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Pain and Sensitisation after Total Knee Replacement or Non-Surgical Treatment in Patients with Knee Osteoarthritis: Identifying Potential Predictors of Outcome at 12 Months

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Predicting outcome after TKR and non-surgical treatment

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None

Significance:
Human experimental pain assessment was used to assess the degree of pain sensitisation in patients with painful knee osteoarthritis. High sensitisation before total knee replacement predicted worse outcome. Outcome after non-surgical interventions could not be predicted.

Abstract

Background: This study is a secondary analysis of 12-month follow-ups from two parallel, randomised controlled trials (RCT) in painful knee osteoarthritis patients. RCT1: Total knee replacement (TKR) followed by non-surgical treatment compared with non-surgical treatment. RCT2: Non-surgical treatment compared with usual care.

The aims were to investigate 1) possible predictors of treatment outcome after TKR and non-surgical interventions at 12 months, 2) associations between pain intensity and pressure pain thresholds (PPTs) (pain sensitisation) at baseline and after 12 months, and 3) possible gender differences.

Method: Each RCT included 100 patients. Pain intensities, PPTs, and number of painful sites were assessed at baseline and after 12 months.

Results: In all groups pain improved and pain sensitisation decreased. In RCT1, the TKR group had the greatest improvements in pain. In RCT2 the non-surgical group had the greatest improvement, with no between-group differences in PPTs. Lower PPTs at baseline predicted higher pain after TKR. Baseline pain intensity and PPT levels were associated with the number of painful sites. Subjects with the highest pain and lowest PPTs at baseline showed the largest relative improvement in pain and sensitisation but were still experiencing highest absolute pain and lowest PPTs after 12 months (combined cohorts).

Conclusion: Low PPTs at baseline predicted worse pain outcome after TKR, but did not predict outcome after non-surgical interventions. The number of painful sites was weakly associated with pain and PPTs, and the higher pain/lower PPTs, the higher pain/lower PPTs at 12 months with females showing the lowest PPT values.

Registration: ClinicalTrials.gov (NCT01410409 and NCT01535001).

Introduction

Recent projections estimate a six- to seven-fold increase in total knee replacements (TKRs) by 2030 (Kurtz et al., 2007) in patients with osteoarthritis (OA). While most patients experience pain relief after TKR, approx. 20% of the patients do not improve or are doing worse compared with before surgery (Beswick et al., 2012). However, this prevalence depends on the duration after TKR (e.g. 6 or 12 months).

This calls for a research focus on the selection of the right patients for TKR, i.e. those who will benefit the most, and on the criteria that may aid in selecting the optimal combination of non-surgical treatments. Recently, mechanistic biomarkers have been used as pain assessment tools to evaluate patients at risk of developing continued post-operative pain after an otherwise successful joint replacement (Arendt-Nielsen, 2017). Few formal predictive tools are available to determine good or poor responders to TKR (Dowsey et al., 2014). Therefore, comprehensive sensory testing platforms are needed for more mechanistic profiling (Arendt-Nielsen et al., 2015a).

A study by Wylde et al. (Wylde et al., 2015) showed an association of pressure pain thresholds (PPTs) (assessed from a site (arm) extrasegmentally to the affected knee) with higher pain severity 12 months after hip replacement. However, despite the association between PPTs and pain severity, preoperative PPTs did not predict the efficacy of joint replacement in providing pain relief. Therefore, assessing PPT from further locations could provide a more complete pain profile (compared with other studies using a sole measure of PPT at the arm as an indicator of widespread sensitization). So far no studies have investigated if the degree of pain sensitisation (assessed by PPTs from different sites) can predict the effect of non-surgical interventions compared with TKR in a cohort of similar patients.

As an alternative to TKR due to the high prevalence of chronic postoperative pain, the role of non-surgical procedures, e.g. comprehensive exercise programs, has attracted increased interest (Skou et al., 2015b). Exercise-induced analgesia has been specifically investigated in patients with OA, but without significantly positive effect on the pain sensitisation (Kosek et al., 2013). However, it may be one contributing factor to the modulation of clinical pain in general (Skou et al., 2016c). The fundamental aspects of exercise-induced analgesia have been studied intensively and some of the involved central pathways identified (Lima et al., 2017). In patients with OA, exercise has been shown to reduce pain sensitivity (increased PPTs) (Burrows et al., 2014). This has been associated with beneficial clinical effects in some studies (Henriksen et al., 2014), but not in others (Kosek et al., 2013). Currently, no studies have identified predictors of outcome after exercise in OA patients.

The aims of this study were to investigate: 1) possible predictors of treatment outcome after both TKR and non-surgical interventions at 12 months, 2) associations between pain intensity and PPTs (surrogate for pain sensitisation) at baseline and after 12 months and compare between the two groups, and 3) possible gender differences in predictors and associations.

Methods

Study Design
This was an ancillary analysis of predictors of the 12-month results from two two-arm parallel group assessor-blinded randomised controlled trials (RCTs) conforming to the CONSORT statement for reporting RCTs (Moher et al., 2010) and the STROBE statement for reporting observational studies (von Elm et al., 2007). The analyses of the change in outcomes from baseline to 12 months were pre-

defined in the statistical analysis plans, which were made available before any analyses commenced (Skou et al., 2014b; Skou et al., 2014c).

All details of the recruitment process, full eligibility criteria, the process of randomisation, study flow, allocation concealment, and detailed description of the interventions were published in the study protocols (Skou et al., 2012a; Skou et al., 2012b) and two papers (Skou et al., 2015a; Skou et al., 2015b).

Subjects

Subjects were recruited via the Department of Orthopaedics in the Northern Denmark Region, Denmark, between September 2011 and December 2013. Data from the 200 patients with symptomatic knee OA considered eligible (N=100) (Skou et al., 2015b) or not eligible (N=100) (Skou et al., 2015a) for TKR were included in the analyses.

The two RCTs (Skou et al., 2015a; Skou et al., 2015b) had the following shared inclusion criterion: aged≥18 years. Further, the following major, shared exclusion criteria applied: 1) mean pain the previous week >60 mm on a 100 mm visual analogue scale (VAS) and 2) previous knee replacement in the same side. When the studies were initiated, the surgeons found it unethical not to offer surgery to patients with pain above 60 mm on a 0-100 VAS.

The first RCT (Skou et al., 2015b) had two additional inclusion criteria: 1) considered eligible for TKR by the orthopaedic surgeon (decision among other factors typically based on pain, function, and radiographic severity (Carr et al., 2012)) and 2) diagnosed with radiographic knee OA (Kellgren-Lawrence (K&L) score≥2 on the original scale (Schiphof et al., 2011)). Further, the study had one major additional exclusion criterion: a need for bilateral simultaneous TKR.

The second RCT (Skou et al., 2015a) had two additional inclusion criteria: 1) considered not eligible for TKR by the orthopaedic surgeon and 2) diagnosed with knee OA with a K&L score≥1 on the original scale (Schiphof et al., 2011). Further, RCT2 had one major additional exclusion criterion: 1) scores higher than 75 on a 0-100 worst to best scale in the self-report questionnaire Knee Injury and Osteoarthritis Outcome Score ($KOOS_4$) defined as the average score for the subscale scores for pain, symptoms, activities of daily living (ADL), and quality of life (QOL) (Collins et al., 2016).

The subjects of the two RCTs were of similar age and reported similar baseline pain levels (Skou et al., 2016a). The major differences were the radiographic OA severity, functional limitations, and whether they were eligible for TKR or not (Skou et al., 2016a).

The local North Denmark Region Committee on Health Research Ethics (N-20110024 and N-20110085) provided ethical approvals for both studies, the participants gave informed consent to participate, and the studies were conducted in accordance with the Helsinki Declaration. The studies were registered at ClinicalTrials.gov (NCT01410409 and NCT01535001).

Interventions

The first RCT randomised to TKR followed by non-surgical treatment or non-surgical treatment alone (Skou et al., 2015b) while the second RCT randomised to non-surgical treatment or usual care (Skou et al., 2015a). The non-surgical treatment of the two RCTs was the same.

Total Knee Replacement
Subjects randomised to TKR followed by non-surgical treatment had a totally cemented prosthesis with patellar resurfacing (NexGen, CR-Flex, fixed bearing or LPS-Flex, fixed bearing, Zimmer, Warsaw, Indiana, USA) using standard surgical methods (Endres, 2011).

Non-surgical Treatment
The 3-month non-surgical treatment included education, exercise, and insoles while weight loss and/or pain medication were prescribed if indicated. Physiotherapists and dieticians gave the treatments at Aalborg University Hospital, Denmark. The selection of procedures and interventions were composed based on clinical experience and practice. Hence, it is not possible to judge the relative contributions from the individual procedures/interventions.

Education
The education comprised two 60-min sessions engaging the subjects and focusing on disease characteristics, OA pain, and how to control and monitor the pain during exercise, advice on treatment, and help to self-help.

Exercise
The NEuroMuscular EXercise training program (NEMEX), previously found feasible in patients with moderate to severe OA (Ageberg et al., 2010b), was delivered under supervision twice weekly with each session lasting 60 min. The program is based on neuromuscular and biomechanical principles and has different difficulty levels for each individual exercise (Ageberg et al., 2010b). The exercise program was followed by a transition period of eight weeks to gradually accustom the subjects to continue exercising after termination of the supervised program.

Dietary Advice
Subjects with a body mass index (BMI) ≥25 at baseline underwent a dietary weight loss program based on principles from motivational interviewing (Miller and Rollnik, 2002) consisting of four 60-min sessions aiming at reducing the body weight by at least 5% (Christensen et al., 2007).

Insoles
The subjects received individually fitted full-length Formthotics Original Dual Medium (perforated) insoles with medial arch support (Foot Science International, Christchurch, New Zealand). The subjects were tested with the valid and reliable Single Limb Mini Squat Test (Ageberg et al., 2010a). A 4° lateral wedge was added to the insoles of the subjects with a knee-lateral-to-foot position in the test (the knee moves over or lateral to the 5th toe in three or more of five trials).

Pain Medication
Paracetamol 1 g four times daily, ibuprofen 400 mg three times daily, and pantoprazole 20 mg daily were prescribed by the treating orthopaedic surgeon if indicated. The prescription was reassessed every three weeks to assess whether continuation was needed to control the pain.

Usual Care

The subjects in the usual care group were given two standardised information leaflets: One with information on knee OA with regard to etiology, symptoms, common functional limitations, recommended treatments, and general advice on how to address the symptoms and a second leaflet with information as to where to seek advice in The North Denmark Region regarding treatment and how to achieve a healthy lifestyle.

Outcomes

Baseline and 12-month follow-up were carried out at the Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital, Denmark. The assessor was not affiliated with the treatment sites and was specifically trained in all aspects of the assessments. The assessor was blinded to the treatment allocation by instructing the subjects in the first RCT (Skou et al., 2015b) to cover the study knee with three layers of white elastic tape covering a potential scar after surgery before meeting with the assessor.

Assessment of Pain Intensity

Peak pain intensity in the most affected knee during the previous 24 h assessed on a 100 mm VAS with terminal descriptors of 'no pain' and 'worst pain possible' was chosen since it has been frequently applied in studies on sensitisation in knee OA-related pain (Arendt-Nielsen et al., 2010; Skou et al., 2013a; Skou et al., 2014a). The VAS is a pain measure widely used which is valid, reliable, and responsive (Hawker et al., 2011). A VAS of 0-4 mm can be considered equivalent to no pain (Jensen et al., 2003). This limit was used to evaluate how many of the patients in each group that did not have knee pain at the 12-month follow-up.

The knee pain intensity after 30 min of walking assessed on a 100 mm VAS with terminal descriptors of 'no pain' and 'worst pain possible' was included as an indirect measure of how knee pain affects function.

Assessment of Sensitisation

Bilateral PPTs were obtained using a handheld algometer with a 1 cm^2 probe (Algometer Type II, Somedic AB, Hoerby, Sweden). The pressure was applied perpendicularly to the skin at a constant rate of 30 kPa/s and was increased until the subject felt a shift of the pressure into pain. At this shift in perception, the subject was informed to press a button, and the pressure value was stored defining the PPT in kPa. A previous assessment of the test procedure in a test-retest reliability and agreement study with 20 patients with knee OA demonstrated intra-class correlation coefficients and 95 % Limits of Agreement (LoA) (95% LoA; the difference between the mean difference and the upper and lower LoA) ranging from 0.84 to 0.91 and from 199.6 to 434.0 kPa for the different sites (Skou et al., 2015c). The 95% LoA corresponds to the minimal detectable change (MDC) for the assessment method.

PPTs from four sites on the knee and one on the lower leg were used: 1) 3 cm medial to the midpoint of the medial edge of patella, 2) 2 cm proximal to the midpoint of the superior edge of patella, 3) 3 cm lateral to the midpoint of the lateral edge of patella, 4) at the centre of patella, and 5) lower leg (at the tibialis anterior muscle 5 cm distal to the tibial tuberosity) (Arendt-Nielsen et al.,

2010). PPTs were obtained twice at each site, and the means of all five sites from the most affected and contralateral lower extremity (as defined by the subject at baseline) were calculated as aggregated PPT values and used in the analyses.

Spreading of Pain

The subjects shaded body sites with pain in the previous 24 hours on a region-divided body chart (26 sites in total) at baseline and at the 12-month follow-up. The total number of pain sites was used to quantify the spreading of pain (Coggon et al., 2013).

Statistical Analysis

Sample Size

The sample size for the two respective RCTs was powered based on the primary outcome $KOOS_4$, with scores ranging from 0 (worst) to 100 (best) (Roos et al., 1998; Roos and Toksvig-Larsen, 2003). The sample size needed to detect a 10-point difference (with a standard deviation of 14) between groups in $KOOS_4$ was 41 subjects in each group (power of 90 % and a significance level of 0.05). To account for crossovers to TKR and for missing data, the dropout rate was set to 20%, and a total of 100 patients were randomised in both studies. In this pre-specified ancillary analysis, we were interested in exploring pain and PPTs 12 months after: 1) TKR followed by non-surgical treatment, 2) non-surgical treatments alone, and 3) usual care.

Ancillary Analyses

The analyses of peak pain intensity, pain intensity after 30 min, PPTs from the most affected extremity and PPTs from the contralateral extremity were conducted using a mixed-effects model (including all available data points in an intention-to-treat analysis) with subject as a random effect and time (baseline, 12 months) and group (TKR+non-surgical, non-surgical OR non-surgical, usual care) as fixed effects. Interaction between time and group was also included in the model. The analyses were adjusted for baseline scores, gender, age, and BMI. The analyses of spreading of pain were conducted using Wilcoxon Signed-Rank Test (paired data) and Mann-Whitney U test (unpaired data) as the count data were not normally distributed.

Furthermore, the subjects from both RCTs were combined, re-grouped, and analysed crudely and adjusted using the same procedure as above according to the treatment which they actually received. Subjects undergoing TKR during the 12-month follow-up were analysed in a TKR group while subjects attending at least 75% of the supervised exercise sessions (≥18 of 24 sessions) without undergoing TKR were analysed in a non-surgical group. The subjects in the usual care group and the subjects in the non-surgical groups attending less than 75% of the supervised exercise sessions without undergoing TKR were not included in this secondary analysis. The cut-off of 75% was chosen to ensure that the patients had the possibility to improve from the non-surgical treatment as the results from a meta-analysis suggested that more supervised exercise sessions would result in a larger effect than fewer supervised exercise sessions (Juhl et al., 2014). Linear

regression was applied to identify predictors of improvements in the outcomes of the group undergoing TKR during the 12 months and in the group attending at least 75% of the supervised exercise sessions without undergoing TKR, respectively. The regression analyses were adjusted for gender, age, and BMI.

Finally, correlations between the outcomes and change in each individual outcome were assessed with Pearson's Product-Moment Correlation for the two RCTs combined.

As endorsed by The European Agency for the Evaluation of Medicinal Products, no adjustments for multiplicity were conducted as this was an ancillary analysis declared as supportive of the primary reports from the two RCTs (The European Agency for the Evaluation of Medicinal Products, 2002).

The results are presented as means with 95% confidence intervals (CI). The significance level was set at $P < 0.05$, and all analyses were performed in IBM SPSS Statistics for Windows (Version 24.0, IBM Corporation, Armonk, NY, USA).

Results

Subject characteristics as well as baseline and 12-months data for the outcomes are presented in table 1.

RCT of TKR in addition to non-surgical treatment cohort: A total of 1475 patients seen in secondary care by orthopaedic surgeons were assessed for eligibility of which 1348 were ineligible, and 27 did not want to participate. One hundred subjects were randomised, with 46/50 (one subject did not undergo TKR) in the TKR + non-surgical group and 49/50 (13 subjects underwent TKR during follow-up) in the non-surgical group completing both baseline and 12-month follow-up (Figure 1A).

RCT of non-surgical treatment vs. usual care cohort: A total of 654 patients seen in secondary care by orthopaedic surgeons were assessed for eligibility of which 553 were ineligible, and one was not willing to undergo randomisation. One hundred subjects were randomised with 47/50 (three subjects underwent TKR during follow-up) in the non-surgical group and 44/50 (five subjects underwent TKR during follow-up) in the usual care group completing both baseline and 12-month follow-up (Figure 1B).

Predictors of Pain Outcomes and Gender Differences

In TKR subjects (N=70), aggregated PPTs at the affected limb (R^2=0.110) and at the contralateral limb (R^2=0.09) predicted a change from baseline to 12 months in pain intensity after walking ($P < 0.05$) (lower PPTs were associated with less pain improvement) while PPTs did not predict the pain outcome from non-surgical treatment (N=49; $P > 0.05$). Baseline measures of all outcomes predicted their own change from baseline to 12 months in both cohorts (R^2=0.141-0.496; $P < 0.05$) (table 2).

Males had mean baseline PPTs of 776-857 kPa while females had 408-464 kPa. The corresponding PPTs were 877-947 kPa and 545-576 kPa at 12-months ($P < 0.001$), respectively.

Although low baseline PPTs were associated with more PPT increases after treatment, the subjects (both cohorts) with low baseline PPTs still had the lowest 12-month PPTs for both the most affected side (r =0.73, $P < 0.001$, figure 2A) and for the contralateral side (r =0.73; $P < 0.001$; figure 2B). Furthermore, women had lower PPTs (both the most affected side and non-affected side) at baseline (mean difference 368-393 KPa) and at 12-months compared with men (mean difference 332-371 KPa; $P < 0.001$; Figure 2A and B). A weak association (r=0.145, P =0.048) was found for baseline pain during 30 min walking and the same parameter after treatment.

Associations between Clinical and Experimental Pain Parameters

At baseline a weak positive association ($r = 0.24$; $P <0.001$) was found between peak pain intensity and number of body sites with pain. Furthermore, a weak, but negative association ($r = -0.19$; $P = 0.01$) was found between PPT (both the most affected side and non-affected side) and number of body sites with pain (table 3).

Weak positive associations were found between improvements in pain parameters from baseline to 12 months and improvements in the number of body sites with pain ($r = 0.32$-0.40; $P <0.001$), and weak negative associations were found with PPTs ($r = 0.17$-0.23, $P < 0.05$). Furthermore, a weak negative association was found between improvements in PPT (non-affected side) and improvements in the number of body sites with pain ($r = 0.16$; $P = 0.045$; table 4).

Intention-to-treat Analysis

RCT of TKR in addition to non-surgical treatment: In the intention-to-treat analysis, the group randomised to TKR followed by non-surgical treatment had a 15 mm significantly ($P < 0.05$) greater improvement in peak pain intensity during the last 24h than the group randomised to non-surgical treatment alone. The differences between groups were not significant for pain intensity after 30 min walking and PPTs (table 5). In the adjusted within-group analyses, both groups improved significantly in peak pain intensity, pain intensity after 30 min walking, and both PPT measures (table 5). Twenty-five of the patients randomised to TKR followed by non-surgical treatment and 15 of the patients randomised to non-surgical treatment alone had not had knee pain during the last 24h at the 12-month follow-up. The group randomised to TKR followed by non-surgical treatment had a significantly larger reduction in the number of body sites with pain at the 12-month follow-up compared with the group randomised to non-surgical treatment alone ($Z = -2.116$; $p = 0.034$; Table 1).

Both the group randomised to TKR followed by non-surgical treatment ($Z = -4.195$; $p < 0.001$; Table 1) and the group randomised to non-surgical treatment alone ($Z = -2.349$; $p = 0.019$; Table 1) had significantly fewer body sites with pain at the 12-month follow-up compared with baseline.

RCT of non-surgical treatment vs. usual care: In the intention-to-treat analysis, the group randomised to non-surgical treatment had a significantly greater improvement in peak pain intensity of 16 mm and pain intensity after 30 min walking of 27 mm than the group randomised to usual care ($P < 0.05$). The differences between groups were not significant for PPTs (table 5). In the adjusted within-group analyses, both groups improved significantly in peak pain intensity and both PPT measures while only the group randomised to non-surgical treatment improved significantly in pain intensity after 30 min walking (table 5). Fourteen of the patients randomised to non-surgical treatment and 7 of the patients randomised to usual care had not had knee pain during the last 24h at the 12-month follow-up. The group randomised to non-surgical treatment did not have a larger reduction in the number of body sites with pain at the 12-month follow-up compared with the group randomised to usual care ($Z = -1.046$; $p = 0.296$; Table 1).

Neither the group randomised to non-surgical treatment ($Z = -1.773$; $p = 0.076$; Table 1) nor the group randomised to usual care ($Z = -0.511$; $p = 0.609$; Table 1) had fewer body sites with pain at the 12-month follow-up compared with baseline.

Secondary Analysis

Combined analysis of subjects undergoing TKR vs. subjects undergoing non-surgical treatment:

In the secondary analysis, the 70 subjects from the two RCTs undergoing TKR during follow-up were compared with the 49 subjects attending at least 75% of the supervised exercise sessions without undergoing TKR during follow-up. The group undergoing TKR had a 14 and 13 mm significantly ($P < 0.05$) greater improvement in pain intensity after 30 min walking (in the crude and the adjusted analysis) than the group undergoing non-surgical treatment. The differences between groups were not significant for peak pain intensity and PPTs (table 6). In the adjusted within-group analyses, both groups improved significantly in peak pain intensity, pain intensity after 30 min walking, and PPTs (table 6). The group undergoing TKR had a significantly larger reduction in the number of body sites with pain at the 12-month follow-up compared with the group undergoing non-surgical treatment ($Z = -2.377$; $p = 0.017$). The group undergoing TKR had significantly fewer body sites with pain at the 12-month follow-up compared with baseline ($Z = -4.471$; $p < 0.001$) while the group undergoing non-surgical treatment had not ($Z = -1.305$; $p = 0.192$).

Discussion

The present data showed that: 1) low aggregated PPTs (from both affected and non-affected lower limbs) at baseline predicted higher clinical pain after TKR, 2) the number of painful body sites predicted higher clinical pain after TKR and lower aggregated PPT values, 3) subjects with the highest pain and lowest aggregated PPTs at baseline showed the largest relative improvement in both pain and PPTs, but were still experiencing the highest absolute pain levels and lowest aggregated PPTs after 12 months (combined cohorts), and 4) baseline pain intensity and PPT levels were associated with the number of painful body sites.

Females had the lowest PPTs both at baseline and after 12 months.

This OA study is the first to include: A) an aggregated PPT measure from different locations in the prediction of the outcome after TKR, and: B) to investigate if the effect on non-surgical interventions could be predicted.

Predicting Outcome of Intervention

In recent years, possible clinical and experimental parameters predicting outcome after TKR (Mannion et al., 2009; Gandhi et al., 2010; Sullivan et al., 2011; Merle-Vincent et al., 2011; Petersen et al., 2015b) have been a focus, but no studies have investigated possible associations between preoperative pain sensitisation parameters and outcome after non-surgical interventions for managing OA pain. Approximately one quarter of all patients undergoing joint (hip and knee) replacements are suggested to be considered inappropriate candidates for joint surgery (Quintana et al., 2009; Cobos et al., 2010). Specific sub-groups of OA pain patients with different degrees of sensitisation have been identified (Finan et al., 2013; King et al., 2013; Skou et al., 2014a; Arendt-Nielsen et al., 2015a),and such specific sub-groups may respond differently to the interventions.

In recent years, different pain sensitisation measures have been developed and applied in addition to PPTs. In the current comprehensive RCTs, it was only possible for practical reasons to assess PPTs although other measures have shown promising results. Preoperative temporal summation has, for example, been consistently shown to predict continued pain following TKR surgery in patients with OA (Petersen et al., 2015a; Petersen et al., 2016).

More consistent mechanisms related to centralised sensitisation such as facilitated temporal summation seem to be a characteristic of those patients experiencing less pain relief after TKR (Petersen et al., 2016) and seem related to the present findings where low PPTs predicted less beneficial effect of TKA surgery. This has important clinical implications as the risk of re-revision is four to five times higher than the risk of revision of the original primary procedure (Australian Orthopaedic National Joint Replacement Registry, 2010) and since patients with pain afte one or more revision TKRs are severely affected by pain and sensitisation (Skou et al., 2013b). The study also showed a consistent influence of the preoperative pain level for the 12-month pain outcome after TKR and hence supports previous studies (Hovik et al., 2016).
In both the surgical and non-surgical group, the pain and PPT levels individually predicted their own outcomes.

Associations Between Clinical and Experimental Pain Parameters

When an experimental pain stimulus (e.g. for assessing PPT) is applied to an extraterritorial (outside the nerve innervation area with the painful condition such as OA), contralateral or extrasegmental site, it can provide information about the spreading of pain hypersensitivity outside the affected area (Arendt-Nielsen et al., 2017). Furthermore, the spreading of pain and pain hypersensitivity tend to follow this pattern involving an increasing part of the central nervous system and end up eventually mimicking a widespread pain condition (Arendt-Nielsen et al., 2015b).

Therefore, experimental pain assessment by PPT outside a painful area may be interpreted as spreading sensitisation, and in OA patients the degree of sensitisation depends on the clinical pain intensity and pain duration (Arendt-Nielsen et al., 2015a). This further supports the concept that the ongoing nociceptive activity is the driver for increased central gain (Voscopoulos and Lema, 2010; Shipton, 2011). In parallel, the descending pain pathways may start to enhance the excitability along the entire neuroaxis due to a shift in balance between pain inhibitory and pain facilitatory pathways (Millan, 2002; Vanegas and Schaible, 2004). In addition, the present study showed that the clinical pain intensity, the number of painful sites assessed clinically, and the PPTs were all associated.

Successfully relieving joint pain in OA patients by surgery normalises PPTs (resets the centralised sensitisation processes) (Graven-Nielsen et al., 2012; Aranda-Villalobos et al., 2013), supporting the notion that ongoing pain may be the driving factor for development of sensitisation (Noiseux et al., 2014). Further, this is supported by animal model studies (Scholz et al., 2005).

In the present study, each of the three interventions significantly increased the PPTs from both the affected and non-affected sides.

The Effect of the Interventions on Pain and PPTs

The compiled data from the two RCTs confirmed TKR in addition to non-surgical treatment as the most efficient treatment followed by the non-surgical procedure alone and with usual care as the least efficient (Skou et al., 2015a; Skou et al., 2015b).

The most commonly used technique to assess pain sensitisation in OA patients is externally applied pressure and assessment of the associated PPT (Suokas et al., 2012; Fingleton et al., 2015). Approximately, 70% of knee OA patients have at least one somatosensory abnormality (Wylde et al., 2012).
However, it is not obvious which structures the pressure is activating, but it may predominantly be extra-articular structures as patients with pain after TKR still have lowered PPTs when assessed over the replaced joint structures (Skou et al., 2014a).
Pain sensitisation is confirmed to play an important role in the clinical presentation of knee OA pain (Kidd, 2012). Therefore, attempts have been made to develop clinical (Akinci et al., 2016) and experimental quantitative measures (Arendt-Nielsen et al., 2015b) for assessing sensitisation in OA. The present study collected PPTs from the most affected leg (interpreted as segmental sensitisation) as well as the contralateral leg (interpreted as wide-spread sensitisation).

The lowest PPTs at baseline were found in females which supports the data by Bartley et al. (Bartley et al., 2016). We extended those findings and showed that this lower level lasted 12 months after treatment.

As a novel finding from this study, the number of painful body sites was associated with the lower PPTs from the non-affected side. This corresponds to the previously proposed concept that spreading of pain and spreading of sensitisation gradually develop over time as the pain persists (Arendt-Nielsen and Graven-Nielsen, 2011).

Associations between the number of painful body sites, pain intensity, and catastrophising have previously been shown (Dave et al., 2015; Skou et al., 2016b; Skou et al., 2016c). Previously, body maps of pain have shown extensive increases in the pain areas when the patients experience continued pain after TKR (Skou et al., 2013b).

Limitations

The paradigms used for the non-surgical procedure were based on current evidence. However, it is not known whether it could be further improved to address other problems related to OA such as sensitisation. Furthermore, since all patients were included from an orthopaedic outpatient clinic in secondary care, and due to the specific eligibility criteria, it is unknown whether the results can be generalised to all patients with knee OA. The quantitative sensory testing (QST) modality used in the present studies was limited to PPTs. As the study had to fit into the clinical routines, it was unfortunately not possible to include more QSTs although it would have been very interesting as, e.g. temporal summation is a strong predictor of the outcome after hip replacement (Petersen et al., 2015a; Petersen et al., 2016; Izumi et al., 2017). Static PPT assessments with a handheld algometer have the limitation that they assess only the sensitivity at the very local site. Previously, the PPT has been shown to vary along a muscle (Andersen et al., 2006) and at an OA affected knee joint (Arendt-Nielsen et al., 2015a).

Many factors including psychological factors (e.g. catastrophising) are important in OA (Egsgaard et al., 2015) and are also predictors of continued post-operative pain in most studies (Lewis et al., 2015),but not in all (Hovik et al., 2016).

The RCT2 (non-surgical treatment compared with usual care) included patients with K&L of 1-4 while the RCT1 (Non-surgical treatment +/- TKR) included patients with K&L of 2-4, indicating that there might be differences in the radiographic severity which could potentially affect the comparability of the non-surgical groups of the two RCTs. However, the improvements from the non-surgical treatment were comparable in the two RCTs (Skou et al., 2015a; Skou et al., 2015b), and a previous meta-analysis has highlighted that radiographic severity at baseline is not associated with the outcome from non-surgical treatment (Juhl et al., 2014).

As a new composit measure of pressure pain hypersensitivity, the aggregated PPT values from all the points on the affected and un-affected limb were also used. It would have been possible to analyse all the individual PPT values, but this was not the major aim and purpose of the present study.

Conclusion

The main findings based on the secondary analysis of two RCT cohorts were: 1) low PPTs (from affected and non-affected sites) at baseline were weakly associated with worse clinical outcome after TKR, but did not predict the outcome after non-surgical interventions, 2) the number of painful body sites was weakly associated with pain and PPTs, and 3) and the higher pain/lower PPTs, the higher pain/lower PPTs after 12 months with females showing the lowest PPT levels. As previously reported, TKR followed by a non-surgical program

improved pain more than the non-surgical program alone, and the non-surgical program improved pain more than usual care.

Author Contributions

Each of the below author contributions was based on the following parameters: 1) substantial contribution to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published:

- Lars Arendt-Nielsen - 1, 2, 3
- Ole Simonsen - 1, 2, 3
- Mogens B. Laursen - 1, 2, 3
- Ewa M Roos - 2
- Michael S. Rathleff - 1, 2, 3
- Sten Rasmussen - 1, 2, 3
- Søren T. Skou - 1, 2, 3

All authors discussed the results and commented on the manuscript.

Figure Legends

Figure 1.

Study flow of the randomized, controlled trials of patients eligible for total knee replacement (TKR; Figure A) and not eligible for TKR (Figure B) from which data in the present study are derived.

Figure 2.

The association between baseline pressure pain thresholds (PPTs) and PPTs assessed after 12 months (available data from the 200 subjects from the two randomised, controlled trials were included). Lower PPTs were associated with lower 12-month PPTs assessed at the most affected side (r =0.73, P < 0.001, panel A) and from the contralateral side (r =0.73, P < 0.001, panel B). Red diamonds represent females and blue represent males. Females had lower PPTs from the affected and non-affected side at baseline (mean difference 368-393 KPa) and at 12-months when compared with males (mean difference 332-371 KPa; P < 0.001). Males had mean baseline PPTs of 776-857 kPa while females had 408-464 kPa. The corresponding PPTs at 12-months were 877-947 kPa and 545-576 kPa, respectively.

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Table 1. Subject characteristics, baseline and 12-months data for the outcomes. RCT: Randomized, controlled trial; TKR: Total knee replacement; PPT: Pressure pain threshold (kPa) assessed with a handheld pressure algometer at the knee and lower leg. N= number of subjects.

	RCT of TKR + non-surgical		RCT of non-surgical vs. usual care	
Subject characteristics	**TKR + non-surgical** **N=50**	**Non-surgical** **N=50**	**Non-surgical** **N=50**	**Usual care** **N=50**
Women, N (%)	32 (64)	30 (60)	26 (52)	25 (50)
Age (years), mean (SD)	65.8 (8.7)	67.0 (8.7)	64.8 (8.7)	67.1 (9.1)
Body mass index, mean (SD)	32.3 (6.2)	32.0 (5.8)	30.6 (5.6)	29.4 (5.2)
Bilateral knee pain, N (%)	18 (36)	17 (34)	18 (36)	21 (42)
Duration of knee symptoms, N (%)				
0–6 months	0 (0)	6 (12)	4 (8)	2 (4)
6–12 months	5 (10)	2 (4)	9 (18)	6 (12)
1–2 years	8 (16)	8 (16)	10 (20)	5 (10)
2–5 years	15 (30)	10 (20)	11 (22)	13 (26)
5–10 years	11 (22)	12 (24)	4 (8)	8 (16)
More than 10 years	11 (22)	12 (24)	12 (24)	16 (32)
Radiographic knee OA severity (Kellgren-Lawrence), N (%)				
Grade 1	----	----	7 (14)	11 (22)
Grade 2	7 (14)	5 (10)	13 (26)	15 (30)
Grade 3	21 (42)	21 (42)	13 (26)	10 (20)
Grade 4	22 (44)	24 (48)	17 (34)	14 (28)
Peak pain intensity in the previous 24h, (0–100), mean (SD)				
Baseline	52 (26)	55 (22)	60 (23)	56 (25)
12 months	19 (26)	35 (31)	26 (23)	39 (30)
Pain intensity after 30 min				

walking, (0–100), mean (SD)				
Baseline	63 (29)	67 (25)	62 (26)	47 (24)
12 months	19 (26)	38 (32)	28 (26)	42 (28)
PPTs at affected extremity, mean (SD) (kPa)				
Baseline	554 (318)	573 (322)	549 (257)	592 (314)
12 months	720 (336)	669 (295)	699 (289)	661 (310)
PPTs at contralateral extremity, mean (SD) (kPa)				
Baseline	661 (365)	610 (332)	606 (264)	660 (336)
12 months	750 (346)	734 (307)	726 (308)	728 (338)
Number of body sites with pain in the previous 24h, mean (SD)				
Baseline	3.1 (2.2)	3.3 (2.6)	3.2 (2.9)	2.8 (2.1)
12 months	1.4 (1.7)	2.5 (2.6)	2.3 (2.8)	2.8 (2.5)

Table 2. Predictors of improvements in outcome from baseline to 12 months in subjects undergoing TKR and subjects undergoing non-surgical treatment only. A total of 70 subjects from the two randomized controlled trials undergoing total knee replacement (TKR) during follow-up and 49 subjects attending at least 75% of the supervised exercise sessions without undergoing TKR during follow-up (non-surgical treatment) were included in the analyses; the results were adjusted for age, gender, and body mass index. *P*-values indicate the *P*-values for the specific predictor in the model. PPT=Pressure Pain Threshold (kPa).

Condition	R^2	*P*-value	Unstandardized Beta (95% CI)
Total knee replacement group			
Peak pain intensity as a predictor of improvement in peak pain intensity	0.448	< 0.001	0.907 (0.618 to 1.196)
Pain intensity after walking as a predictor of improvement in pain after walking	0.496	< 0.001	0.881 (0.645 to 1.117)
PPTs at affected extremity as a predictor of improvement in peak pain intensity	0.096	0.30	0.018 (-0.016 to 0.053)
PPTs at affected extremity as a predictor of improvement in pain after walking	0.110	0.02	0.041 (0.007 to 0.075)
PPTs at contralateral extremity as a predictor of improvement in peak pain intensity	0.082	0.69	0.006 (- 0.025 to 0.037)
PPTs at contralateral extremity as a predictor of improvement in pain after walking	0.090	0.04	0.032 (0.002 to 0.062)
PPTs at affected extremity as a predictor of improvement in PPTs at affected extremity	0.141	0.02	- 0.358 (- 0.654 to - 0.061)
PPTs at contralateral extremity as a predictor of improvement in contralateral PPTs	0.161	0.01	- 0.361 (- 0.618 to - 0.103)
Non-surgical treatment group			
Peak pain intensity as a predictor of improvement in peak pain intensity	0.295	< 0.001	0.853 (0.432 to 1.274)
Pain intensity after walking as a predictor of improvement in pain after walking	0.256	0.01	0.671 (0.281 to 1.061)
PPTs at affected extremity as a predictor of improvement in peak pain intensity	0.047	0.34	0.022 (- 0.025 to 0.069)
PPTs at affected extremity as a predictor	0.065	0.46	0.017 (- 0.029 to 0.063)

of improvement in pain after walking			
PPTs at contralateral extremity as a predictor of improvement in peak pain intensity	0.032	0.64	0.012 (- 0.039 to 0.063)
PPTs at contralateral extremity as a predictor of improvement in pain after walking	0.084	0.23	0.030 (- 0.019 to 0.079)
PPTs at affected extremity as a predictor of improvement in PPTs at affected extremity	0.287	< 0.001	- 0.375 (- 0.585 to - 0.165)
PPTs at contralateral extremity as a predictor of improvement in contralateral PPTs	0.268	< 0.001	- 0.456 (- 0.709 to - 0.204)

Table 3. Associations between baseline parameters for available data from all subjects from the two RCT cohorts combined (N=200). PPT = Pressure Pain Threshold (kPa).

Parameters	Pain intensity after 30 min walking	PPTs at affected extremity	PPTs at contralateral extremity	Number of body sites with pain
Peak pain intensity in the previous 24h	$r = 0.41$ $P < 0.001$	$r = -0.10$ $P = 0.19$	$r = -0.13$ $P = 0.07$	$r = 0.24$ $P < 0.001$
Pain intensity after 30 min walking	-------	$r = 0.03$ $P = 0.72$	$r = 0.02$ $P = 0.84$	$r = 0.07$ $P = 0.34$
PPTs at affected extremity		-------	$r = 0.90$ $P < 0.001$	$r = -0.19$ $P = 0.01$
PPTs at contralateral extremity			-------	$r = -0.19$ $P = 0.01$

Table 4. Associations between the improvements in outcome parameters from baseline to 12 months for available data from all subjects from the two RCT cohorts combined (N=200). PPT=Pressure Pain Threshold (kPa).

Parameters	Pain intensity after 30 min walking	PPTs at affected extremity	PPTs at contralateral extremity	Number of body sites with pain
Peak pain intensity in the previous 24h	*r = 0.60* *P < 0.001*	*r = 0.20* *P = 0.01*	*r = 0.20* *P = 0.01*	*r = 0.40* *P < 0.001*
Pain intensity after 30 min walking	-------	*r = 0.23* *P = 0.01*	*r = 0.17* *P = 0.04*	*r = 0.32* *P < 0.001*
PPTs at affected extremity		-------	*r = 0.71* *P < 0.001*	*r = 0.14* *P = 0.09*
PPTs at contralateral extremity			-------	*r = 0.16* *P = 0.045*

Table 5. Group differences in the adjusted intention-to-treat analysis. In the adjusted analyses the results were adjusted for baseline scores, gender, age, and BMI. For the 'Mean improvement' column a positive number indicates an improvement for that parameter. For the 'Difference in mean improvement' column a positive number indicates a larger improvement in the intervention group (TKR/non-surgical) for that parameter. #: $P< 0.05$, ##: $P<0.001$. PPT=Pressure Pain Threshold (kPa).

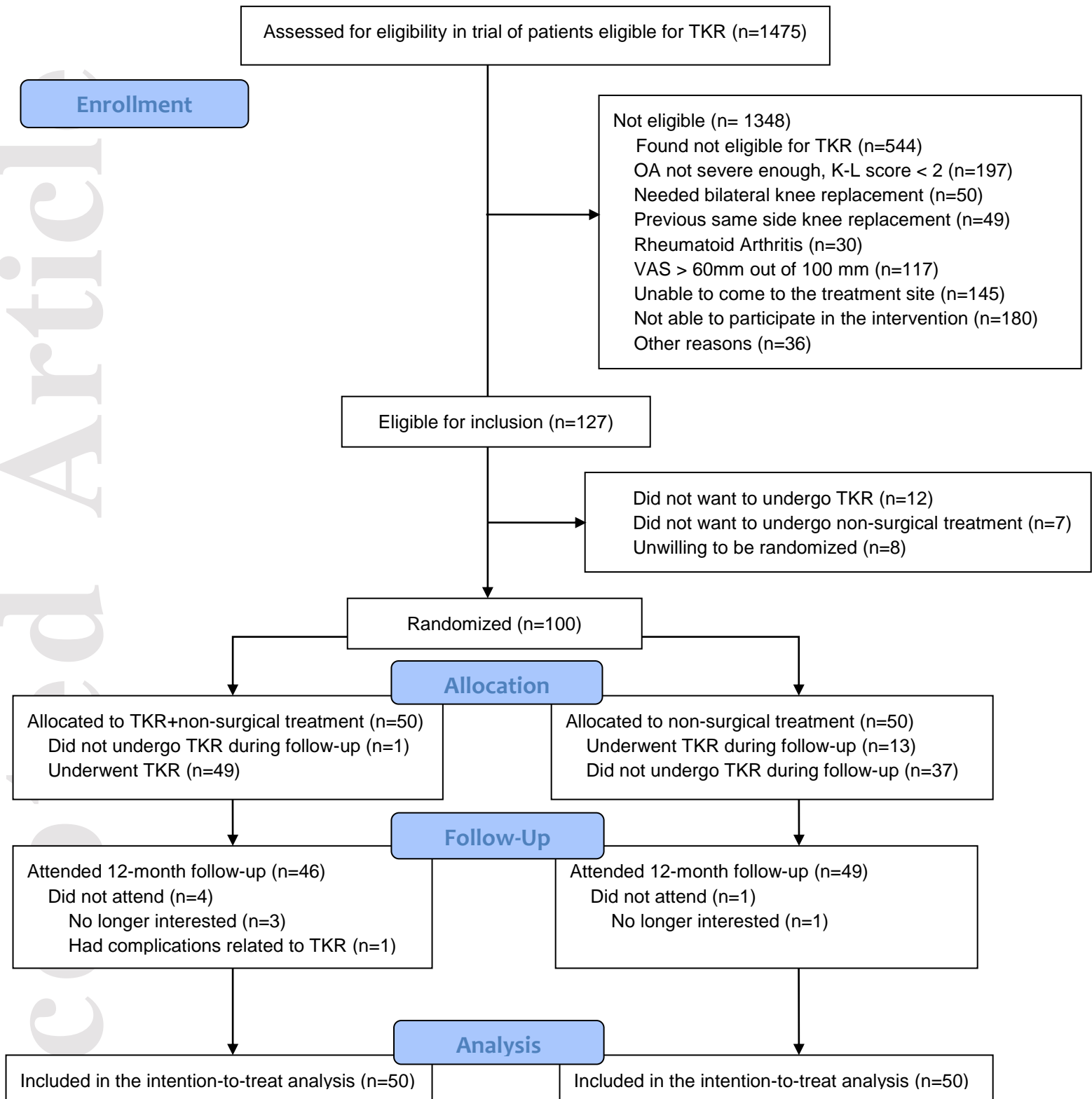|	Mean improvements in RCT of TKR + non-surgical vs. non-surgical (95% CI)		Diff. in mean improvement TKR – non-surgical (95% CI)	Mean improvement in RCT of non-surgical vs. usual care (95% CI)		Diff. in mean improvement non-surgical – usual care (95% CI)
Outcomes	TKR+ Non-surgical	Non-surgical		Non-surgical	Usual care	
Peak pain intensity in the previous 24h	34.6## (23.5 to 45.7)	19.6## (9.7 to 29.5)	15.1# (0.3 to 29.8)	33.1## (24.1 to 42.1)	17.2# (6.0 to 28.4)	15.9# (1.8 to 29.9)
Pain intensity after 30 min walking	42.9## (32.0 to 53.8)	29.2## (18.8 to 39.6)	13.7 (-1.2 to 28.6)	33.4## (24.2 to 42.6)	6.7 (-3.5 to 17.0)	26.6## (13.1 to 40.1)

PPTs at affected extremity	198.8## (114.1 to 283.5)	102.4# (34.0 to 170.8)	93.6 (-12.6 to 199.9)	143.8## (81.1 to 206.5)	80.4# (15.3 to 145.5)	63.0 (-26.0 to 152.1)
PPTs at contralateral extremity	127.1# (47.1 to 207.2)	126.4# (51.6 to 201.3)	-3.3 (-111.6 to 105.1)	121.0# (45.0 to 196.9)	97.9# (24.9 to 171.0)	23.0 (-81.0 to 127.0)

Table 6. Group differences in the secondary analysis. In the secondary analysis, the 70 subjects from the two randomized controlled trials undergoing total knee replacement (TKR) during follow-up were compared with the 49 subjects attending at least 75% of the supervised exercise sessions without undergoing TKR during follow-up. In the adjusted analyses the results were adjusted for baseline scores, gender, age, and BMI.

For the 'Mean adjusted within group improvement" column a positive number indicates an improvement for that parameter. For the 'Difference in mean improvement" column a positive number indicates a larger improvement in the intervention group (TKR/non-surgical) for that parameter. #: $P < 0.05$; ##: $P < 0.001$. PPT=Pressure Pain Threshold (kPa)

Outcomes	Mean adjusted within group improvement (95% CI)		Difference in mean improvement TKR – non-surgical (95% CI)	
	TKR	**Non-surgical**	**Crude**	**Adjusted**
Peak pain intensity in the previous 24h	33.2## (24.6 to 41.9)	21.6## (11.4 to 31.8)	10.8 (-2.2 to 23.8)	11.6 (-1.6 to 24.8)
Pain intensity after 30 min walking	42.9## (34.4 to 51.3)	29.6## (19.5 to 39.6)	14.1# (1.3 to 26.9)	13.3# (0.3 to 26.3)
PPTs at affected extremity	174.2## (101.1 to 247.2)	124.8## (71.2 to 178.3)	53.1 (-40.5 to 146.7)	51.4 (-42.3 to 145.1)
PPTs at contralateral extremity	143.9## (72.4 to 215.3)	110.0## (51.1 to 168.8)	36.0 (-58.5 to 130.5)	36.2 (-58.5 to 130.8)

Figure 1a

Assessed for eligibility in trial of patients eligible for TKR (n=1475)

Enrollment

Not eligible (n= 1348)
  Found not eligible for TKR (n=544)
  OA not severe enough, K-L score < 2 (n=197)
  Needed bilateral knee replacement (n=50)
  Previous same side knee replacement (n=49)
  Rheumatoid Arthritis (n=30)
  VAS > 60mm out of 100 mm (n=117)
  Unable to come to the treatment site (n=145)
  Not able to participate in the intervention (n=180)
  Other reasons (n=36)

Eligible for inclusion (n=127)

Did not want to undergo TKR (n=12)
Did not want to undergo non-surgical treatment (n=7)
Unwilling to be randomized (n=8)

Randomized (n=100)

Allocation

Allocated to TKR+non-surgical treatment (n=50)
  Did not undergo TKR during follow-up (n=1)
  Underwent TKR (n=49)

Allocated to non-surgical treatment (n=50)
  Underwent TKR during follow-up (n=13)
  Did not undergo TKR during follow-up (n=37)

Follow-Up

Attended 12-month follow-up (n=46)
  Did not attend (n=4)
    No longer interested (n=3)
    Had complications related to TKR (n=1)

Attended 12-month follow-up (n=49)
  Did not attend (n=1)
    No longer interested (n=1)

Analysis

Included in the intention-to-treat analysis (n=50)

Included in the intention-to-treat analysis (n=50)

Figure 1b