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Pre-treatment exercise-induced hypoalgesia is associated with change in pain and function after standardized exercise therapy in painful knee osteoarthritis

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Abstract

Objectives: Exercise-induced hypoalgesia (EIH), a measure of descending pain inhibitory control, has been found hyperalgesic in subgroups of painful knee osteoarthritis (KOA) patients. The effect of standardized exercise therapy (ET) on clinical pain intensity in KOA has been demonstrated. However, the prognostic value of EIH in KOA patients completing an ET program has not been investigated. This study investigated the prognostic value of EIH on pain relief following ET in KOA patients.

Methods: In 24 painful KOA patients (numeric rating scale [NRS, 0-10] ≥3), EIH was assessed as change in pressure pain threshold (PPT) after 2-minute 'lateral raises' (2MLR) before and after ET in this observational study. In addition, temporal summation of pain (TSP), clinical pain scores (NRS, Knee injury and Osteoarthritis Outcome Score [KOOS] and PainDETECT [PDQ]) were assessed before and after ET. The KOOS-4 is defined by the KOOS subscale scores for Pain, Symptoms, Activities of daily living, and Quality-of-life and was used as primary outcome.

Results: Following ET, all clinical pain scores improved (P<0.01) but no changes in PPT, TSP or EIH were found (P>0.05). Linear regression models identified pre-treatment EIH (beta=0.59, P<0.005) and PDQ (beta=0.57, P<0.005) as independent factors for relative change in KOOS-4 after ET (adjusted R^2=46.8%).

Discussion: These preliminary and exploratory results suggest that patients with a high EIH response prior to a standardized ET program may be associated with large improvement in pain after treatment. This measure may potentially help clinicians as a prognostic tool for outcome prediction following ET in KOA patients.

Key words: Exercise-induced hypoalgesia, knee osteoarthritis, painDETECT, mechanistic pain profiling, exercise therapy.

Introduction

Knee osteoarthritis (KOA) is the most common joint disease and a leading cause of years lived with disability world-wide[1]. The prevalence of KOA has increased markedly over the last 20 years[2] and is expected to increase further[2,3]. No or poor association between radiological findings (e.g. Kellgren-Lawrence score) and self-reported pain intensity have been demonstrated in KOA patients[4–6] suggesting that other factors than the joint pathology are driving the pain.

Standardized exercise therapy (ET) is recommended as first-line treatment for painful KOA[7,8] demonstrating improved pain intensity, physical function and quality of life in the majority of patients with painful KOA[9–11]. Exercise is targeting several peripheral and central pain mechanisms including the activation of descending inhibitory mechanisms[12–14]. However, the underlying pain mechanisms of ET remain largely unknown[15].

The Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative and the Outcome Measures in Rheumatology Committee (OARSI-OMERACT) has defined responder criteria for osteoarthritis clinical trials[16]. However, only small to moderate effect sizes have been found for non-pharmacological treatment options including ET for painful KOA patients[8,17] indicating that a large group of painful KOA patients do not gain clinically relevant benefits including pain relief following ET. Therefore, it is relevant to focus on predicting the ET outcome to optimize treatment algorithms.

Pain sensitization has been associated with pain severity in KOA[18–20] and a neuropathic-like pain component has been identified in up to 32% of KOA patients[21]. In addition, measures of pain sensitization have been utilized to identify KOA patients with no or limited pain relieving effects from, e.g., total knee replacement (TKR)[22–27], pharmaceutical treatment[28,29] and ET[27,30]. Similarly, impaired endogenous pain modulation has been associated with KOA and treatment outcome[23,31].

Exercise-induced hypoalgesia (EIH) is believed to reflect endogenous pain modulation and is commonly assessed as the change in pressure pain thresholds (PTTs) after a short bout of exercise[32]. Currently, there is no consensus on how to best evoke EIH, but assessments of EIH elicited with muscles involved (local effect) or not involved (remote effect) in the short bout of exercise have been utilized[32]. In patients with chronic pain problems localized to one body region, including KOA, hypoalgesic responses to an EIH exercise condition have been reported when evoked with exercises of unpainful remote body regions, while hyperalgesic EIH responses have been observed when exercising the local painful regions[33–36]. Studies indicate that the hypoalgesic EIH response is seen in asymptomatic subjects[37–40] and that a hyperalgesic EIH response has been found in subgroups of painful KOA patients[26,31,33]. A hypoalgesic EIH response does not change after ET in KOA patients with mild pre-treatment pain[41], but this has not been investigated in KOA patients with moderate to high pre-treatment pain intensity or hyperalgesic EIH responses. Furthermore, EIH has also been utilized as a predictive factor for pain progression following TKR[26], but EIH has not yet been investigated as a prognostic tool for standardized ET."

The aims of this exploratory study were 1) to investigate the association between measures of mechanistic pain profiling including EIH before ET and self-reported pain relief after ET in patients with KOA and 2) to investigate the modulatory effect of ET on the EIH response.

It was hypothesized that 1) the EIH response measured before standardized ET was associated with pain relief after ET and 2) a decrease in clinical pain due to ET would increase the EIH response.

Materials and methods

Procedure

Patients with painful KOA (peak pain within the last 24 hours on a 0-10 numerical rating scale [NRS] ≥ 3) from the Central Region of Denmark who were referred to standardized ET by a

hospital or general practitioner and contacted Viby Physiotherapy Clinic, Aarhus, Denmark, were invited to join the study. Painful KOA was defined following the American College of Rheumatology criteria without use of radiological assessment[42]. Exclusion criteria were the following: Known rheumatoid arthritis or other rheumatoid diseases, neurological diseases, mental impairments, previous partial knee replacement or TKR, presence of other pain problems (e.g. hip or back pain) with more intense pain than the knee pain, any kind of surgery within the last 6 months, pregnancy, addictive behavior to opioids or any kind of narcotics, and lack of cooperation. All subjects were asked to refrain from regular physical exercise on the days of participation in the test procedures.

Peak pain within the last 24 hours (NRS, 0-10), Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire, PainDETECT questionnaire (PDQ), and quantitative sensory testing (QST) measures were collected within 1 week before and 1-2 weeks after the standardized ET program. Consumption of analgesics (categorized into 'yes' or 'no' to taking paracetamol, nonsteroidal anti-inflammatory drugs and opioids before the experiments on the days of participation in the test procedures) was recorded.

The study was conducted in accordance with the Declaration of Helsinki, approved by the local ethical committee (N-20170070), registered at clinicaltrials.gov (NCT03718663) and all subjects gave written informed consent prior to enrollment. The subjects were included between October 2017 and October 2018. The same person (SH, an experienced physiotherapist with QST-training) conducted the data collection and performed all the tests.

Skou et al.[9] reported a KOOS-4 of 48.9 (SD: 11.8) in KOA patients prior to ET. A power calculation based on these data which enables to detect an increase by 20%, with a statistical power

of 80% and a significance level of 0.05, yielded that 23 KOA patients were needed for this study. Twenty-eight subjects were recruited to account for dropouts during the study.

Standardized exercise therapy

The standardized ET program comprising 12 sessions of NEuroMuscular Exercises (NEMEX)[9,10,43,44] was delivered approximately twice weekly as commonly applied to patients with KOA in Denmark[11] and other countries[45]. The exercise therapy program utilized in the current study has previously been described in detail by Ageberg et al.[43,44]. In short, the exercises were performed with both the non-affected and the OA affected knee, although focus was on the OA affected knee. Four levels of difficulty for each exercise was presented to allow for progression. Based on visual inspection by a specially trained physiotherapist, progression was made when an exercise was performed with good sensorimotor control and good quality of the performance, and with minimal exertion and control of the movement as evaluated by the patient. 2-3 sets of 10-15 repetitions of each exercise was performed, with a resting period corresponding to one set between each set of exercise. The subjects were encouraged to participate in group-based sessions, but were allowed to combine group and home-based sessions, or home-based sessions only, after detailed instructions by their physiotherapist. This procedure is also used in the recommended ET program for KOA patients in Denmark[11]. Furthermore, meta-analysis on patients with musculoskeletal pain has found the same benefits including pain relief from group-based and individual physiotherapy ET programes[46] and from group-based compared to individual ET programs[47]. In accordance with clinical guidelines[7,8], patient education and self-management advice were given, and shoe insoles and weight loss were recommended, if assessed relevant by the physiotherapist. A treatment attendance score (%) was calculated for each participant by dividing the number of sessions attended/completed by the number of scheduled sessions[48](twice per week) as used in a similar

study on knee OA patients and ET[30]. An attendance score above 100% describes subjects who attended/completed more sessions than scheduled.

Functional outcome measure

The 6-minute walk test (6MWT) was used as a functional outcome measure. The 6MWT is recommended by the Osteoarthritis Research Society International (OARSI) as a component of the minimal core set of performance-based physical function tests for KOA[49]. The 6MWT is a simple clinical outcome measure used to assess functional performance in elderly people and patients. The test has been found reliable and valid in KOA patients and measures how far a person can walk in 6 minutes[50–53]. The test was performed according to the guidelines of the American Thoracic Society[54]. In brief, a test course of 20 meters (corresponding to one lap of 40 meters) was used as previously tested and found acceptable for this test[54]. Every three meters of the course, except the last two meters, were marked with tape to ensure correct recording of the walking distance. The patients were given standardized verbal instructions on how to perform the 6MWT[55]. It was marked on a worksheet each time a 40-meter lap had been completed. After six minutes, the patient was told to stop, the position of the patient was marked and the total distance was calculated.

Assessment of self-reported pain

KOOS is a well-established questionnaire containing five subscales: Pain, other symptoms (Symptoms), function in activities of daily living (ADL), function in sport and recreation (Sport) and knee related quality of life (QoL). The questionnaire has been found responsive, reliable and valid in KOA patients with scores ranging from 0 (worst) to 100 (best) for each subscale[56,57]. The OMERACT-OARSI defined the responder criteria for osteoarthritis clinical trials, a responder is defined as having either (1) an improvement in pain and function by at least 50% or (2) an improvement by at least 20% in two of the following three categories: pain, physical function, or global assessment of the patient[16]. Therefore, the primary outcome of the current study was the

KOOS-4, which is defined as the average score of the subscale scores for Pain, Symptoms, ADL and QoL and has previously been applied in follow-up studies of KOA patients[9,10,58]. The KOOS-4 relative change after ET was calculated as the percentage change comparing baseline with follow-up values and used for the linear regression analysis. A positive value indicates improvement after ET.

The clinical pain intensity was assessed as the peak pain within the last 24 hours on the NRS before and after ET.

PDQ is a reliable and valid screening questionnaire assessing whether the pain phenotype is neuropathic-like, probably nociceptive or uncertain based on a score from 0 to 38[21]. A neuropathic-like pain phenotype (PDQ score $\geq$ 19[59]) has been reported in up to 32% of KOA patients using PDQ[21]. A recent study in patients with KOA demonstrated that preoperative PDQ scores were associated with pain six months after TKR[22], indicating that the PDQ might hold prognostic values and therefore the PDQ was included in the current study.

Mechanistic pain profiling

PPTs and temporal summation of pain (TSP) were assessed at the knee joint most affected by KOA. If both knees were painful, the knee with the highest pain intensity was chosen for examination. All sensory tests were conducted with the subject lying supine on a couch with a cushioned bolster (~15 cm in diameter) under the knees. TSP was always assessed first, followed by PPTs including the sites used for EIH in a non-standardized order.

Five sites in the peripatellar region, one control site at the m. tibialis anterior ([TA], 5 cm distal to the tibial tuberosity), one control site at the m. quadriceps femoris ([QF], 20 cm proximal to the center of patella), and one control site at the contralateral m. deltoideus ([DE], at the middle part of the muscle belly of the middle deltoid) were located and marked.

The five peripatellar sites were located as follows with reference to patella: Site 1: 3 cm medial to the midpoint on the medial edge of patella; site 2: 2 cm proximal to the superior medial edge of patella; site 3: 2 cm distal to the inferior medial edge of patella; site 4: 3 cm lateral to the midpoint on the lateral edge of patella; site 5: 2 cm proximal to the superior lateral edge of patella.

A handheld pressure algometer (Somedic AB Type II, Sweden) was used to assess PPTs. The probe (1 cm^2) was placed perpendicularly to the skin and pressure was applied at approximately 30 kPa/s until the subject defined the pressure as pain and pressed a button. In patients with chronic pain, assessment of pain sensitivity with handheld pressure algometry within- and between-session test–retest reliability has previously been demonstrated[60].

The PPTs were measured three times at each site with a 20-second break in between assessments and the average was used for statistical analysis. An average of the five peripatellar sites was calculated to give a general measure of sensitivity of the knee, which has previous been utilized in QST studies of patients with KOA[23,24], while the average of each control site was used separately. Three measurements were made on the contralateral knee to accustom the subject to the procedure.

The change in PPTs measured at QF[26,41,60] and DE[41] before and after an exercise condition of 2-minute shoulder abductions (known as 'lateral raises', 2MLR) was used to assess EIH. As in previous studies[35,41,61], the PPTs were normalized (i.e. the ratio between the individual's mean PPT after the exercise condition divided by the mean PPT before the exercise condition for the corresponding measuring site) to investigate EIH. Therefore, a value larger than 1.0 indicates increased PPT (hypoalgesic response) after the exercise condition. *Local EIH* was assessed at a muscle (DE) primarily involved in the exercise condition, while *remote EIH* was assessed at a muscle (QF) remote to the exercising body region.

For the 2MLR, the subjects were instructed to stand at the middle of a Theraband elastic band (Theraband, Hygenic Corporation, Akron, USA) while holding the band on each side of the body. The resistance of the band was tailored to the individual subject in co-operation between the tester and the subject using a "pilot-test" of 5-8 repetitions of the exercise to assess that exercising for two minutes would lead to failure. Both arms were elevated to approximately 90° shoulder abduction and 30° shoulder horizontal flexion while the elbows were in a slightly (~5°) flexed position. Instructions were given to perform the exercise in a controlled manner ensuring that the duration of raising and lowering the arms took approx. two seconds in each direction[62] corresponding to approximately 30 repetitions. The exercise quality including the speed of motion was supervised (and corrected, if needed) by the tester. Then, the elastic band was released and the subjects immediately lay down on the couch for PPT assessment. The 2MLR was used as an exercise condition because it involves muscles remote to the painful knee and the intensity is high; both factors which are known to increase the likelihood of a hypoalgesic EIH response[32].

The order of 6MWT and 2MLR was block randomized with four patients in each block to ensure counterbalancing. The hypoalgesic effect of a single bout of exercise is short-lasting[37,39] and therefore a 15-minute break was included between the 6MWT and the 2MLR. In the break the patient was resting in a sitting position and water (but not caffeine) was allowed.

A modified von Frey stimulator with a weighted load (Aalborg University, Aalborg, Denmark) was used to induce pinprick TSP. A force of 25.6 g was applied once on the subject's knee (site 1 described above) and at TA, and the subject was asked to rate the pain intensity from 0-10 on the NRS. Then, 10 consecutive stimulations were applied (1-second intervals between stimulations) to the same sites, one at a time, and the subject was asked to rate the pain intensity of the last stimulation on the NRS at each of the stimulation sites. TSP was calculated as the absolute

difference in pain intensity between the last and first stimulation. This TSP method has previously been used in similar studies[22,23,25]. High TSP scores indicate facilitated central pain mechanisms. TSP was assessed once in each location. Three stimulations were made on the contralateral knee to accustom the subject to the procedure.

Statistics

All data are presented as mean and standard error of the mean (SEM) if not otherwise stated. Normally distributed data (Shapiro-Wilks, $P > 0.05$) were analyzed with parametric statistics, otherwise a non-parametric analysis was applied. For single comparisons between pre-treatment and follow-up data (NRS, PDQ, 6MWT), paired t-tests or Wilcoxon tests were applied.

For paired samples analysis, individually repeated-measures analysis of variance (RM-AVOVA) or related-samples Friedman's 2-way ANOVA by ranks was used for normally and non-normally distributed data, respectively. For PPTs, the factors site (knee, TA, QF, DE) and treatment effect (baseline, follow-up) were applied to investigate for treatment effects of ET on PPTs. To investigate if the exercise condition induced EIH at baseline, the change in PPTs after the exercise condition was analyzed with the factors time (before, after) and site (DE, QF). Similar, for the treatment effect of ET on EIH, the factors site (QF, DE) and treatment effect (baseline, follow-up) were applied. Finally, the treatment effect of ET on TSP was analyzed with factors treatment effect (baseline, follow-up) and site (knee, TA). Bonferroni post hoc correction for multiple comparisons was applied for significant main effects or interactions.

A linear regression analysis with backward selection using all mechanistic pain profiling parameters and clinical parameters before ET was used to define independent predictive factors for the pain relieving effect of ET. The OMERACT-OARSI responder criteria for osteoarthritis clinical trials recommend that both pain and function scores are utilized when assessing outcomes of treatment in

patients with KOA[16]. Therefore, the relative change in KOOS-4 was utilized as depending factor in the linear regression models. $P < 0.05$ was considered significant. All statistical analyses were performed in SPSS version 25 (IBM Corporation, Armonk, NY).

Results

Demographic

Twenty-eight subjects with painful KOA were recruited. From these, 24 subjects had complete baseline and follow-up data and were included in the analysis. Four subjects were excluded due to the following: Missing data because of apparatus failure (n=1), not attending follow-up because of personal problems (n=2), and withdrawal from participation in ET before attending follow-up (n=1).

The excluded subjects were not significantly different compared with the included subjects regarding age (t-test, $P = 0.438$), number of positive KOA criteria (Mann-Whitney U, $P = 0.082$), self-reported peak pain intensity (Mann-Whitney U, $P = 0.465$), PDQ score (Mann-Whitney U, $P = 0.635$), KOOS-4 and all KOOS subscales (Mann Whitney-U, $P > 0.05$).

The average number of completed standardized ET sessions was 12.5 ± 0.3 (range 11-18) during 6.6 ± 0.1 (range 6-9) weeks for the subjects included in the analysis. Attendance score was 94.9 ± 2.4% (range 66.7 – 128.5). None of the subjects had taken any analgesics (paracetamol, non-steroid anti-inflammatory drugs or opioids) before the experiments on the testing day at baseline measurements, while one subject had taken paracetamol before the experiments on the testing day at follow-up session.

Functional improvement

All subjects completed the 6MWT at baseline and follow-up. A significant increase in walking distance (P = 0.036) was observed at follow-up (482.0 ± 14.6 meters) compared with baseline (459.3 ± 17.0 meters).

Pain relief

Significantly lower peak pain intensity (Wilcoxon; $P < 0.001$) and PDQ scores (t-test, $P = 0.009$) were found at follow-up compared with baseline (table 1). In addition, a significant main effect of the KOOS data was found (Friedman's, X^2 (9) =107.3; $P < 0.001$), with post hoc tests showing significant improvements in KOOS-4 (effect size: Cohen's d = 0.65) and the KOOS subscales for Pain and ADL (Wilcoxon; $P < 0.05$) and a trend towards a significant KOOS subscale for Symptoms (Wilcoxon; $P = 0.050$) (table 1), indicating improvement following ET.

At baseline 19 subjects (79.1%) had nociceptive pain, 4 (16.7%) had uncertain pain, and 1 (4.2%) had neuropatic-like pain based on PDQ, while the distribution at follow-up was 23 (95.8%), 1 (4.2%) and 0 (0.0%) respectively.

Mechanistic pain profiling

Pressure pain thresholds

Friedman's ANOVA with the factors site (Knee, TA, QF and DE) and time (baseline, follow-up) showed a significant main effect (Friedman's, X^2 (7) =23.6; $P = 0.001$) with post hoc tests showing significant differences between baseline PPTs at the knee and QF (Wilcoxon; $P = 0.024$), knee and DE (Wilcoxon; $P = 0.006$), and follow-up PPTs at the knee and QF (Wilcoxon; $P = 0.024$). No other significant PPT differences were found between sites at baseline (Wilcoxon; $P > 0.10$) and follow-up (Wilcoxon; $P > 0.06$). In addition, post hoc tests showed no changes in PPTs from all

sites comparing baseline with follow-up (Wilcoxon; $P > 0.6$) (table 2), indicating that ET did not modulate pressure pain sensitivity.

Exercise-induced hypoalgesia

All subjects completed the 2MLR exercise condition at baseline and follow-up.

Friedman's ANOVA with the factors site (DE, QF) and time (before and after exercise condition) at baseline showed a significant main effect (Friedman's, $X^2(3) = 8.100$; $P = 0.044$). The post hoc test showed significant changes in PPTs at DE (Wilcoxon; $P = 0.008$), but no change at QF (Wilcoxon; $P = 0.346$) indicating that the exercise condition induced local but not remote EIH at baseline (Figure 1).

The normalized local EIH responses at baseline and follow-up were 1.16 ± 0.04 and 1.13 ± 0.04, respectively, with the corresponding remote EIH responses being 1.04 ± 0.03 and 1.05 ± 0.03, respectively. The RM-ANOVA showed a significant main effect of measurement site (DE vs. QF) ($F_{1,23} = 11.855$; $P = 0.002$) with the post hoc test showing a significantly larger EIH response from DE compared with QF (Wilcoxon; $P = 0.004$). No significant effect of time (baseline vs. follow-up) ($F_{1,23} = 0.045$; $P = 0.835$) or interaction between site and time ($F_{1,23} = 0.603$, $P = 0.445$) were found indicating that standardized ET did not change EIH in painful KOA patients.

Temporal summation of pain

Baseline TSP at the knee and TA was 1.5 ± 0.2 (range 0-4) and 1.3 ± 0.4 (range -3 - 5), respectively. At follow-up, TSP at the knee and TA was 1.6 ± 0.3 (range -2 - 4) and 1.5 ± 0.3 (-1 - 4), respectively, with no change at both sites (Wilcoxon; $P > 0.600$), indicating that standardized ET did not change TSP.

Predicting pain relief and improvement in function after exercise therapy

Linear regression analyses were conducted to investigate a possible predictive value of baseline mechanistic pain measures and clinical pain parameters on the pain relieving outcome after ET. Model 1 included all mechanistic pain profiling assessments and clinical parameters, showing a predictive value of adjusted R^2 = 40.6% for relative change in KOOS-4 (Table 3). Model 2, using backward selection aimed to identify independent factors and identified remote EIH (beta = 0.59; $P < 0.005$) and PDQ score (beta = 0.57; $P < 0.005$) before standardized ET as significant independent factors, with a predictive value of adjusted R^2 = 46.8% for relative change in KOOS-4 after treatment (table 3).

Discussion

This exploratory study found that standardized ET improved pain and function outcomes in patients with KOA and is the first study to demonstrate that EIH and PDQ before treatment are associated with the treatment effect of ET. Further, the current study demonstrated that standardized ET did not change EIH, PPT or TSP suggesting that the pain relieving effect of ET is not associated with an improvement in maladaptive neuroplasticity.

Improved function after exercise therapy

Previous studies report improved function after a similar ET program for KOA patients as used in the current study[9–11]. OARSI recommendations state 50.2 m improvement for 6MWT as the minimal improvement to reach clinical relevance[53]. Therefore, it can be questioned if the change found in this study (22.7 ± 10.2 meters) is clinically relevant although statistical significant.

Pain relief after exercise therapy

The mechanisms underlying the pain relieving effect of ET are largely unknown[15] but might include activation of descending pain inhibitory pathways in the central nervous system[33,38,41,60], a possible decreased pro-inflammatory cytokine response[63] and a reduction in psychological impairments[64].

ET is well established providing moderate pain relief in KOA patients for at least 6 months[17] although Collins et al. argue that this might be below the clinically relevant pain relief in these patients[56]. According to the OMERACT-OARSI set of responder criteria for osteoarthritis clinical trials, a responder is defined as having either (1) an improvement in pain and function by at least 50% or (2) an improvement by at least 20% in two of the following three categories: pain, physical function, or global assessment of the patient[16]. Previously, a reduction in pain intensity of either 30% or 50% has been utilized as the golden standard for responders to treatments[65,66]. The current study reports improvements after ET of 46.4%, 17.6%, and 13.3% in NRS peak pain, KOOS-pain and KOOS-4, respectively; thus highlighting that the responder criteria are crucial when assessing if a given intervention is effective, since the results from the current study can either be interpreted as ET providing or not providing clinically relevant improvements depending on the criteria classification utilized.

Mechanistic pain profiling and exercise therapy

A hypoalgesic EIH response has been reported in patients with KOA[41], RA[67], chronic low back pain[36], chronic shoulder pain[35] and chronic unspecific musculoskeletal pain[68], although a hyperalgesic EIH response has also been reported in subgroups of KOA patients[26,31,33]. Furthermore, lower EIH has been reported in physically inactive individuals compared with physically active people[69,70] indicating that exercise or an active lifestyle may improve EIH. However, studies did not find this relationship in healthy subjects[39,71–73] making this area relevant for future research. The current study was unable to demonstrate improvement in EIH after ET.

This finding is in line with previous follow-up studies on ET or surgery in KOA[26,41] and RA[67] patients, indicating that analgesic response of ET in pain patients is more complicated than just improvement EIH, which has also recently been argued in a review by Sluka et al.[14] suggesting that other pain modulatory mechanisms must be investigated to explain the analgesic effect of exercise programs. Pre-clinical trials have demonstrated changes after vigorous exercise programs in brainstem areas such as the rostral ventromedial medulla (RVM) and periaqueductal gray (PAG), possibly involved in EIH mechanisms[13,14]. Future human studies are encouraged to investigate if vigorous exercise programs can improve EIH in healthy subjects or patients with different chronic pain conditions.

Systematic reviews and meta-analyses have found that painful KOA patients present with enhanced local and widespread pain sensitivity[18–20], and studies have demonstrated that local and widespread hyperalgesia improve when the clinical pain is removed after, e.g., a pain-free recovery after total joint replacement[74,75]. The current study found that PPTs both locally and widespread were unaffected after ET. Henriksen et al., found increased extrasegmental pain sensitivity at short-term follow-up (similar to the current study) after ET in a randomized controlled trail in KOA patients[76]. Studies have found that widespread pressure hyperalgesia is driven by the clinical pain intensity in KOA[77]. The current study reported decreased pain intensity, but unlike Graven-Nielsen et al.[75] and Kosek et al.[74], the subjects in the current study were not pain-free at follow-up, which may explain the lack of normalization of PPTs.

Previous studies have shown that KOA patients have enhanced TSP compared with pain-free controls[77]. One previous study found decreased extrasegmental TSP after ET[76]. Normalization of central pain mechanisms has been reported in pain-free KOA[75] and hip OA[74] after total joint replacement. TSP was unaffected both locally and extrasegmentally after ET in the current study, indicating that pain intensity might be a driving factor for maintaining this phenomenon.

Exercise-induced hypoalgesia

The EIH response consists of several local, extrasegmental and descending pain mechanisms[13,32,78,79]. However, it is generally seen as a measure of descending pain inhibitory control[32] with some similarities between EIH and condition pain modulation (CPM)[31,37]. Currently, there is no golden standard for evoking EIH[32], but previous studies on patients with KOA[33], chronic low back pain[36] or chronic shoulder pain[35] show significant EIH response after exercising pain-free body regions, which is in agreement with the current findings. Burrows et al. studied KOA using dynamic upper body strength exercise to elicit EIH and found both local and remote EIH responses[33], while the current study was only able to find a significant local EIH response at a group level. Burrows et al.[33] used a longer exercise procedure to induce EIH compared with the current study, indicating that exercise duration might be important to evoke EIH.

Utilizing mechanistic pain profiling to predict pain relief after exercise therapy

Studies have found that preoperative single site or single body region measures of PPT[24], TSP[23–25], CPM[26] or EIH[26] are associated with poor outcome after TKA, although other studies have found that single site or single body region measures of PPT[30,76] or TSP[30,76] have no predictive value. In contrast, a recent study found that indexes combining several PPT or TSP measures are predictive of non-response to ET[30]. This is similar to the current study, which found that combining, PDQ, PPT and EIH yielded a predictive model for the analgesic effect of ET. Collectively, the results from the current study indicate that KOA patients presenting with nociplastic pain have an unfavorable prognosis benefitting from ET. In an enriched randomized controlled trial focusing on KOA patients with central sensitization, Koh et al. administrated duloxetine (a serotonin–norepinephrine reuptake inhibitor) before and 6 weeks after TKA and found that this reduced the postoperative pain until week 12 compared with placebo[80], indicating that treating central pain mechanisms might be able to improve the pain management in the future.

The current study is the first to report that patients with lower remote EIH response at baseline after an upper body dynamic strengthening exercise had less pain relief after ET and that the baseline EIH response was an independent factor for this association. Assessment of descending pain inhibitory control has previously been utilized to assess patients at risk of, e.g., chronic postoperative pain following thoracotomy[81], abdominal[82], and TKR[26] surgery and therefore the results from the current study supports previous findings.

Furthermore, although the PDQ score at baseline indicated an average of nociceptive pain phenotype, with only one subject (4.2%) having neuropatic-like pain and four subjects (16.7%) having an uncertain pain phenotype, the baseline PDQ as an independent factor predicted a relative change in KOOS-4 after standardized ET. This association has not been described previously, and it indicates that lower baseline PDQ scores are associated with more pain relief from ET than in patients with lower baseline PDQ. Assessed with PDQ, studies report 5.4% to 32% of KOA patients having neuropatic-like pain[21], which is higher than the findings from the current study. This difference may explain the direction of the association and the results might have been different with a wider distribution of PDQ scores. Therefore, the difference in PDQ score distribution between our results and the expected distribution may lower the external validity of these results.

Kurien et al., found that higher pre-operative PDQ scores were independently predictive post-operative pain following TKR in KOA patients[22], indicating that a more neuropathic pain-like phenotype is associated with poor outcome after TKA. PDQ is recommended as a pain phenotype screening tool and not as a diagnostic assessment tool[83] because the differences between the diagnosis of neuropathic pain with the system of the International Association for the Study of Pain (IASP)[84] vary from the classification of neuropathic pain with the use of PDQ[85]. The current results and the results from Kurien et al.[22] suggest that PDQ can also be used as a screening tool to predict the at baseline treatment outcome in KOA patients. However, large-scale controlled trails need to

validate the clinically usefulness and therefore the results from the current study should be interpreted with care.

Limitations

It could be argued that the current exploratory study is limited by the small sample size, but the current study does present a significant treatment effect of ET on pain and function, which are crucial outcome parameters in treatment of KOA[16].

Furthermore, this study is limited by the lack of a control group and therefore the modulatory capacity of the exercise program on pain mechanisms should be interpreted with care. Recent studies conclude that the exercise therapy program utilized in the current study reduces self-reported pain and enhances function[11], also when compared with no or minimal interventions in patients with KOA[9].

Conclusion

The current exploratory study reports that low pre-treatment EIH and high PDQ are independently associated with limited improvement in self-reported pain and function following standardized ET treatment in patients with KOA. This study adds to the emerging evidence that a subgroup of KOA patients characterized as "centrally pain sensitive" may exist and that these patients may require specialized treatment options targeting these mechanisms.

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Figure legends

Figure 1. Pressure pain thresholds before and after 2-minute lateral raises (2MLR) at baseline. *Indicates significant change ($P < 0.05$) in PPT after the exercise condition. QF, m. quadriceps femoris; DE, m. deltoideus. Values represent mean ± SEM and range (n=24).

Variable	Baseline		Follow-up		*P*
	Mean ± SEM	Range	Mean ± SEM	Range	
Age (y)	64.3 ± 1.5	51 - 78			
BMI (kg/m^2)	29.6 ± 0.9	20.7 – 36.6			
Sex (% female)	66.7				
Positive KOA criteria (0-6)	5.8 ± 0.1	4-6			
Pain duration (month)	48.3 ± 12.8	3 - 240			
Pain intensity (NRS 0-10)	5.6 ± 0.3	4 - 8	3.0 ± 0.4	0 - 8	<0.001
PDQ score (0-38)	8.4 ± 1.0	1 - 19	5.9 ± 0.6	0 - 14	0.009
KOOS subscales (0-100)					
Pain	57.3 ± 2.6	31 - 83	67.4 ± 3.1	44 - 94	0.005
Symptoms	63.2 ± 3.3	32 - 93	71.1 ± 3.0	39 - 96	0.050
ADL	68.2 ± 2.5	37 - 88	76.3 ± 2.8	43 - 94	0.010
QoL	46.6 ± 2.8	25 - 63	51.7 ± 3.4	13 - 81	0.205
KOOS-4	58.8 ± 2.3	33.3 – 81.8	66.6 ± 2.6	40.8 – 88.3	0.005

Table 1. Patient characteristics and self-reported variables before and immediately (1-2 weeks) after standardized exercise therapy. BMI, body mass index; KOA, knee osteoarthritis; NRS, numerical rating scale; PDQ, PainDETECT; KOOS, Knee Injury and Osteoarthritis Outcome Score; ADL, activities of daily living, QoL, quality of life; NSAIDs, non-steroid anti-inflammatory drugs. Values represent mean ± SEM and range (n=24).

PPT site	Baseline		Follow-up		*P*
	Mean ± SEM	Range	Mean ± SEM	Range	
Knee	363.1 ± 33.2	143 - 728	340.1 ± 27.3	138 - 634	0.775
TA	351.2 ± 34.7	112 - 831	324.7 ± 27.2	69 - 616	0.689
QF	318.2 ± 35.6	126 - 804	289.0 ± 25.1	125 - 608	0.710
DE	292.3 ± 31.4	109 - 579	286.4 ± 29.4	104 - 638	0.903

Table 2. Pressure pain thresholds before and after standardized exercise therapy. A significant main effect on PPTs from all measuring sites at baseline and follow-up was found (Friedman's, X^2 (7) =23.6; P = 0.001), with post hoc tests showing no changes in PPTs from all sites after exercise therapy (Wilcoxon; P > 0.6). TA, m. tibialis anterior; QF, m. quadriceps femoris; DE, m. deltoideus. Values represent mean ± SEM and range (n=24).

Model	Variable	Relative change KOOS-4		
		Standardized coefficient beta	*P*	Adjusted R^2
1				0.406
	PPT, knee	0.745	0.401	
	PPT, TA	-0.032	0.970	
	PPT, QF	-0.886	0.109	
	PPT, DE	0.411	0.312	
	TSP, knee	0.123	0.635	
	TSP, TA	-0.255	0.284	
	EIH, QF	0.392	0.196	
	EIH, DE	0.160	0.639	
	Pain duration	-0.013	0.960	
	Peak pain, NRS	0.384	0.199	
	PDQ score	0.620	**0.026**	
2			**0.002**	**0.468**
	PPT, knee	0.283	0.088	
	EIH, QF	0.594	**0.001**	
	PDQ score	0.570	**0.002**	

Table 3. Linear regression models using all mechanistic pain profiling parameters and clinical parameters before standardized exercise therapy to identify independent factors for relative change in KOOS-4 at follow-up. Model 1 included all baseline measures of pain pressure thresholds (PPTs), temporal summation of pain (TSP), normalized exercise-induced hypoalgesia (EIH), pain duration, clinical peak pain (NRS) and PainDETECT (PDQ) score. Model 2 included significant factors from model 1 using backwards selection. R^2 indicates the predictive value of each model. TA, m. tibialis anterior; QF, m. quadriceps femoris; DE, m. Deltoideus. 2MLR, 2-minute lateral raises. Bold p-values indicate significant factors in the models.