square and Fischer´s exact were used when appropriate.

Descriptive statistics were used to describe difference in gender and presence of comorbidities, and t-tests were used to investigate difference in presurgical age, BMI, and pain in the last 24 hours at 5 years follow-up between the two groups of the patients enrolled in the study.

Binary logistic regression (backward selection) models were used to identify patients with moderate-to-severe pain or mild-to-no pain 5 years after TKA using the following preoperative factors: gender, age at the time of surgery, BMI, KSS and presurgical comorbidities. Odds ratios (OR) were calculated for each of the significant preoperative factors. An OR higher than 1 indicates that the patient will have a higher risk of developing chronic postsurgical pain after TKR. Correspondingly an OR lower than 1 indicates lower risk. OR is presented with 95% confidence interval (95% CI).

Sensitivity, specificity, positive predictive value, and negative predictive value were calculated for the model.

Result

A total of 604 patients with osteoarthritis were operated with TKR in the North Denmark Region in 2011, 493 patients responded to the questionnaire. 352 patients provided a complete dataset, and were included in the analysis.

No significant differences were found for gender (p=0.69), presurgical BMI (p=0.64) and pain in the last 24 hours at 5-year follow-up (p=0.47) in patients with and without complete dataset, but a trend toward significance indicated that non-completion group were younger (p=0.07). The presence of presurgical history of erysipelas (p=0.03) was higher in the patients with complete dataset compared with the patients with non-complete dataset.

Pain at 5-year follow-up

A total 107 patients were classified with moderate-to-severe CPSP in the index knee at the 5-years follow-up. Thus, a minimum of 18% (107 out of 604 patients) experience moderate-to-severe CPSP (NRS≥3) 5 years following primary TKR. The mean chronic postsurgical knee-pain was 5.28 (±2.0) in the moderate-to-severe pain group and 0.35 (±0.7) in the mild-to-no pain group.

Demographics

No significant difference were found for presurgical age, gender or BMI comparing the patients with mild-to-no pain and moderate-to-severe pain (Table 1).

Reason for surgery

The majority of patients 316 (89.8%) received surgery due to primary idiopathic osteoarthritis, 23 (6.5%) patients due to secondary osteoarthritis, and 13 (3.7%) patients due to other reasons. No significant difference in number of patients with mild-to-no pain and moderate-to-severe pain was found between the three groups (table 1).

Presurgical comorbidities

The mean number of comorbidities present in the group of patients with moderate-to-severe pain was significantly higher compared with the mild-to-no pain group (1.18 (±0.92) vs 0.89 (±0.92), p=0.007) (Table 2).

The number of patients with a history of previously diagnosed cancer (Pearson Chi-square=8.436, p=0.004), fibromyalgia (Fischer´s exact test, p=0.001) and chronic pain in other site than the knee (Fischer´s exact test, p=0.012) were significantly higher in the moderate-to severe pain group compared with the mild-to-no pain group (Table 3).

Pain prediction model

Factors significantly associated with moderate-to-severe chronic postsurgical pain were fibromyalgia with OR 20.66 (95% CI 1.50-284.88), chronic pain in other body parts than the knee with OR 6.70 (95% CI 1.16-38.64), previously diagnosed cancer with OR 3.06 (95% CI 1.58-5.95), presurgical knee instability with OR 2.16 (95% CI 1.12-4.14), age at time of surgery under 65 with OR 2.15 (95% CI 1.24-3.73), and severity of presurgical knee-pain with OR 1.61 (95% CI 1.01-2.56) based on a binary logistic regression.

The binary logistic regression identified 36 out of 107 (33.6%) patients with moderate-to-severe chronic postsurgical pain based on presurgical factors, and 231 patients out of 245 (94.3%) patients with mild-to-no pain were classified correctly. The model showed an overall classification accuracy at 75.9%. Global fit of the model showed a significant improvement of fit over a no-model (75.9% vs 69.6%, $p \leq 0.001$).

The area under the curve (AUCs) for the prediction models was 0.596 (95% CI 0.534-0.662, p=0.003) which indicate a poor accuracy of the model (Figure 1). For the overall model, the sensitivity and specificity for the positive predictive value were 72.9 and 76.3, and for the negative predictive value were, 33.6, and 94.3%, respectively.

Discussion

The current study showed that that a minimum of 18% (107 out of 604 patients) of patients experience moderate-to-severe (NRS≥3) CPSP 5 years after primary TKR.

Presurgical fibromyalgia, chronic pain in other body parts than the knee, history of previously diagnosed cancer, presurgical knee instability, age at time of surgery under 65, and severity of presurgical knee-pain are associated with the development of moderate-to-severe CPSP 5 years after TKR. In addition, a binary logistic regression, using presurgical available data, correctly classified 33.6% of patients for the development of CPSP 5-years following TKR.

1. **Prevalence of chronic postsurgical pain 5-years following total knee replacement**

A large meta-analysis reported that an unfavorable pain outcome was seen in at least 8.0% and up to 26.5% of patients 6 to 60 months after primary TKA. (4).

In the present study, when assessing the 604 patients invited to participate in the study 18% reported moderate-to-severe pain (NRS≥3) 5 years after TKR. When assessing the patients who replied to the questionnaire, 30.4% reported moderate-to-severe pain (NRS≥3) 5 years after TKR, which is higher compared with previous reports.

Currently, no firm definition (e.g. how long time after surgery are data collected and NRS levels) of chronic postsurgical pain exists and therefore the prevalence between studies vary (23). An important parameter seems to be that postsurgical pain may decrease over time (24), and thereby it would have been expected a lower number of patients with moderate-to-severe pain at 5-years follow-up. However, when comparing mean peak pain intensity in the last 24 hours in present study with the mean from two parallel, randomized controlled trails in painful knee osteoarthritis patients from the same hospitals in the Northern Denmark Region at 1-year follow-up, it demonstrates the exact same mean (1.9 ±2.6) (25) indicating that pain not necessarily decrease over time, beyond a certain point. Previously studies support this, they have reported best result 1 year after TKR and a decline in the outcome until 5 years after surgery (26), but also an decreased in overall activity limitation (27).

A recent initiative based on the International Association for the Study of Pain (IASP) global year for pain after surgery aimed to standard the report of postsurgical pain, which could increase the comparability between studies in the future (23).

2. **Presurgical comorbidities and chronic postsurgical pain**

It has recently been shown that the severity and number of comorbidities may be associated with moderate-to-severe CPSP (5,7,8,10,11,20,28–31). In the present study the number of comorbidities were achieved by revising the patients' medical journals but the actual severity of the comorbidities were not available. Previously studies used comorbidity-indexes, such as Charlton Comorbidity Index (CCI) (20,32), and the Cumulative Illness Rating (CIRS) (31) to rate number and severity of comorbidities when predicting CPSP. However, these index focus more heavily on cardiopulmonary and other systems, which are less relevant to pain. Despite some knowledge about the comorbidities association with CPSP, little is known about individual comorbidities contribution to develop CPSP.

In present study it was found that the pain comorbidities fibromyalgia, chronic pain in other body parts than the knee, and the severity of presurgical pain in the index knee will increase the risk of developing CPSP. Despite the low number of patients with fibromyalgia and chronic pain in other body parts than the knee this is in line with previous studies showing that both fibromyalgia (33,34), and chronic pain in another body parts than the knee are associated with CPSP (35–37). Further, the current study found that the severity of presurgical pain is associated with developing CPSP which correspond with findings in several studies (36–40).

In previously studies, it has been demonstrated that low back pain influence the functional outcome after TKR (41) and the current study found a trend towards significant effect of low back pain. Previous it is also found that presurgical knee instability is associated with CPSP (42–44), which is supported by the current study. No other parameters from Knee Society Score were found associated with CPSP in present study.

The musculoskeletal features found to predict outcome seems all be related to increasing the drive which facilitate the central pain amplification (i.e. central sensitization) (45). Furthermore we have recently shown that the degree of central sensitization assessed by experimental pain tools (e.g. temporal summation of pain) is predictive for development of CPSP after TKA (39).

Previously no association were found between cancer and CPSP (13), which is in contrast to the current study, that found presurgical history of previously diagnosed cancer was a risk factor for moderate-to-severe CPSP. Future research could focus on identifying the severity and characteristics of cancer to identify which kind of cancer there is a risk factor for CPSP following primary TKR.

The current study demonstrates age as a significant risk factor for developing CPSP in young patients. Previous studies have found that young age is associated with high acute postsurgical pain intensity both in general and after TKR (28,46–48). Petersen et al., 2015 found that patients scheduled for revision TKR were younger compared to patients scheduled for primary TKR, which could indicate that age is a risk factor for unfavorable outcome after TKR (6). In the analyze "age under 65" were used as a dichotomous value. Despite no difference in mean age in the two groups, 45% of the patients in the moderate-to-severe pain group were under 65, and 33% of the patients in the mild-or-no pain group.

Recently a study found that knee OA patients with diabetes report higher pain intensity compared with patients without diabetes. Despite this a previously study investigating 1400 OA patients, found no association between obesity and risk of complications after TKR (49), which is in line with the results from the current study.

3. Prediction model

This combined in a prediction model made it possible to predict 1/3 of the patients who will suffer from CPSP. Only 5.6% of the patients were insufficient classified with respect to develop CPSP. Others have developed a clinical prediction model for patient-reported pain and function after primary total knee replacement surgery and were able to predict 21.1% of the variance of outcome

(17). They found that clinical factors associated with worse outcome in Oxford Knee Score 12 month after TKR were worse presurgical physical status, presence of other conditions affecting mobility and previous knee arthroscopy, which is in line with present study (17).

Limitations

In present study there were 252 patients (41.7%) with complete dataset which is similar to previous studies within the field with longer duration follow-ups. (13,20,27,50) However, the majority (56%) of the patients with non-complete dataset were due to the lack of KSS obtained from a register. 493 patients responded on the questionnaire which gives a respond rate on 81.6%. 107 patients reported NRS≥3 and thereby a minimum of 18% patients out of the complete cohort with moderate-to-severe pain 5 years after TKR. However, when assessing the investigated sample, 30.4% of the patients with complete dataset reported NRS≥3. However, it is not known in which degree the patients with non-complete dataset distinct from the patients with complete dataset. In addition, it is important to note that a different cutoff value would influence the percentage of patients with CPSP.

Present study is retrospective and not prospective, which makes that only associations can be determined, and the predictions can only show a tendency. Preferably, data on the presence and severity of comorbidity should be gathered presurgical by examination of the medical records in addition to an presurgical medical examination. Although the presence of a wide range of comorbidities presurgical is needed, the results of the present study indicate that a number of different comorbidities have an impact on patients' pain status after surgery. As many comorbidities are chronic by nature and therefore likely to have been present before surgery as well, their presence should probably be ascertained before surgery and treated if possible.

Studies have found that presurgical levels of anxiety, depression and pain catastrophizing are predictors of CPSP following TKR and therefore these are of high relevance to include in further studies regarding TKR.

Another limitation is despite that the purpose of total knee replacement is to provide long-lasting improvement in both pain and physical function, no information about physical function were obtained. In future studies one should see pain in the context of physical function and quality of life to get a more nuanced and correct picture of the outcome of total knee replacement.

In conclusion, the current study showed that presurgical fibromyalgia (OR 20.66), chronic pain in other locations than the knee (OR 6.70), previous diagnosis of cancer (OR 3.06), presurgical knee instability (OR 2.16), age at time of surgery under 65 (OR2.15), and severity of presurgical knee-pain (OR1.61) are risk factors with the development of moderate-to-severe CPSP 5 years after TKR. A binary logistic regression, using presurgical available medical data, correctly classified 33.6% of patients for the development of CPSP 5 years following TKR. This is important for presurgical counselling patients undergoing TKA, for evaluating risk, and maybe for continuing conservative treatment options.

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Table 1: Demographics characteristics, and reason for surgery of the patients with and without CPSP included in analysis. Abbreviation: BMI: Body Mass Index, SD: standard deviation.

Characteristic	Mild or no-pain group	Moderate-to-severe pain group
Age, mean (SD)	68 (10)	67 (9)
Gender, male, n (% of total group)	102 (42%)	36 (33%)
BMI, mean (SD)	29.9 (5.0)	30.7 (5.2)
Number of patients, n (% of total group)	245 (69,6%)	107 (30.4%)
Reason for surgery		
Primary idiopathic osteoarthritis, n (% of sub group)	220 (90%)	96 (89%)
Secondary osteoarthritis, n (% of sub group)	17 (7%)	6 (5.5%)
Other reason for surgery, n (% of sub group)	7 (3%)	6 (5.5%)

*Table 2: Number of comorbidities present in the two groups of patients. * indicates a significant difference in number of comorbidities with $p<0.05$.*

Number of comorbidities without arthritis	**0**	**1**	**2**	**3**	**4**
Percentage of patients in mild pain group, n	41.8%	34.4%	17.6%	5.7%	0.4%
Percentage of patients in moderate-to-severe pain group, n	26.9%	35.2%	32.4% *	4.6%	0.9%

*Table 3: Percentage of patients with various comorbidities among patients with and without CPSP. * indicates a significant difference in number.*

	Mild pain group	Moderate-to-severe pain group	P-value
Fibromyalgia *	0%	5.6%	0.001
Previous diagnosis of cancer *	11.9%	24.1%	0.004
Chronic pain in other body parts than the knee*	0.8%	5.6%	0.012
Lumbar issues	21.3%	29.6%	0.091
Stroke	7.4%	3.7%	0.189
Erysipelas	4.1%	6.5%	0.336
COPD	4.1%	6.5%	0.336
Rheumatic disease	10.7%	8.3%	0.502
Pacemaker	2.0%	2.8%	0.705
Diabetes	23.9%	20.4%	0.809
Osteoarthritis in more than 2 other joints	26.6%	27.8%	0.824
Osteoarthritis in the other knee	78.7%	79.8%	0.842
Dementia	4.5%	3.7%	1.000
Epilepsy	1.6%	0.9%	1.000
Gastric bypass	0.8%	0%	1.000

Figure 1 illustrating ROC curve, with a sensitivity of 72.9 and a specificity 76.3 for the positive predictive values of the prediction model. AUC is 0.596 (95% CI 0.534-0.662, p=0.003).