Pain, Sensitization, and physical performances in patients with chronic painful knee osteoarthritis or chronic pain following total knee arthroplasty

an explorative study

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Abstract

Background:

The aim of this study was to assess clinical pain, pain sensitization, and physical performances to profile patients with chronic painful knee osteoarthritis (OA) or pain after total knee arthroplasty (TKA). Examining the interactions between pain mechanisms and physical performances would enable us to investigate the underlying explanatory relationships between these parameters.

Methods:

In this explorative study, 70 patients with chronic painful knee OA (N=46) or chronic pain after TKA (N=24) were assessed for clinical pain, quantitative sensory profiling (mechanical pinprick pain sensitivity, temporal summation (TS), and conditioned pain modulation), physical performances (chair stand, walk, and stair climb tests), and self-reported outcomes. Between-group comparisons were made using ANCOVA tests and associations between outcomes were analyzed using multivariate linear regression models.

Results:

Overall, no differences between groups regarding clinical pain and quantitative sensory profiling outcomes were observed. Physical performances were lower in the TKA group compared with the OA group with moderate-to-large effect sizes, and a tendency towards better scores in self-reported outcomes for the OA group was observed with small-to-moderate effect sizes. Self-reported function seems to be associated with physical performances in the TKA group. Sensitization (TS) appears to be associated with poorer physical performances in the OA group.

Conclusions:

Similar profiles for pain intensity, signs of sensitization, and conditioned pain modulation were observed. Patients with TKA seem to have impaired physical performance compared with the OA group, underlining the importance of targeting physical performances. Only the OA patients showed an association between sensitization (TS) and physical performance.

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PAIN, SENSITIZATION, AND PHYSICAL PERFORMANCES IN PATIENTS WITH CHRONIC PAINFUL KNEE OSTEOARTHRITIS OR CHRONIC PAIN FOLLOWING TOTAL KNEE ARTHROPLASTY: AN EXPLORATIVE STUDY

Running head: Profiling of pain and physical performance

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Conflict of interest:

Jesper Bie Larsen and Ole Simonsen declare that they have no conflict of interest. Pascal Madeleine declare the following conflicts of interest: travel/accommodations/meeting expenses (Institut National des Risques et Securité), and Lars Arendt-Nielsen declare the following conflicts of interest: consultancies (C4Pain) and travel/accommodations/meeting expenses (Grünenthal).

Significance:

Quantitative pain profiling assessment was used to assess pain intensities and pain mechanism. We observed associations between physical performances and temporal summation in the OA group underlining the importance of assessing motor functions and pain mechanisms in the same trial. We observed lower levels of physical performances in the TKA group compared with the OA group, suggesting that examination and rehabilitation of physical performances is essential for TKA patients with chronic pain.

1. Introduction

Osteoarthritis (OA) is considered the leading cause of pain and disability in the elderly population, and the knee joint is commonly affected (Palazzo et al., 2016). The hallmark symptom of OA is pain accompanied by functional limitations and reduced quality of life (Neogi, 2013). End-stage knee OA is often treated with knee replacement, and total knee arthroplasty (TKA) is considered an effective treatment to achieve pain relief and improved function (Price et al., 2018). During the eventual transition from knee OA to post-TKA, improvements in pain, physical performances, and patient-reported outcomes usually occur after successful surgery (Artz et al., 2015,Jakobsen et al., 2014,Fransen et al., 2017). However, studies have described that up to 20% of patients suffer from chronic pain following TKA (Beswick et al., 2012).

Pain sensitization has emerged as an important mechanism in developing chronic pain among OA and TKA patients (i.e. patients continuing to suffer from chronic pain after TKA) (Arendt-Nielsen et al., 2010,Wright et al., 2015,Skou et al., 2014). Further, mechanistic quantitative sensory profiling may provide useful diagnostic insight and information regarding possible sensitization in patients with OA and chronic pain after TKA (Egsgaard et al., 2015). Some studies have proposed the sensitization to diminish after successful surgery and other have not reported any changes in sensitization (Graven-Nielsen et al., 2012,Skou et al., 2016,Kosek et al., 2013); thus warranting further examination of the sensitization before/after knee replacement surgery in order to understand the associations between sensitization and outcomes after TKA. Profiling of OA and TKA populations with chronic pain will enable a general benchmarking of pain mechanisms and physical performances. This insight could be used to evaluate the mechanisms and deficits to be targeted in priority and whether differences between the populations will require different treatment focus. It has been shown that patients with knee OA have signs of sensitization associated with significantly lower physical performances (chair rises, fast-paced walking, and stair climbing) compared with knee OA patients without signs of sensitization (Guerard et al., 2020). Furthermore, an association between sensitization and non-response (low or no improvement in pain and function) to physiotherapy treatment has been established, suggesting that patients with sensitization suffer from impaired physical performances and are difficult to treat (O'Leary et al., 2018). To the best of our knowledge, the association between performance parameters and pain mechanisms including pain sensitization has not been investigated thoroughly.

Comparison of clinical pain features, quantitative sensory profiling (assessing evoked pain response and pain sensitization), and physical performances parameters would allow comprehensive profiling of chronic OA/TKA pain patients and possibly provide a better understanding of the potential differences and similarities between groups; thus enhancing individualized treatment (exercising and rehabilitation) for patients with chronic pain (Gay et al., 2016). Examining associations between sensitization parameters and physical performances for both knee OA and TKA patients would enable delineating sensory-motor interactions.

Therefore, the objectives of this explorative study were to 1) profile and compare OA patients and TKA patients with chronic pain with respect to pain outcomes, physical performances, and self-reported outcomes and 2) evaluate associations between physical performances, self-reported function, clinical pain, and quantitative sensory profiling for both groups.

It was hypothesized that TKA patients would exhibit more signs of pain sensitization (defined in the present study as temporal summation (TS)) compared with the OA group since patients with chronic post-operative pain after TKA have shown enhanced TS compared with knee OA patients (Skou et al., 2014).

2. Methods

2.1 Study design

This exploratory study was carried out in patients with either knee OA or having undergone primary TKA between May and December 2018. The settings included two locations at the Physiotherapy Department at Aalborg University Hospital, Denmark, and at the outpatient clinic Center for Clinical and Basic Research in Aalborg, Denmark. The study was conducted in accordance with the TIDier and STROBE guidelines (Hoffmann et al., 2014,von Elm et al., 2014). All patients were recruited from the North Denmark Region. The study was conducted in accordance with the Helsinki Declaration and had been approved by the local ethics committee (The North Denmark Region Committee on Health Research Ethics, Aalborg, N-20170088). All patients signed an informed consent.

2.2 Participants

Potential patients with moderate-to-severe pain because of knee OA or after TKA were identified using the medical journals. Patients with moderate-to-severe pain intensity were targeted since high pain intensity can be a first indicator of sensitization (Lluch et al., 2017).

Potential patients were contacted by phone and an information leaflet was mailed to all interested patients. Afterwards, the patients were contacted by phone again and if agreeing to participate, they were screened for inclusion. For patients with knee OA, the following inclusion criteria applied: 1) moderate-to-severe pain (average numerical rating scale (NRS) during last week ≥4/10) (Gerbershagen et al., 2011), 2) unilateral or bilateral knee OA diagnosis according to the American College of rheumatology criteria (Altman et al., 1986) and based on clinical and radiographic evidence of ≥ grade 2, 3) duration of pain >6 months, 4) aged 40-80 years, and 5) body mass index (BMI) between 19-40 kg/m^2. For the TKA patients, the following inclusion criteria applied: 1) moderate-to-severe pain (average NRS during last week ≥4/10), 2) primary TKA, 3) duration of pain >6 months, 4) aged 40-80 years, and 5) BMI between 19-40 kg/m^2.

Exclusion criteria were: 1) secondary causes of arthritis to the knee, such as rheumatoid arthritis or sequelae from previous accidents, 2) surgery (including arthroscopy) of the index knee within 3 months prior to visit, 3) injury to the index knee within 12 months prior to visit, 4) acute pain, other than in the index knee, affecting the lower limb and/or trunk at the time of participation, 5) consumption of alcohol, caffeine, nicotine, or painkillers on the day of the study, 6) pregnancy, 7) drug and alcohol abuse, 8) rheumatoid arthritis, neurologic illnesses or primary pain area other than the knee (e.g. low back pain or upper extremity pain), and 9) lack of ability to adhere to protocol. In total, 61 patients with knee OA were screened and 15 were excluded as they did not fulfil the inclusion criteria, leaving 46 knee OA patients for inclusion. For the TKA patients, 124 patients were screened from which 61 were excluded as they did not fulfil the inclusion criteria and 39 patients were not interested in participating in the study, leaving 24 patients for inclusion. In total, 70 patients with knee OA and TKA were included in the analysis (table 1). Due to the explorative nature of the study and the inclusion of several outcome measures, no sample size calculations were made. All patients completed the study with no loss to follow-up.

2.3 Protocol

The patients took part in a single session, lasting approx. 2 hours. The principal investigator (JBL) conducted all tests. Demographic data and duration of knee pain were retrieved before assessment. Pain-related outcomes consisted of clinical pain intensity and quantitative sensory profiling. The assessment of the physical performances were based on the recommendations from OsteoArthritis Research Society International (Dobson et al., 2013).

During the pain assessment, the patients were placed in a comfortable supine position. A predetermined assessment sequence was used; starting with the pain-related outcomes and followed by the physical performance outcomes. The sequence was pain intensity, mechanical pinprick pain sensitivity, TS, and conditioned pain modulation (CPM) followed by completion of the Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire (Roos et al., 1998). Finally, assessment of physical performances consisting of the 30-second chair stand test, the 40-meter fast-paced walk test, and the stair climb test were conducted.

2.4 Clinical pain intensity

Clinical pain was assessed as the average pain intensity in the knee over the last week prior to the visit using a NRS in which "0" represented "no pain" and "10" represented "worst pain imaginable".

2.5 Quantitative sensory profiling

2.5.1 Mechanical pin-prick pain sensitivity

A single pinprick using a nylon filament of 0.7mm (Chicago Medical Supplies, Chicago, USA) was applied perpendicularly to the skin (90° angle) until slight bending of the hair when a force of 75 gram was applied. The patients were asked to rate the pain intensity of the pin-prick pain on a NRS. The test was conducted localized in the most affected knee (index), adjacent to the knee (10 cm above the knee, ventral thigh), and extra-segmentally on the medial side of the forearm (muscle belly of flexor digitorum superficialis).

2.5.2 Mechanical temporal summation

A pinprick using a nylon filament of 0.7 mm (Chicago Medical Supplies, Chicago, USA) was applied as a single stimulus perpendicularly to the skin, and the patients rated the pain intensity on a NRS. After this, the nylon filament was re-applied for stimuli of 10 repeated pinpricks within an area of 1 cm^2 with a repetition rate of 1/second, and the patients rated the pain intensity of the last stimulus on a NRS. The TS calculation was the pain rating from the single stimulus subtracted from the pain rating of the repeated stimuli. This measure represents aspects of sensitization (Arendt-Nielsen et al., 2010). The tests were conducted localized in the most affected knee (index), adjacent to the knee (10 cm above the knee, ventral thigh), and extra-segmentally on the medial side of the forearm (muscle belly of flexor digitorum superficialis).

2.5.3 Conditioned pain modulation

Conditioned pain modulation was assessed using a novel bed-side method described in detail elsewhere (Larsen et al., 2019). The test stimulus was applied with a 6 kg standardized pressure algometer for 10 seconds to the mid part of the tibialis anterior muscle, contralateral to the index knee. Afterwards, the conditioning stimulus was applied using a clamp inducing a pressure of 1.3 kg and attached to the ipsilateral earlobe for 60 seconds. After the 60 seconds of conditioning stimulus, the test stimulus was re-applied for 10 seconds in a parallel design with the conditioning stimulus being applied simultaneously. The pain intensities of the test and conditioning stimuli were measured using a visual analog scale (VAS) anchored with "0: no pain" and "10: worst pain imaginable". The CPM was calculated as the difference in pain intensity between the pain ratings with and without conditioning stimuli. A positive difference indicated a facilitatory CPM response while a negative difference indicated an inhibitory CPM response (Yarnitsky et al., 2015). Facilitatory CPM represents aspects of impaired central pain inhibition (Arendt-Nielsen et al., 2010).

2.6 Physical performances

2.6.1 30-second chair stand test

From a sitting position, the patients stood up completely, fully extending hips and knees, and then sat back down with the bottom fully touching the seat. Arms were crossed and placed across the chest during the test. This was repeated for 30 seconds and the number of repetitions was registered (Dobson et al., 2013).

2.6.2 40-meter fast-paced walk test

The patients were asked to walk as quickly and as safely as possible, without running, along a 10-meter walkway and turn around a cone, return, and then repeat for a total distance of 40 meters. If needed, patients were allowed to use their regular walking aids, such as canes or a walker. The amount of time it took to complete the 40 meters was recorded (Dobson et al., 2013).

2.6.3 Stair climb test

A staircase with nine stairs was ascended and descended once, and the subjects were asked to conduct the test as safely as possible. The use of a handrail was permitted. The amount of

time it took to complete the ascending and descending of the stairs was recorded (Dobson et al., 2013).

2.7 Self-reported outcomes

The KOOS questionnaire covers five subscales: pain, symptoms, activities of daily living (ADL), sports/recreation, and quality of life (QOL). Each KOOS subscale consists of multiple items which are to be scored on a 5-point Likert scale from 0 (none) to 4 (extreme). The KOOS ranges from 0 (worst) to 100 (best) (Roos et al., 1998). Knee injury and Osteoarthritis Outcome Score is a patient self-reported outcome measure, which has been found valid and reliable during short-term and long-term follow-up in patients with TKA (Collins et al., 2011,Gandek and Ware, 2017). The KOOS subscales ADL and sport/recreation measuring self-reported physical function were used in the regression models.

2.8 Data analysis

Data were checked for normality by assessing the data frequency in histograms, QQ-plots, and Shapiro-Wilk tests. The majority of these tests found data to be normally distributed. Thus, data are presented as mean (SD) unless otherwise stated. Due to significant differences in BMI between groups, an ANCOVA test adjusting for BMI was applied for group comparisons for all continuous outcomes and the results are reported as both unadjusted and adjusted estimates. To enhance the interpretation and discussion of differences (Wasserstein et al., 2019), effect sizes were calculated as Hedges´ *g* for between-group differences. Effect sizes were interpreted as < 0.2 = "very small", 0.2 = "small", 0.5 = "medium", 0.8 = "large", 1.2 = "very large", and 2.0 = "huge" as suggested by Sawilowsky (Sawilowsky, 2009) and Cohen (Cohen, 1988).

Associations between objective physical performances (dependent variables) and clinical pain, quantitative sensory profiling, and self-reported function (independent variables) were analyzed separately for both groups using multivariate linear regression models based on the enter method with adjustment for age, BMI, and sex. Dependent variables were 30-second chair stand test, 40-meter fast-paced walk test, and stair climbing test. Independent variables were clinical pain, quantitative sensory profiling of mechanical pinprick pain sensitivity, TS, CPM, and the KOOS subscales ADL and sport/recreation. The β-coefficients indicate how strongly the independent variables influenced the dependent variable. The R^2 indicates the ratio of variability explained by the independent variable or the adjusted regression model.

The significance level was set to 0.05, and exact p-values and effect sizes are provided due to the explorative design of the study. All analyses were conducted with the use of the statistical software SPSS, Version 25.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1 Demographics

A significant difference was seen in BMI between the groups ($p = 0.007$), with higher BMI in the TKA group, whereas age and sex did not differ. On average, it was 11.1 years since the OA patients had been diagnosed with knee OA and 4 years since TKA patients had undergone TKA surgery (table 1).

**** Insert table 1 near here ****

3.2 Clinical pain and quantitative sensory profiling

Overall, similar pain and quantitative sensory profiling outcomes were observed in the groups with no significant differences (table 2). The clinical pain differed only marginally with a very small effect size of 0.06. Mechanical pinprick pain sensitivity exhibited differences of NRS of 0.3 (adjusted means) for both localized and extra-segmental sites with small effect sizes of 0.23 and 0.29, respectively. No differences between groups were observed for TS on neither localized nor extra-segmental sites with very small effect sizes of 0.00 and 0.09. No difference in CPM was observed between the groups with an effect size of 0.15. A similar distribution of facilitatory CPM responses was seen in the groups (OA group: 48% and TKA group: 46%). The conditioning stimulus pain intensity was VAS 6.7 (±2.6) in the knee OA group and 5.4 (±2.3) in the TKA group. None of the two groups exhibited a significant CPM effect (0.2 ±1.3, $p= 0.181$). However, when analyzing and ranking the individual data, the CPM showed a distribution (fig. 1) reflecting both facilitatory and inhibitory CPM responses.

**** Insert figure 1 near here ****

3.3 Physical performances

The outcomes concerning physical performances, revealed differences between groups for the 30-second chair stand test ($p = 0.015$), the 40-meter fast-paced walk test ($p = 0.081$), and the stair climb test ($p = 0.002$). The OA group performed more chair stand repetitions, walked 40-meter and climbed the stairs faster than the TKA group (table 2). Effect sizes were moderate to large with estimates of 0.74 for the 30-second chair stand test, 0.64 for the 40-meter fast-paced walk test, and 0.98 for the stair climb test.

3.4 Self-reported outcomes

For the self-reported functions, there was a tendency for the OA group to report higher KOOS values than the TKA group for the subscales pain, symptoms, ADL, and QOL with differences ranging from 0.5 to 5 points. Effect sizes were small with estimates of 0.21, 0.41, 0.21, and 0.31, respectively. For the KOOS subscale sport/recreation, a significant difference of 14.1 points (adjusted mean) was observed, with the OA group reporting the highest outcome ($p = 0.005$, table 2) with a moderate effect size of 0.73.

**** Insert table 2 near here ****

3.5 Associations

The results from the regression analysis are presented in table 3 and 4. In the OA group, KOOS sport/recreation and facilitatory CPM were significantly ($p= 0.032$ and $p= 0.043$, respectively) associated with the 30-second chair stand test (R^2: 0.094 and 0.088, respectively), whereas the mechanical pinprick pain sensitivity at the knee and extra-segmentally was significantly ($p= 0.035$ and 0.017, respectively) associated with the 30-second chair stand test (R^2: 0.169 and 0.137) in the TKA group. The remaining independent variables for the 30-second chair stand test had R^2 estimates ranging from 0.001 to 0.077 (table 3 and 4).

For the OA group, TS at the knee was a significant ($p= 0.031$) predictor for the 40-meter fast-paced walk test (R^2: 0.081). For the TKA group, KOOS subscales ADL and sport/recreation were significantly ($p= 0.012$ and $p= 0.026$, respectively) associated with the 40-meter fast-paced walk test (R^2: 0.210 and 0.172, respectively). The remaining independent variables for

the 40-meter fast-paced walk test had R^2 estimates ranging from 0.000 to 0.047 (table 3 and 4).

For the OA group, TS at the knee and facilitatory CPM were significantly (p= 0.007 and p= 0.029, respectively) associated with the stair climb test (R^2: 0.108 and 0.072, respectively, whereas in the TKA group, KOOS subscales ADL and sport/recreation were significantly (p= 0.017 and p= 0.001, respectively) associated with the stair climb test (R^2: 0.159 and 0.253, respectively). The remaining independent variables for the stair climb test had R^2 estimates ranging from 0.001 to 0.068 (table 3 and 4).

**** Insert table 3 near here ****

**** Insert table 4 near here ****

4. Discussion

The present study delineated that physical performances seems to be affected in patients with chronic pain after TKA compared with knee OA chronic pain patients. No differences between groups were found regarding clinical pain intensity and quantitative sensory profiling, which was contrary to our hypothesis expecting more pronounced signs of different sensitization parameters in the TKA patients. Knee injury and Osteoarthritis Outcome Score differed significantly for the sport/recreation subscale with higher scores indicating better sport/recreation performance in the OA group compared with the TKA group. The regression analysis revealed that self-reported function seems to be associated with physical performances in the TKA group. In the OA group, associations appear to exist between physical performances and signs of sensitization (TS) and facilitatory CPM.

4.1 Pain and quantitative sensory profiling

Overall, the pain and quantitative sensory profiling revealed similar traits between the groups. The profiles of the patients with chronic knee OA pain and the group with chronic pain after TKA were similar in terms of pain intensity, signs of sensitization (TS), localized and extra-segmental pinprick hyperalgesia, and distributions reflecting both facilitatory and inhibitory CPM responses. Between groups, no difference in clinical pain was observed, but after

adjustment for BMI the clinical pain was higher in the OA group compared with the TKA group with a very small effect size. This is in accordance with previous findings reporting higher BMI to be associated with persistent knee pain (van Tunen et al., 2018).

For the test of mechanical pinprick pain sensitivity at the knee and extra-segmentally, the OA patients had higher pain intensity ratings compared with the TKA patients, but the effect sizes were small. Thus, similar signs of pinprick hyperalgesia seem to be present in both groups. We expected the pain sensitization to be more pronounced in patients with chronic pain after TKA as this is often a sign of more complex pain manifestations (Skou et al., 2014). Both groups showed the same signs of sensitization evaluated as TS. Temporal summation is thought to reflect symptoms of central sensitization (O'Leary et al., 2018) and sensitization has been shown to be a common feature in both patients with painful knee OA and chronic pain after TKA (Skou et al., 2014,Arendt-Nielsen et al., 2010,Wright et al., 2015). Both the localized and extra-segmental tests were enhanced indicating sensitization and widespread pain in both groups.

Further, both groups showed similar signs of facilitatory CPM although a distribution reflecting both facilitatory and inhibitory CPM responses was observed in the study. Previous studies on healthy volunteers have shown that some subjects within this population respond more strongly than others to the CPM paradigm, but in general the averaged CPM effect is inhibitory in healthy volunteers (Oono et al., 2011). In the present OA/TKA patient study, the net CPM effect was close to zero, which is in agreement with other studies (Arendt-Nielsen et al., 2010). If such a distribution can be shown for other pain patient populations, it would be interesting to further investigate if the two groups have different pain trajectories and if these patients respond differently to physical or pharmacological intervention.

4.2 Physical performances

In the physical performance tests, the OA group performed better than the TKA group with medium-to-large effect sizes. Despite the explorative nature of the study, the considerable effect sizes indicate that physical performance seems to be impaired in TKA patients compared with OA patients. It is unknown if these physical performance deficits were present before the joint replacement surgery or have occurred after the TKA, but studies have shown that the level of physical activity is affected after TKA (Groen et al., 2012). Groen and colleagues found that 12 months after TKA 49% of patients did not meet the general health recommendations of being physically active at moderate intensity for 30 minutes at least 5

days per week. This further underlines the importance of supporting physical activity after surgery. As similar pain and quantitative sensory profiles were observed in the groups, this could suggest that the differences in physical performance might not be due to pain sensitization. Obesity is associated with physical inactivity (Gray et al., 2018) and therefore the presence of a higher BMI in the TKA group could be associated with a less active lifestyle.

4.3 Self-reported outcomes

The KOOS showed a tendency towards higher scores in the OA group for all subscales with small-to-moderate effect sizes observed. The subscale sport/recreation yielded the largest difference between groups with an adjusted difference of 14.1 points. This difference could be considered clinically relevant (Roos and Lohmander, 2003) although threshold values for clinical relevance remain debatable due to lack of golden standards (Lyman et al., 2018). However, it indicates that self-reported sport/recreation is particularly experienced as very challenging in the group of TKA patients with chronic pain. The remaining sub-scales indicate better self-reported pain, symptoms, ADL, and quality of life in the OA group compared with the TKA group. However, effect sizes were small and differences were smaller than what could be considered clinically relevant.

4.4 Associations

In the present study, we observed a significant association between physical performance outcomes and signs of sensitization (TS) in the OA group. The findings indicate that high TS was associated with poor physical performances in the OA group. This is in line with results from previous studies; Guerard et al. observed an association between sensitization and poor performance for the stair climb test in OA patients (Guerard et al., 2020) and Echeita et al. observed an association between lifting capacity (box lifting) and sensitization in patients with low back pain (Echeita et al., 2020). The observed associations were based on the localized (index knee) measurements and not on the extra-segmental measurements. This could indicate that primary hyperalgesia and peripheral sensitization were more potent than central sensitization. Contrary to the TS findings, facilitatory CPM was associated with better physical performance. This unexpected finding should be interpreted with caution since no overall averaged CPM effect was observed in the study. The patients exhibited facilitatory or inhibitory CPM responses underlining that CPM varies in chronic pain populations (Potvin and Marchand, 2016).

For the TKA group, we observed associations between self-reported function and physical performances. These findings indicate that the worse self-reported function, the worse the objective physical performances. This might emphasize that other mechanisms besides sensitization may be important for the physical performances after TKA. Fear-avoidance behavior, catastrophizing, anxiety, depression, comorbidities, and poor pain coping have been shown to contribute to chronic pain (Borsook et al., 2018,Schug and Bruce, 2017), thereby potentially impacting the physical performances. These features should be studied in more detail to develop better management strategies for this vulnerable group of patients with chronic pain. An association between increased pain rating during assessment of the mechanical pinprick pain sensitivity, measured both localized and extra-segmentally, and poor performance in the 30-second chair stand test was observed. However, this was not observed for the other physical performance outcomes. This suggests that some of the quantitative sensory profiling tests were associated with one type of physical performance, but appeared not to be related to other types of physical performance. This explorative finding will require further validation in other chronic knee pain populations using larger sample sizes.

In both groups, the adjusted variables, i.e., age, BMI, and sex, explained more variation than the self-reported functions, clinical pain, or quantitative sensory profiling. A similar finding was recently described by Burgess et al. (Burgess et al., 2020), underlining age and BMI as strong predictors for functional outcome in musculoskeletal disorders, including OA and TKA. Further, observations by Gay et al. (Gay et al., 2019) found that the level of physical activity was associated with sex and BMI but not with pain in knee OA patients.

4.5 Limitations

Pain during the physical performance tests was not assessed. The difference in sample sizes has most likely affected the ability to detect differences among groups and to establish relationships among the parameters. In the present study, we could not retrieve data on the time since knee OA diagnosis in the TKA group and further we did not have retrospective data on the pain intensity prior to surgery. Both parameters are assumed to have an impact on the central processing of pain and hence the sensitization processes (Arendt-Nielsen et al., 2015,Schug and Bruce, 2017). It has also been shown that psychological factors, such as pain catastrophizing, anxiety, and depression can influence chronic pain in patients with knee OA or chronic pain after TKA (Belford et al., 2020,Helminen et al., 2020). In the present study

focusing on physical performances and pain mechanisms, no psychological measurements were included, and therefore we cannot infer the potential influence of these parameters on the outcomes. Differences in outcomes of TS and CPM have been observed depending on the methodology, e.g. type of stimuli to assess TS and CPM (Horn-Hofmann et al., 2018,Vaegter et al., 2018,Kennedy et al., 2016), which calls for caution when interpreting our findings.. Further, since no control condition was used, it is unclear whether the increased or decreased ratings in the CPM paradigm reflect indeed inhibitory and facilitatory responses or whether these are random variations in pain ratings. Thus, the CPM findings should be interpreted with caution.

5. Conclusion

In this explorative study, we observed similar profiles for the OA and TKA groups regarding clinical pain and quantitative sensory profiling. Lower physical performances were observed in patients with chronic pain after TKA compared with patients with chronic knee OA pain suggesting that activities of daily living (chair rises, walking, and stair-climbing) could be more affected in the TKA group. In line with the levels of physical performances, a tendency towards lower scores for the self-reported outcomes was observed for the TKA patients.

In the OA group, an association was shown between physical performances and quantitative sensory profiling parameters representing sensitization (TS) indicating that increased TS is associated with poor physical performances. On the contrary, an association was observed between facilitatory CPM and improved physical performance.

The findings emphasize the importance of investigating the interaction between motor functions and pain sensitization mechanisms. These different relationships underline that pain mechanisms influence the physical performances to different extents, i.e. depending on the type of ADL. For the TKA group, associations were observed between objectively measured physical performances and the self-reported function. These results most likely indicate that thorough examination of physical performances remains of high importance for the exercising and rehabilitation of patients with chronic pain after TKA.

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Author contributions:

JBL, LAN, OS and PM made substantial contributions to the conception and design of the study. JBL conducted the data collection and the data analysis. All authors have read, provided critical feedback on the intellectual content, and approved the final manuscript. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure legends

Figure 1: All patients ranked on basis of the conditioned pain modulation effect

Table legends

Table 1: Patient characteristics. Values are mean (SD) unless otherwise stated.

Table 2: Results from clinical pain, quantitative sensory profiling, physical performances, and self-reported outcomes.

Table 3: Associations between objective physical performances, self-reported function, clinical pain, and quantitative sensory profiling for the osteoarthritis group.

Table 4: Associations between objective physical performances, self-reported function, clinical pain and quantitative sensory profiling for the total knee arthroplasty group.

Mean	Osteoarthritis (n: 46)	Total knee arthroplasty (n: 24)
Age (years)	66.4 (8.2)	66.5 (7.2)
BMI (kg/m^2)	28.0 (3.7)	30.8 (4.5)*
Sex (females, %)	19 (41 %)	15 (63 %)
Time since knee osteoarthritis diagnosis (years)[a]	11.1 (7.6)	NA
Time since surgery (years)[b]	NA	4.0 (1.9)

BMI: Body Mass Index. NA: Not applicable. [a] Time since osteoarthritis diagnosis is the period from being diagnosed with knee osteoarthritis to the date of measurement. [b] Time since surgery is the period from the date of total knee arthroplasty surgery to the date of measurement.

* P-value = 0.007 between groups.

	Unadjusted means (SD)		Adjusted means (SE)§		
	Osteoarthritis (n: 46)	Total knee arthroplasty (n: 24)	Osteoarthritis (n: 46)	Total knee arthroplasty (n: 24)	P-value for adjusted differences
Pain intensities					
Clinical pain (NRS)	5.2 (1.8)	5.3 (1.7)	5.3 (0.3)	5.0 (0.4)	0.589
Mechanical pinprick Pain sensitivity index knee (NRS)	1.4 (1.9)	1.0 (1.4)	1.4 (0.3)	1.1 (0.4)	0.552
Mechanical pinprick Pain sensitivity extra-segmental (NRS)	1.2 (1.5)	0.8 (1.1)	1.2 (0.2)	0.9 (0.3)	0.412
Temporal summation index knee (NRS)	1.6 (1.4)	1.6 (1.9)	1.6 (0.2)	1.6 (0.3)	0.949
Temporal summation extra-segmental (NRS)	1.1 (1.1)	1.2 (1.1)	1.1 (0.2)	1.1 (0.2)	0.974
Conditioned pain modulation[a] (VAS)	0.3 (1.1)	0.1 (1.6)	0.2 (0.2)	0.2 (0.3)	0.828
Physical performances					
30-second chair stand test (repetitions)	11.2 (2.2)	9.5 (2.5)	11.2 (0.34)	9.7 (0.48)	0.015
40-meter fast-paced walk test (seconds)	29.0 (5.3)	32.4 (5.8)	29.3 (0.8)	31.8 (1.1)	0.081
Stair climb test (seconds)	10.8 (3.2)	14.6 (4.9)	11.0 (0.6)	14.2 (0.8)	0.002
Self-reported outcomes					
KOOS pain	59.7 (16.8)	56.3 (15.9)	59.2 (2.5)	57.2 (3.5)	0.653
KOOS symptoms	54.3 (14.2)	48.5 (15.1)	53.6 (2.2)	49.7 (3.0)	0.311
KOOS ADL	62.8 (14.0)	59.7 (16.6)	61.9 (2.2)	61.4 (3.1)	0.898
KOOS sport/recreation	26.1 (20.7)	12.7 (12.2)	26.3 (2.8)	12.2 (3.9)	0.005
KOOS quality of life	39.6 (15.1)	34.3 (14.8)	39.7 (2.3)	34.9 (3.2)	0.171

§ Estimates are adjusted for body mass index. SD: Standard deviation. SE: Standard error. NRS: Numerical rating scale. VAS: Visual analog scale. KOOS: Knee injury and Osteoarthritis Outcome Score. ADL: Activities of daily living.

[a] Positive values indicate facilitatory conditioned pain modulation.

Dependent variables	Independent variables	β	95% CI	R^2 change	R^2 for all independent variables
30-second chair stand test[a]	KOOS ADL	0.017	-0.034 to 0.067	0.009	0.048
	KOOS sport/recreation	0.035*	0.003 to 0.067	0.094	0.140
	Clinical pain	-0.149	-0.518 to 0.220	0.014	0.052
	MPPS knee	-0.338	-0.684 to 0.007	0.076	0.121
	MPPS extra-segmental	-0.185	-0.665 to 0.295	0.013	0.051
	TS knee	-0.428	-0.865 to 0.008	0.077	0.121
	TS extra-segmental	-0.566	-1.157 to 0.025	0.073	0.118
	Facilitatory CPM	0.651*	1.279 to 0.022	0.088	0.120
40-meter fast-paced walk test[a]	KOOS ADL	-0.072	-0.183 to 0.039	0.030	0.215
	KOOS sport/recreation	-0.026	-0.101 to 0.050	0.008	0.191
	Clinical pain	0.541	-0.275 to 1.358	0.031	0.216
	MPPS knee	0.173	-0.637 to 0.982	0.003	0.185
	MPPS extra-segmental	0.089	-0.995 to 1.173	0.000	0.182
	TS knee	1.072*	-0.104 to -2.041	0.081	0.271
	TS extra-segmental	0.792	-0.571 to 2.155	0.024	0.208
	Facilitatory CPM	-1.124	-2.562 to 0.314	0.043	0.240
Stair climb test[a]	KOOS ADL	-0.038	-0.102 to 0.026	0.022	0.316
	KOOS sport/recreation	-0.039	-0.081 to 0.002	0.053	0.350
	Clinical pain	0.290	-0.177 to 0.758	0.024	0.318
	MPPS knee	-0.058	-0.521 to 0.405	0.001	0.293
	MPPS extra-segmental	0.063	-0.555 to 0.682	0.001	0.292
	TS knee	0.758*	-0.223 to -1.292	0.108	0.409
	TS extra-segmental	0.466	-0.311 to 1.243	0.022	0.316
	Facilitatory CPM	-0.892*	-1.686 to -0.098	0.072	0.385

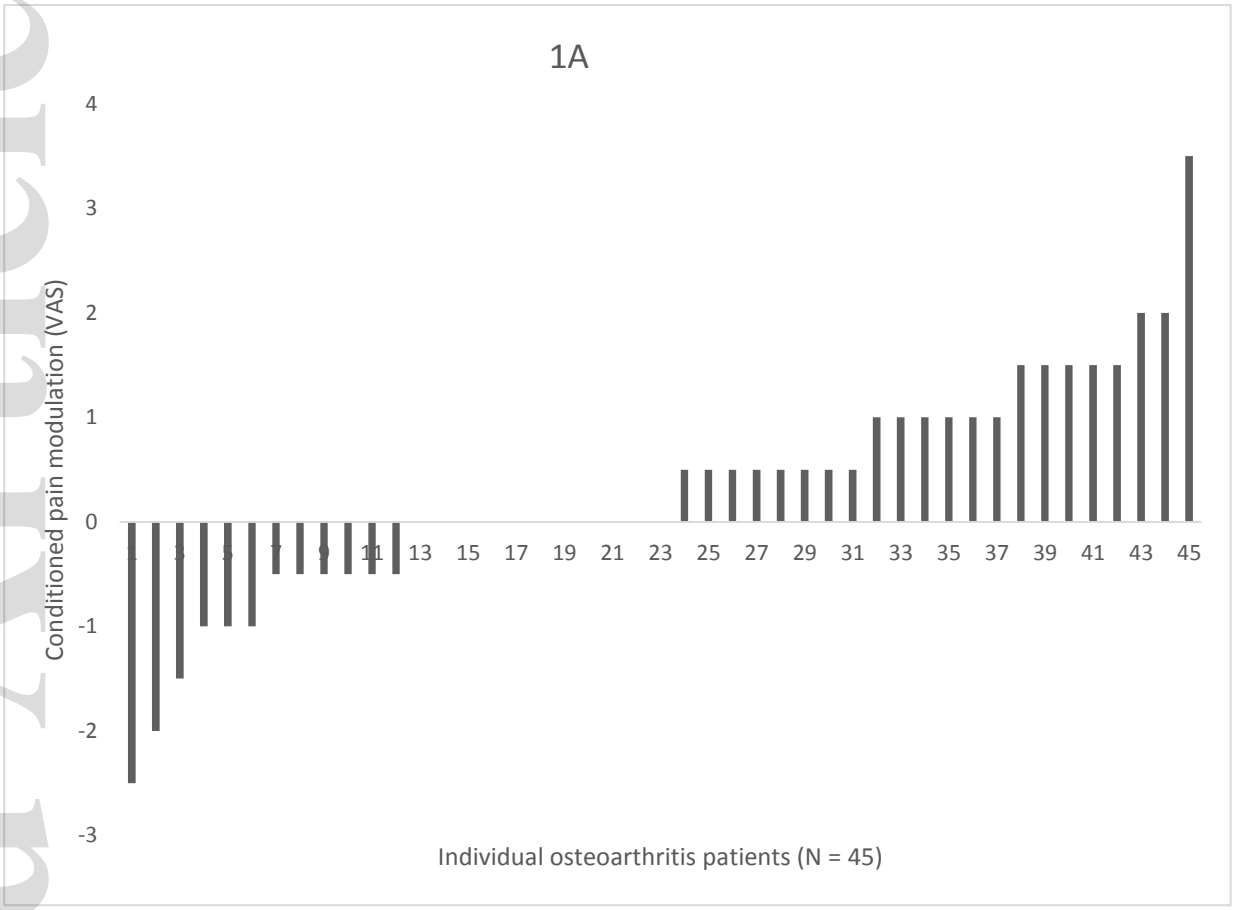
[a] Statistical analysis adjusted for age, body mass index, and sex. KOOS: Knee injury and Osteoarthritis Outcome Score.

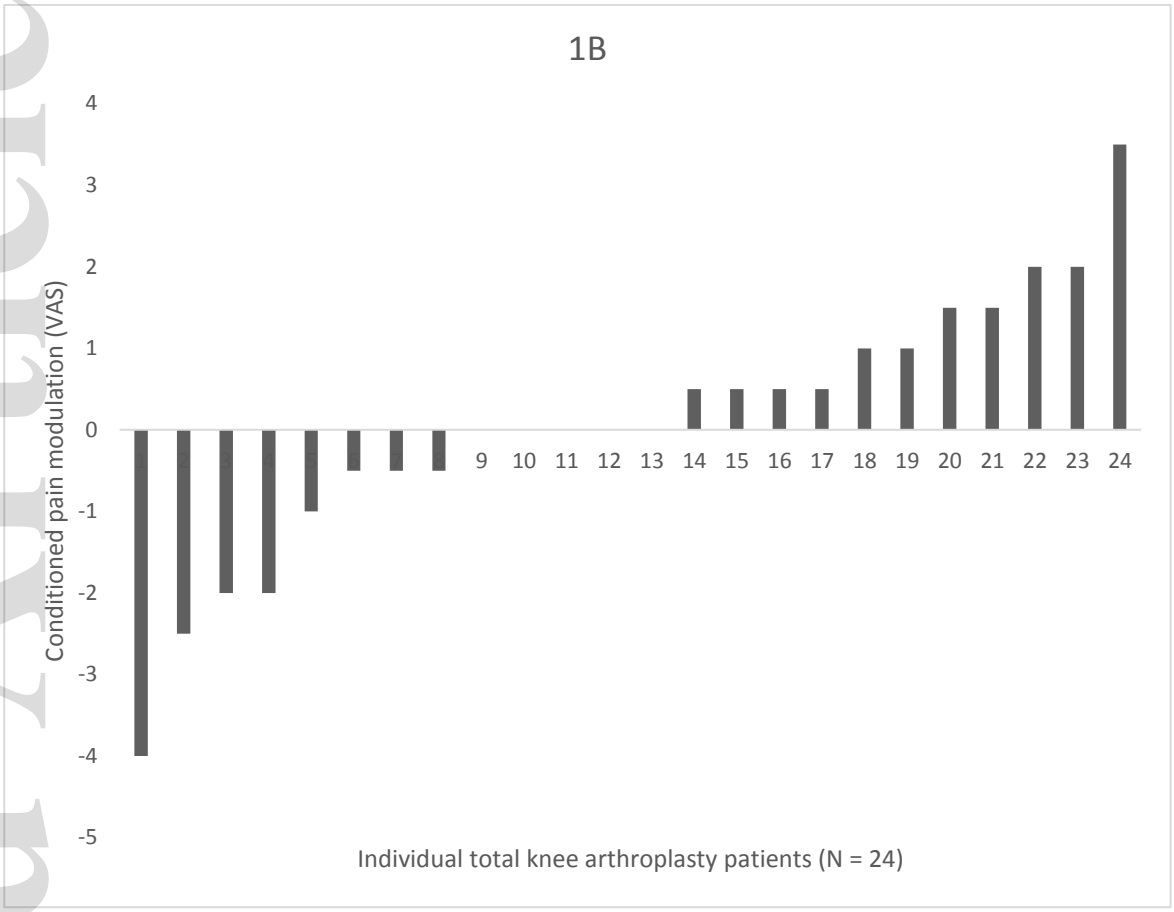
ADL: Activities of daily living. MPPS: Mechanical pinprick pain sensitivity. TS: Temporal summation. CPM: Conditioned pain modulation. * Significant associations (p-value <0.05).

Dependent variables	Independent variables	β	95% CI	R^2 change	R^2 for all independent variables
30-second chair stand test[a]	KOOS ADL	0.039	-0.021 to 0.099	0.056	0.294
	KOOS sport/recreation	0.033	-0.046 to 0.112	0.024	0.255
	Clinical pain	-0.380	-0.953 to 0.193	0.059	0.297
	MPPS knee	-0.717*	-1.377 to -0.057	0.137	0.391
	MPPS extra-segmental	-1.072*	-1.931 to -0.212	0.169	0.430
	TS knee	-0.281	-0.791 to 0.228	0.042	0.277
	TS extra-segmental	-0.080	-1.245 to 1.086	0.001	0.227
	Facilitatory CPM	-0.050	-0.767 to 0.668	0.001	0.227
40-meter fast-paced walk test[a]	KOOS ADL	-0.175*	-0.308 to -0.043	0.210	0.370
	KOOS sport/recreation	-0.202*	-0.378 to -0.027	0.172	0.323
	Clinical pain	0.673	-0.784 to 2.130	0.034	0.156
	MPPS knee	0.492	-1.341 to 2.325	0.012	0.129
	MPPS extra-segmental	-0.115	-2.602 to 2.371	0.000	0.115
	TS knee	0.689	-0.578 to 1.956	0.047	0.171
	TS extra-segmental	-0.419	-3.308 to 2.471	0.004	0.119
	Facilitatory CPM	1.082	-0.624 to 2.788	0.062	0.190
Stair climbing test[a]	KOOS ADL	-0.109*	-0.232 to -0.026	0.159	0.470
	KOOS sport/recreation	-0.208*	-0.325 to -0.092	0.253	0.584
	Clinical pain	0.804	-0.272 to 1.880	0.068	0.360
	MPPS knee	0.322	-1.085 to 1.729	0.007	0.286
	MPPS extra-segmental	0.606	-1.276 to 2.489	0.014	0.295
	TS knee	-0.279	-1.273 to 0.715	0.011	0.291
	TS extra-segmental	-0.105	-2.323 to 2.113	0.000	0.278
	Facilitatory CPM	-0.134	-1.498 to 1.230	0.001	0.279

[a] Statistical analysis adjusted for age, body mass index and sex. KOOS: Knee injury and Osteoarthritis Outcome Score.

ADL: Activities of daily living. MPPS: Mechanical pinprick pain sensitivity. TS: Temporal summation. CPM: Conditioned pain modulation. * Significant associations (p-value <0.05).





VAS: Visual analog scale. Data are missing from one osteoarthritis patient due to unbearable pain during conditioned pain modulation (CPM) test, which led to termination of the test. Positive values indicate facilitatory CPM and negative values indicate inhibitory CPM. A score of 0 indicates no difference in pain ratings with or without conditioning stimulus. 1A: Osteoarthritis patients. 1B: Total knee arthroplasty patients.