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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

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Abstract

Objectives

Total knee replacement (TKR) normally provides improvements of physical function and reduces pain. However, approximately 20% of the patients report chronic postoperative knee pain. The aims of the present study were to assess the pain, physical function, and physiological characteristics 5 years after TKR surgery.

Methods

Eighty patients were recruited 5 years after TKR and divided into two groups based on their average 24-hour knee pain intensity assessed on a visual analog scale (VAS 0-10) ('High Pain Group': VAS≥3; 'Low Pain Group': VAS<3). The patients completed the painDETECT (PD-Q), Oxford Knee Score (OKS), Pain Catastrophizing Scale (PCS), and Forgotten Joint Score (FJS-12). Furthermore, the patients underwent a clinical examination of the knees and high sensitivity serum C-reactive protein (hs-CRP) was measured as an inflammatory marker.

Results

53% of the patients in the High Pain Group was not satisfied with the outcome, while only 11% of the patients in the Low Pain Group was not satisfied, and the pain intensities in the two groups were 5.1 (4.6-5-6) and 1.1 (0.6-1.5), ($p<0.001$), respectively. Furthermore, the High Pain Group demonstrates worse scores in: FJS-12 ($p=0.001$), OKS function ($p<0.001$), OKS pain ($p<0.001$), and PCS ($p<0.001$).

The High Pain Group demonstrated increased level of hs-CRP (4.3mg/L (3.2-5.5) vs 1.7mg/L (1.2-2.2), $p<0.001$), and decreased range of motion in the knee (110-degrees ROM vs 119-degrees ROM, $P=0.013$).

Discussion

Patients with high chronic postoperative knee pain 5 years after TKR demonstrate decreased physical function, higher levels of catastrophizing thoughts, and increased levels of inflammation.

Keywords

C-reactive protein, Total Knee Replacement, Chronic Postoperative Pain, Physical function

Introduction

Osteoarthritis (OA) is the most frequent painful musculoskeletal diagnosis in the elderly population and the most common cause of disability[1] in the United States[2] and in other developed countries.[3] Knee OA accounts for more than 80% of the total burden caused by OA.[3,4]

With an expected growth in the elderly population, the incidence of knee osteoarthritis (KOA) is predicted to increase in the future[4] and thereby the incidence of total knee and hip joint replacements are also expected to increase.[5]

Total knee replacement (TKR) is effective and produces long-lasting improvements of physical function and reduces pain[6] but it is well-described that approximately 20% of TKR patients will develop chronic postoperative knee pain and that these patients are less satisfied with the outcome compared with patients with the expected recovery.[7–10] However, the understanding of chronic postoperative pain and the long-term (>1 year follow up) outcomes is incomplete.[11–14]

Recent data have revealed a relationship between pain and inflammation in patients with painful OA [15–18] but less is known if such relationships exist for patients with chronic postoperative knee pain after TKR. The most common measurement of inflammation is C-reactive protein (CRP), and CRP is used in clinical practice as a rough indicator for infection, inflammatory diseases, or malignancy.[19] In healthy persons, normal CRP levels are generally considered to be below 3 mg/L.[19,20] Low-grade inflammation can be defined as a CRP in the range from 3 to 10 mg/L.[19,20] CRP levels above 10 mg/L may suggest the presence of an underlying inflammatory disease, infection, or malignancy.[19,20]

Traditionally CRP has been used to distinguish systemic inflammatory disorders such as rheumatoid arthritis (RA) from ‘‘noninflammatory’’ diseases such as OA.[21] More recently, low-level elevations in CRP have been observed in diseases where there is a local, low-grade inflammatory component.[21] Previously a study has demonstrated an association between

preoperatively elevated CRP (low-grade inflammation) and potentially worse long-term prognosis after TKR.[22] However, no studies have assessed CRP levels in patients with chronic postoperative pain 5 years following TKR.

The aim of present long-term follow-up study was to evaluate the inflammatory status, along with characterizing the satisfaction, painDETECT scores, physical function, catastrophizing thoughts, and physiological characteristics in TKR patients with low or high chronic postoperative knee pain 5 years after TKR surgery.

Materials and Methods

Protocol

All the patients who underwent TKR in 2011 in the five hospitals of the Northern Region of Denmark were invited to a 5-years follow up examination of the knee operated in 2011. The invitation about whether they wanted an additional examination was a part of a simple questionnaire sent out in connection with another study, and was done according to the published protocol.[8] Patients were assessed between April 2017 and January 2018.

The patients were divided into two groups (a High Pain Group with VAS≥3, and a Low Pain Group with VAS<3), based on the degree of the chronic postoperative average 24-hour knee pain intensity assessed on a 10 cm visual analog scale (VAS, anchored at 0: no pain and 10: worst pain imaginable). Patients were excluded if they had undergone further surgery in the knee operated in 2011, did not understand Danish, had previous neurologic or mental illnesses, or could not cooperate. Furthermore, patients were excluded if they have a recent history of acute pain affecting the lower limb and/or trunk, or any abuse history of alcohol or drug.

The examination was conducted at the Orthopedic Outpatient Clinic at Aalborg University Hospital, Aalborg, Denmark.

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

Enrolled patients were assessed using painDETECT, Forgotten Joint Score, Oxford Knee Score, Pain Catastrophizing Scale, and information from the medical journal which will be described below.

Pain assessment

The patients were asked to rate their average pain within the last 24-hour of the index knee on a visual analog scale (VAS 0-10). Also, the patients were asked to estimate what they believe their knee pain intensity after 30 minutes of walk would be (VAS 0-10). Furthermore, the patients were asked to rate their satisfaction with the outcome of the knee replacement from 2011 as 'Very Satisfied', 'Satisfied' or 'Not Satisfied'. These three measurements were conducted by mail in connection with the screening and the patients were later invited for a medical follow-up examination.

5-year medical follow up examination

The examination included an objective examination of the knee including measurement of passive range of motion (ROM) (degrees from maximal extension to maximal flexion) of both knees with a standard goniometer (Fabrication Enterprises Inc., White Plains, NY, USA). Changes in ROM, and reduction flexion and extension are defined by comparison between the knees with the knee not operated in 2011 as reference. Examination of the patients were conducted by a surgeon with the patients in supine position.

A 5ml blood sample was collected by forearm venipuncture and analyzed the same day. Serum hs-CRP was analyzed on a Roche/Hitachi cobas c-system (Roche Diagnostics GmbH, Mannheim, Germany) with a limit of detection of 0.3 mg/L.

painDETECT Questionnaire (PD-Q)

PainDETECT is a validated self-report questionnaire that can be used in patients with OA to evaluate of the likelihood of neuropathic pain in a range of contexts.[23–29] Total PD-Q scores of ≤ 12 suggests that presence of neuropathic pain components are unlikely, ≥ 19 indicates that presence of neuropathic pain component is likely, and scores between 13 to 18 indicate an uncertain classification.[23]

Pain Catastrophizing Scale (PCS)

Pain catastrophizing thoughts can be assessed by the Pain Catastrophizing Scale (PCS)[30] and it has previously been demonstrated that the degree of pain catastrophizing thoughts is predictive for the outcome after TKR.[31,32] However, it has also been demonstrated that some pain-relieving surgeries may systematically reduce catastrophizing.[33] However, no studies have identified if pain catastrophizing thoughts persists in patients with chronic postoperative pain 5 years after TKR.

The PCS is a 13-item questionnaire focusing on thoughts and feelings in connection with pain. The questions are to be rated on a 5-point Likert scale: 0 (not at all) to 4 (all the time). The PCS total score is computed by adding up the responses to all 13 items. PCS total scores range from 0 – 52. PCS > 30 has been suggest as a clinical cut off point for pain catastrophizing thoughts.[30]

Oxford Knee Score (OKS)

The Oxford Knee Score (OKS) is a disease-specific patient-reported outcomes measures (PROM) which is used to evaluate the knee before and after TKA.[34] The OKS is a 12-item questionnaire assessing pain and function of the OA affected knee.[35,36]

The patient scored each question (item) from 0 to 4, with 0 being the worst outcome and 4 being the best outcome. The summed scores of each subscale were then standardized to a range from 0 (worst) to 100 (best).

Forgotten Joint Score, FJS-12

The Forgotten Joint Score, FJS-12 is a recently published PROM scale to assess joint awareness in hips and knees during various activities of daily living.[37–39] It is based on a descriptive system that defines health in terms of 5 dimensions, each with three response options: mobility, self-care, usual activities, pain/ discomfort, and anxiety/depression.[37] It consists of 12 equally weighted questions, which are scored using five-point Likert scales, with the raw score transformed to range from zero to 100 points. High scores indicate a high degree of being able to forget about the affected joint in daily life.[37]

Comorbidities

It has previously been demonstrated that the presence of different comorbidities postoperatively can be predictive for the outcome of the TKR surgery, with widespread pain conditions as the strongest predictors.[8,40,41] A set of predefined comorbidities was investigated, but only comorbidities noted in the medical record were collected.

The following comorbidities were examined: OA elsewhere than the knee scheduled for surgery, fibromyalgia, chronic pain in body parts other than the knee, previous diagnosis of cancer, chronic obstructive pulmonary disease, diabetes, lumbar issues, history of erysipelas, stroke, rheumatic diseases, and dementia, which, in previous studies were parameters found associated with the development of chronic postoperative knee pain.[8,40–43]

Data Analysis

Descriptive characteristics of the sample are reported using means and 95% confidence interval (95% CI) unless otherwise stated.

Normal distribution was assessed using the Shapiro-Wilk test. Normal distribution was accepted for all parameters except serum hs-CRP.

Between group differences were evaluated with independent sample t-test or the nonparametric Mann-Whitney U-test.

Chi-square tests were used to compare gender, range of motion, and satisfaction.

Statistical analyses were performed in IBM SPSS Statistics (ver. 26, IBM Corporation, New York, USA). $P<0.05$ was considered significant. All outcomes were Bonferroni corrected to account for multiple comparisons when appropriate.

Results

A total of 124 patients out of 493 accepted the invitation to a 5-year follow up examination, 44 patients withdraw their acceptance before the examination, and 80 patients participated in the study. No significant difference were found between the patients responding and patients not responding to the invitation in regards to gender distribution (p=0.779), age (p=0.401), BMI (p=0.108), average 24-hour knee pain intensity (p=0.601) and in pain intensity after 30 minutes of walk (p=0.723).

A total of 18 patients reported pain score lower than VAS 3, and 62 patients reported pain score higher or equal VAS 3.

Patient demographics are listed in Table 1. No differences were found between groups regarding patient demographics.

Medical follow-up examination

The High Pain Group demonstrated a significantly decreased knee range of motion (ROM) (110-degrees ROM) compared with the Low Pain Group (119-degrees ROM, P=0.013). Reduced knee extension was found in 10% of the patients in the High Pain Group, and in none of the patients in the Low Pain Group. Reduced knee flexion was found in 58% of the patients in the High Pain Group, and in 33% of the patients in the Low Pain Group (table 2).

Serum hs-CRP

The High Pain Group have a significantly increased serum hs-CRP level compared with the Low Pain Group (4.3 mg/L (95% CI 3.2-5.5) vs 1.7 mg/L (95% CI 1.2-2.2), p<0.001). None of the patients in the Low Pain Group had a serum hs-CRP level higher than 3 mg/L, and 26 of the patients in the High Pain Group (42%) had a hs-CRP level higher than 3 mg/L. (table 2).

No significant difference in serum hs-CRP level among patients with or without presence of different comorbidities, or with or without osteoarthrosis in other joints (table 3).

Knee pain at 5-years follow-up

For patients in the High Pain Group the average 24-hour knee pain intensity was significantly higher than the patients in the Low Pain Group (5.0 (4.4-5.6) vs 2.1 (1.3-2.8), p<0.001) and had significantly higher pain intensity after 30 minutes of walk (6.0 (5.4-6.7) vs 2.8 (0.7-4.9), p<0.001) (table 2).

Satisfaction

The percentage of patients in the High Pain Group (47%) who were 'very satisfied' or ´satisfied´ with the outcome was significantly lower than in the Low Pain Group (89%) compared with the High Pain Group (p<0.0001). While 33 of the patients in the High Pain Group (53%) were 'not satisfied', only 2 patients in the Low Pain Group (11%) was 'not satisfied' with the TKR (P<0.0001), (table 2).

PainDETECT

The High Pain Group demonstrated the highest painDETECT score (14.8 (95% CI 13.2-16.3) vs 6.8 (95% CI 4.4-9.1), p<0.001) (table 2).

Furthermore, 18 (29%) of the patients in the High Pain Group had a neuropathic pain component according to the painDETECT-score. None of the patients in the Low Pain Group had neuropathic pain components.

Pain Catastrophizing Scale, PCS

The High Pain Group reported a significantly higher score on the PCS (18.9 (95% CI 15.6-22.1) vs 4.0 (95% CI 1.3-6.7), p<0.001) (table 2). Furthermore, 12 out of 62 (19%) patients in the High Pain Group had a PCS ≥30, and 0 out of 18 patients in the Low Pain Group had a PCS ≥30.

Oxford Knee Score

The High Pain Group demonstrated a significantly lower Oxford Knee Score for both the function component (53.7 (95% CI 50.2-57.2) vs. 79.3 (95% CI 71.7-86.9), p<0.001) and the pain component (49.8 (95% CI 46.6-53.0) vs 74.6 (95% CI 67.0 -82.2), p<0.001) compared with the Low Pain Group (table 2).

Forgotten Joint Score, FJS-12

The High Pain Group scored significantly lower on the FJS-12 than the Low Pain Group (22.6 (95% CI 16.9-28.3) vs 42.8 (95% CI 33.2-52.3), p=0.001) (table 2).

Comorbidities

The High Pain Group and the Low Pain Group did not demonstrate a significantly differences in number of comorbidities (1.06 vs 0.8, p=0.265). However, rheumatic diseases (p=0.007), fibromyalgia (p=0.045) and chronic pain in other body parts than the knee (p=0.024) was only present among patients in the High Pain Group (table 2). No other registered comorbidities had any significance in presence in the two groups.

Discussion

The present study found that patients with high chronic postoperative knee pain demonstrate decreased physical function, high levels of pain catastrophizing thoughts, and increased levels of serum CRP as compared with patients with low knee pain 5 years after a TKR.

The primary aims of TKR are pain relief and improve the function of the knee, and thereby increase the quality of life for the patient.[44] However, it is now well documented that a number of patients

report chronic postoperative knee pain with functional limitations.[7,8] Poor outcomes after an elective procedure such as TKR can lead to patient dissatisfaction, poor health-related quality of life and psychological distress[10] as further highlighted in the current long-term 5-years follow-up study. In general, little is known about the long-term (e.g. 5 years) outcome after TKR and its consequences, since most studies have followed patients for one year, when comparing the patients with chronic knee pain with the patients without knee pain.[45,46] It has been shown consistently that around 20% of the patients will experience chronic knee pain up to one year after TKR and a majority of those patients will report to be dissatisfied with the outcome.[10,47–50]

Range-of-motion (ROM) has been linked to the performance of functional activities, with reduced ROM associated to lower degree of satisfaction of the outcome after TKR.[51,52] Despite the relative low degree of reduced ROM, ROM is important for the individual patient, and commonly used as a patient related measurement of the functional outcome. [51–53] Furthermore, it could impact the use and wear of the patients' other knee, with increased overload as a result.[54]

Several studies have sub-grouped the patients according to the degree of satisfaction and have found associations between degree of satisfaction and postoperative knee pain, indicating that low satisfaction and high clinical pain intensities are associated, and therefore both factors should be addressed when assessing patients in the clinic.[48–50,55] Furthermore, associations between low degree of satisfaction and low scores in FJS-12, and OKS have been established.[49,55–58]

The present study demonstrates a substantial degree of dissatisfaction (53%) in the group of patients with chronic postoperative knee pain 5 years after TKR. However, it is interesting that 47% of patients experiencing chronic postoperative knee pain 5 years after TKR either are very satisfied (12%) or satisfied (37%) with the outcome of the knee replacement. The reason why almost half of patients within the high-pain group is satisfied with the knee replacement is unknown but might reflect that the patients have experienced some degree of pain relief compared with the preoperative

status, and that satisfaction with surgery in not solely driven by pain-relief. Clement et al[50] demonstrated that the degree of satisfaction was not stable over a period of 5 years, and that increased pain symptoms were associated with increased dissatisfaction which has been confirmed in other studies.[48,49,55]

Preoperative pain catastrophizing thoughts have widely been used[32,59,60] to predict the pain 1 year after TKR with high preoperative catastrophizing level predicting high postoperative knee pain. However, previous study suggest that some knee OA patients show spontaneous changes in catastrophizing[31] and that pain-relieving surgeries may systematically reduce catastrophizing.[33] Only few studies have evaluated the effect of preoperative pain catastrophizing on long-term (e.g. 5 years) outcomes.[61,62] However, no studies have identified if pain catastrophizing thoughts persists in patients with chronic postoperative pain 5 years after TKR. In accordance with previously demonstrated[62], present study demonstrates that among the patients with chronic knee pain a higher degrees of pain catastrophizing thoughts exists.

Serum hs-CRP

Recently low-grade inflammation has been described having a predictive role in the development and progression of OA [63], with serum CRP levels as a bio-marker associated with local inflammation[21], knee pain and knee stiffness.[22,64,65] Smith et al.[22] showed that KOA patients with high preoperative serum hs-CRP levels (average higher than 7 mg/L) demonstrated high 1-year postoperative serum hs-CRP levels (average higher than 14 mg/L), indicating a continued chronic low-grade inflammation. In addition worse outcome in the Short Form health outcomes survey (SF-12) have been identified in patients with higher preoperative serum hs-CRP levels 6 and 12 months after TKR.[22]

One of the major mediators of inflammatory are cytokines, which induce and maintain the processes in diseases like OA[66], with Interleukin-6 (IL-6) as a key player in systemic inflammation

and OA.[67] In relation to OA, increased serum hs-CRP levels correlates with increased IL-6 levels[21] which correlates with pain intensity[64], suggesting that serum hs-CRP can be an indicator of poor outcomes after TKR[15,22] and the present study can extend these findings to the 5 years postoperative pain status.

Limitations

Recruitment of participants in present study was based on the patient's own response on whether or not they wanted to receive an additional medical examination 5 years postoperatively. They were asked by mail, at the same time as they were asked to rate their worst pain in the last 24 hours. By actively being asked to relate to their TKR and about whether or not their pain originates from the knee, could create a selection bias in which patients from the original cohort accepted the invitation. Furthermore, 44 out of 124 patients (35%) withdraw their acceptance before the examination, ending up with 80 patients out of the original cohort of 604 patients operated with a TKR in 2011. However, no significant difference regarding preoperative demographics between responders and non-responders was detected.

As stated in the introduction, it is broadly accepted that approximately 20% of the TKR patients experience chronic postoperative knee pain. However, it is important highlight that the purpose of present study not is to evaluate this, but to characterize the patients with high and low chronic postoperative knee pain.

Due to the sample size it is not possible to identify if the presence of any comorbidity will have an impact on the serum hs-CRP level in patients with high or low chronic postoperative pain after TKR. However, the study was designed as an explorative study, and as such no firm statistical plan was formulated a priori, which further highlights the preliminary nature at the study. The findings should therefore be replicated in future studies for confirmation.

In general, the conclusion of the study would have been stronger, if presurgical data were available, both to document the development of catastrophizing thoughts, and the low-grade inflammation has been developed before or after the surgery.

Conclusion

The current study found that patients with high chronic postoperative knee pain 5 years after TKR express presence of low-grade inflammation through increased levels of serum hs-CRP, indicating that inflammation can contribute to drive the pain. Furthermore, the patients with high chronic postoperative knee pain 5 years after TKR demonstrate significantly worse outcome as decreased physical function, and higher levels of catastrophizing thoughts compared with patients with low knee pain 5 years after TKR.

Conflict(s) of interest

The authors have no conflict of interest to declare.

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Table 1 Pre-operative demographics retrieved from patients record. BMI, Body Mass Index.

TABLE 1	High Pain Group	Low Pain Group	p-value
Number	62	18	
Gender, male/female	27/35	6/12	0.445
Age at the time of surgery, years	63.9 (61.9-66.0)	65.8 (66.7-69.0)	0.359
BMI, kg/m^2	31.6 (30.2-33.0)	29.4 (26.5-32.3)	0.147

Table 2 Mean range of motion in the index knee, and number of patients with reduced flexion/extension in the knee mean serum hs-CRP, mean pain scores (VAS) in the last 24 hours, and after 30 minutes of walk, the degree of satisfaction 5 years postoperatively and mean, painDETECT, Oxford Knee Score, Pain Catastrophizing Scale, and Forgotten Joint Score, and presence of comorbidities in patients categorized into a Low or a High chronic postoperative pain group.

TABLE 2	High Pain Group	Low Pain Group	p-value
Knee range of motion, extension/flexion (degree)	110 (106-114)	119 (114-123)	0.013
Patients with reduced extension in index knee (n, %)	6(10%)	0 (0%)	<0.001
Patients with reduced flexion in index knee (n, %)	36 (58%)	6 (33%)	<0.001
Serum hs-CRP (mg/L)	4.3 (3.2-5.4)	1.5 (1.0-1.9)	<0.001
Average pain last 24hours (VAS, 0-10)	5.0 (4.4-5.6)	2.1 (1.3-2.8)	<0.001
Pain after 30 minutes of walk, (VAS, 0-10)	6.0 (5.4-6.7)	2.8 (0.7-4.9)	<0.001
Satisfaction (Very satisfied/satisfied/not satisfied)	7/22/33	10/6/2	<0.001
painDETECT	14.8 (13.2-16.3)	6.8 (4.4-9.1)	<0.001
Pain Catastrophizing Scale	18.9 (15.6-22.1)	4.0 (1.3-6.7)	<0.001
Oxford Knee Score, function component	53.7 (50.2-57.2)	79.3 (71.7-86.9)	<0.001
Oxford Knee Score, pain component	49.8 (46.6-53.0)	74.6 (67.0 -82.2)	<0.001
Forgotten Joint Score, FJS-12, (0-100)	22.6 (16.9-28.3)	42.8 (33.2-52.3)	0.001
Number of comorbidities	1.06 (0.8-1.3)	0.8 (0.2-1.4)	0.265
Patients with Rheumatic disease (n)	7	0	0.007
Patients with Chronic pain in other body part than the knee (n)	4	0	0.045
Patients with Fibromyalgia (n)	5	0	0.024

N, number of patients. Hs-CRP, high sensitivity C-reactive protein. VAS, visual analog scale. OKS, Oxford Knee Score.

Table 3 Mean levels of serum hs-CRP in patients with or without the registered comorbidities. Only comorbidities with a presence of more than 3 are calculated.

TABLE 3	Yes	No	p-value
Rheumatic disease	4.8 (1.8-7.9), n=7	3.5 (2.6-4.5), n=73	0.423
Chronic pain in other body part than the knee	7.8 (-3.6-19.2), n=4	3.4 (2.6-4.3), n=76	0.309
Fibromyalgia	2.7 (1.1-4.3), n=5	3.7 (2.7-4.7), n=75	0.593
Osteoarthrosis in other joints	3.7 (2.7-4.7), n=60	3.4 (1.2-5.7), n=19	0.803
Previous diagnosis of cancer	3.0 (0.9-5.0), n=12	3.8 (2.7-4.8), n=68	0.526
Diabetes	4.4 (0.5-8.2), n=10	3.6 (2.6-4.5), n=70	0.567
Lumbar issues	3.1 (1.6-4.7), n=27	3.9 (2.8-5.1), n=53	0.399
History of erysipelas	4.0 (-1.9-9.8), n=5	3.6 (2.7-4.6), n=75	0.863