Exercise-induced hypoalgesia in young adult females with long-standing patellofemoral pain – A randomized crossover study

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EXERCISE INDUCED HYPOALGESIA IN YOUNG ADULT FEMALES WITH LONG-STANDING PATELLOFEMORAL PAIN – A RANDOMIZED CROSSOVER STUDY

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Abstract:	Background Patellofemoral pain (PFP) is a common knee pain condition where hip and knee exercises help improve treatment outcomes. This study compared the acute effect of hip versus knee exercise on anti-nociceptive and pro-nociceptive mechanisms in young females with long-standing PFP. Methods In this randomised cross-over study twenty-nine females with PFP performed hip and knee exercise in randomised order during a single day. Pressure pain thresholds (PPTs) were assessed by handheld pressure algometry at the patella, the tibialis anterior muscle, and the contralateral elbow. Cuff pressure algometry at the lower legs was used to assess pain detection threshold (cPDT) and tolerance (cPTT) as well as conditioned pain modulation (CPM: change in cPDT during contralateral cuff pain conditioning) and temporal summation of pain (TSP: ten painful cuff stimulations assessed on a visual analogue scale [VAS]). Results PPT at the tibialis anterior muscle but not at the patella increased compared with baseline following both exercises ($P<0.002$). Compared with baseline, the cPDTs and cPTTs increased after both types of exercise ($P<0.001$) where the cPTTs increased more after knee than hip exercise ($P<0.007$). VAS scores for TSP were increased following hip exercise ($P<0.001$) although the the rate of VAS increase over repeated stimulations was not significantly affected by exercise. The CPM-effect was reduced after both types of exercise ($P<0.001$). Conclusion A general hypoalgesic response to slowly increasing pressure stimuli was observed following both hip and knee exercise as well as decreased conditioned pain modulation, potentially indicating an attenuated ability from exercise to inhibit pain.

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EXERCISE INDUCED HYPOALGESIA IN YOUNG ADULT FEMALES WITH LONG-STANDING PATELLOFEMORAL PAIN – A RANDOMIZED CROSSOVER STUDY

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Running head: Acute effect of exercises on patellofemoral pain

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Significance: This study is the first to compare the acute effect of hip or knee exercise on exercise-induced hypoalgesia (EIH) in females with long-standing patellofemoral pain. In contrast to the hip exercise, an EIH response was detected following the knee exercise.

Abstract

Background: Patellofemoral pain (PFP) is a common knee pain condition where hip and knee exercises help improve treatment outcomes. This study compared the acute effect of hip versus knee exercise on anti-nociceptive and pro-nociceptive mechanisms in young females with long-standing PFP.

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Conclusion: A general hypoalgesic response to slowly increasing pressure stimuli was observed following both hip and knee exercise as well as decreased conditioned pain modulation, potentially indicating an attenuated ability from exercise to inhibit pain.

INTRODUCTION

Patellofemoral pain (PFP) is a knee condition characterized by diffuse anterior knee pain during activities that load the knee joint (Crossley et al., 2016a). This common pain complaint affects 6-7% of adolescents and a similar amount of adults (Smith et al., 2018). The long-term prognosis is poor, with one in two continuing to experience pain after 2 years that impacts physical activity levels, and quality of life (Noehren et al., 2016; Pazzinatto et al., 2016; Rathleff et al., 2015). Despite being considered as a "local" pain complaint, recent studies have shown localised and widespread pressure hyperalgesia, facilitated pro-nociceptice mechanisms, and impaired anti-nociceptive mechanisms compared to pain free controls (Holden et al., 2018; Rathleff et al., 2016a).

International consensus based on current evidence advocate knee and hip strengthening exercises as the main management strategy for PFP (Crossley et al., 2016b; van der Heijden et al., 2015). The rationale for including both knee and hip exercises in the management is that patients often experience strength deficits in these muscles (Lankhorst et al., 2012; Rathleff et al., 2014). Exercises to target these deficits is thought to improve strength, improve biomechanics of the patellofemoral joint and subsequently improve pain (Powers et al., 2017). However, this mechanism of effect has been challenged in recent studies. These studies found no strong association between improvements in muscle strength, biomechanics and pain (Piva et al., 2009; Rathleff et al., 2016b).

Another plausible explanation of the effect of exercises (and specifically hip exercise) for PFP is the analgesic effect of exercise. An acute bout of resistance exercise is associated with increased pressure pain thresholds (PPTs) in healthy individuals. This effect is termed exercise-induced hypoalgesia (EIH) (Vaegter et al., 2017). In patients however, exercising painful joints can also have the opposite effect and aggravate pain (cause hyperalgesia) (Vaegter et al., 2017), whereas exercising a distant non-painful joint may be associated with EIH (Burrows et al., 2014; Vaegter et al., 2017).

It has previously been proposed that the EIH response as an anti-nociceptive mechanism is related to descending pain inhibition which is psychophysically assessed by the conditioning pain modulation (CPM) paradigm (Lemley, Hunter, & Bement, 2015). Recently CPM was shown to be attenuated following EIH (Gajsar et al., 2018). Moreover, temporal summation of pain (TSP), a pro-nociceptive pain mechanism which is evaluated as the relative increase in pain to sequential stimuli with equal intensity, has also been shown to be attenuated by exercise (Alsouhibani et al., 2018; Vaegter et al., 2015a).

The aim of the current study was to investigate the acute effect of a hip exercise *versus* a knee exercise on local and widespread pain sensitivity in young female adults with PFP. A secondary aim was to compare their effects on anti- and pro- nociception (CPM and TSP respectively). It was hypothesised that 1) the hip exercise would have a greater EIH effect compared to the knee exercise, and 2) the knee exercise would induce more self-reported pain during the exercise 3) the hip exercise would reduce the gain of temporal summation of pain and reduce conditioned pain modulation to a greater extent compared to the knee exercise.

METHOD

Participants

This randomized crossover study was conducted at the Center for General Practice at Aalborg University in Aalborg, Denmark. Reporting of the study follows the CONSORT guidelines for randomized trials of Non-pharmacologic Treatment (Boutron et al., 2008). Ethical approval was obtained from the local ethics committee in the North Denmark Region (N-20160058). All participants received oral and written information before providing informed consent to enter the study. The study was pre-registered at Clinicaltrials.gov (NCT03054701) before the first subject was enrolled. The current study was imbedded within a larger cross-sectional study comparing pain sensitivity in young adults with current PFP, to those recovered from PFP and pain free controls (Clinicaltrial.gov, NCT03051412) (Holden et al., 2018).

Prior to conducting this study, a pilot study including 10 healthy participants was used to test the protocol and estimate the effect of hip and knee exercise on PPTs. Data from the published literature (Rathleff et al., 2016c) and results from the pilot study informed the sample size calculation. Based on data from the pilot study~~this~~, we estimated a 44 kPa larger EIH effect on PPTs after hip exercises compared to knee exercises. A common standard deviation of 80 kPa on PPTs (Rathleff et al., 2013a), a significance level of 0.05 and power set to 0.80, resulted in a minimum of 28 participants needed for this randomised cross-over design.

Participants were recruited from the population-based Adolescent Pain in Aalborg 2011 cohort (AA2011) (Rathleff et al., 2015; Rathleff et al., 2013b). In 2011, 153 participants with knee pain were diagnosed with PFP by a rheumatologist (Rathleff et al., 2015). In 2016, a five-year follow-up was conducted and a random sample of those who were initially diagnosed with PFP and still reported knee pain in 2016 were contacted to participate in the

current study.

Participants reporting knee pain at follow-up were contacted and screened via telephone. They were eligible for physical screening if they: reported ongoing or recurrent anterior or retro-patellar knee pain, worst knee pain last week above 3 points on a numeric rating scale, and experienced pain during at least two of the following activities: prolonged sitting or kneeling, single leg squatting, running, hopping, or stair walking, tenderness on palpation of the patella or double leg squatting. During the physical screening, it was confirmed that subjects still suffered from PFP. In addition, it was established that none of the subjects usually experienced pain radiating to their lower leg. Individuals with other identifiable knee conditions in isolation were excluded. However, participants who had other knee conditions, which occurred concurrently with PFP were eligible for inclusion. Individuals were excluded if they had sustained a traumatic injury to the hip, knee, ankle or the lumbar spine up to 3 months prior to enrolment, had rheumatoid arthritis, knee joint effusion, self-reported patellofemoral instability, known malign conditions, neurological disease or previous knee surgery.

Protocol

Participants were instructed not to consume caffeine, alcohol, or nicotine, and to avoid physically demanding activities 24 hours prior to participation as these factors potentially could influence the results. Moreover, ~~T~~they were requested to abstain from analgesics on the day of participation in the study. Participants were blinded to the study hypothesis. To ensure blinding to exercise order, two assessors were present for all participants. The first assessor obtained subject demographics including; age, gender, duration of pain and knee pain intensity on the day of inclusion. The first assessor also assigned the order in which participants would complete the hip and knee exercise and delivered the exercises. The test limb was selected as the knee in which they reported pain, or the most painful knee in cases of bilateral pain. The second assessor then completed all quantitative sensory testing (QST) assessments pre and post exercises, being blinded to the exercise order for each participant. The order of the exercises was randomised using www.random.org by an independent researcher, and stored in sequentially numbered, opaque sealed envelopes. The test-battery (Fig. 1) was completed before and immediately after the exercise and included assessment of pressure pain thresholds, cuff pain detection thresholds (cPDT) and cuff pain tolerance thresholds (cPTT), as well as temporal summation of pain (TSP) and conditioning pain

modulation (CPM). A 15-minute break separated the three test-conditions and the two exercises in order to avoid carryover effects. After testing, a short familiarisation session was undertaken, and then the exercise-sessions were completed. Post-testing occurred immediately after exercises.

Handheld pressure algometry

PPTs were collected with a handheld pressure algometer (Algometer type II by SOMEDIC Electronics, Solna, Sweden) with participants resting in a supine position. PPTs were collected at the centre of patella, the muscle belly of tibialis anterior and, the lateral epicondyle of the contralateral elbow (contralateral to the painful / most painful knee). The pressure was applied at a rate of 30 kPa/s at a perpendicular angle, to the skin surface. Participants pressed a handheld switch as soon as the stimulus changed from pressure to pain (defined as the pressure pain threshold). Two measures were repeated at each site with a short break in between, with the average being used for analysis. This method has been shown to be reliable with interclass correlation (ICCs) of 0.85-0.98 (Rathleff et al., 2017). PPTs at the centre of patella were the pre-defined primary outcome.

Computer-controlled cuff algometry

Participants were fitted bilaterally with 13-cm-wide silicone tourniquet cuffs (VBM, Düsseldorf, Germany) on the lower limbs. The superior rim of the cuff was placed 5 centimetres distal to the most prominent part of the tibial tuberosity. This was marked to ensure that the cuff was replaced at the same location at all time-points. The cuff inflation was controlled by a cuff algometry system (Cortex Technology, Hadsund, Denmark). A 10-cm electronic visual analogue scale (VAS) ("0 cm" corresponding to no pain and "10 cm" representing worst possible pain) with a stop button, was used to report the cuff pressure pain sensation. The cuff-system is user independent and has been shown to be reliable for the outcomes assessed (Graven-Nielsen et al., 2015; Polianskis et al., 2001).

To assess cuff pain detection thresholds (cPDT) and pain tolerance thresholds (cPTT), the cuff was inflated at a rate of 1 kPa/s to a maximum of 100kPa. Participants were instructed to rate the pressure pain continuously on the electronic VAS, until the pain became intolerable, at which point they should press the stop button to terminate the test. This point was defined as the cuff pain tolerance threshold (cPTT). If the tolerance threshold was not achieved before the 100 kPa limit, cPTT was defined as 100 kPa. Cuff pain detection threshold (cPDT) was

defined as the pressure at which the VAS rating was 1 cm. This procedure was completed at the leg with the most affected PFP knee and the contra-lateral leg.

Temporal summation of pain (TSP) was assessed by administering ten rapid cuff pressure stimuli at a pressure equivalent to the intensity of the cPTT. Each stimulus held this pressure for a duration of 1 s, followed by 1 s break before the next stimulus. Participants rated the pain intensity for each stimulus without returning the VAS to zero between inflations. For each stimulus, the recorded VAS score was extracted. The average VAS scores for the interval between the 1st and the 4th stimuli (VAS-I), and the average of the 8th to the 10th VAS score (VAS-II) were calculated. The TSP-effect was defined as the difference between VAS-I and VAS-II, (i.e. VAS-II minus VAS-I). This procedure has previously been found to be reliable with ICCs of 0.7-0.77 (Graven-Nielsen et al., 2015).

Conditioned pain modulation (CPM) was evaluated by re-assessing the cPDT of the test limb during a simultaneous painful conditioning stimulus on the contralateral leg. An increase in cPDT from baseline would indicate a CPM response. The conditioning stimulus on the contralateral leg was induced by the cuff, at the pressure equivalent to 70% of the cPTT of that leg. Upon commencement of the CPM test, the cuff inflated immediately at a rate of 100 kPa/s and maintained this pressure throughout the duration of the test. The cuff on the test limb simultaneously began to inflate at a rate of 1kPa per second, and cPDT was re-assessed as previously described. Participants were instructed to rate the pain on the test limb only, and to ignore the constant pressure pain on the contralateral limb from the conditioning stimulus. Both cuffs deflated at the end of the test when participants pressed the release button, or when the 100kPa limit was reached. The CPM-effect was calculated as the absolute change in cPDT ratings from baseline, to ratings obtained during the presence of the painful conditioning stimulus. Participants who reached the 100kPa limit at baseline, (i.e. prior to application of conditioning stimulus) were excluded from the CPM analysis.

Exercises-induced hypoalgesia

The hip exercises consisted of side-lying hip abduction, while the knee exercise were sitting knee extension. Exercises were performed with external resistance in the form of an elastic band (Thera-Band). To ensure the relative exercises intensity was identical between the exercises, the load (i.e. number of repetitions and sets), time under tension and rest between sets were the same for both exercises. The load during the exercise was the 12-repetition maximum (12RM), i.e. the elastic resistance at which participants were able to perform 12

repetitions only. This was established prior to each exercise during familiarisation, by using elastic bands with different thickness. After the training, the load was selected, participants performed three sets of 12 repetitions with a 120-s break between each set, for both the hip and the knee exercise. The concentric and the eccentric phase had a duration of 3 seconds, with a 2-second isometric phase in between. There was no rest between repetitions. The pace was maintained by a metronome (Metronom: Tempo Lite, 3.9.2 retrieved from AppStore). Full description of the exercises can be found online in supplementary material S1.

The EIH response was quantified by evaluating PPTs, cPDTs and cPTTs immediately before and after each exercise condition (hip or knee exercise). An increase in thresholds (assessed by subtraction) would indicate a positive EIH response.

During both hip and knee exercise sessions, participants rated pain on a 0 to 10 numeric rating scale (NRS) where 0 indicated "no pain" and 10 indicating "worst possible pain". This was done before, and immediately after each three exercise set. The NRS is applicable for quantifying pain in patients with chronic conditions and a change of 2 points in the NRS is considered clinically meaningful (Hawker et al., 2011).

*****Fig. 1 HERE *****

Statistical analyses

All statistical analyses were conducted in IBM SPSS statistics version 25. Unless stated otherwise, data are presented as means and 95% confidence intervals (95% CI) or median and inter-quartile range (IQR). P-values of <0.05 were considered significant. An assessment for approximate normal distribution was done by inspection of QQ-plots and with the Shapiro Wilks test.

The assumption of negligible carryover effects and effect of exercise order were investigated with unpaired t-tests and inspection of mean values and 95% confidence intervals (Wellek & Blettner, 2012) on the primary outcome (PPT at the centre of patella). To investigate whether there was a difference in response to the hip and the knee exercise, two-way repeated measures analysis of variances (ANOVAs) were used with the within subject factors being time (pre *versus* post exercise), and type of exercise (knee *versus* hip) for each of the following outcome: PPTs at the three locations, cPDTs, cPTTs, CPM-effect, TSP-effect and

EIH-effect. In cases of significant interaction, post-hoc comparison was done using Fisher's least significant difference (LSD).

Assessing the effect of the hip and the knee exercise on knee pain during exercise, all sessions which lead to a clinically meaningful increase of two NRS points or more from before to after exercise (pain flare) were identified and compared with Chi^2 statistics.

As an explorative analysis it was tested if those participants with the highest pain NRS score at baseline had a larger EIH response (based on handheld PPTs). In an additional analysis we also tested the association between baseline CPM effect and the EIH effect. These analyses were done using Pearson' correlations.

RESULTS

Participants

Thirty participants were recruited for the study and data was collected between March 7 and May 17, 2017. One rated her worst knee pain during last week as less than 3 on the NRS on the test day and was excluded from the study before undergoing baseline testing. Twenty-nine females [age: median 23 years (range 21-24)]; BMI (body weight in kilos divided by height in meters squared); median 23 kg/m^2 (range 17-32 kg/m^2) who had experienced knee pain for a median duration of 8 years (range 5-12 years) participated and were included in the analysis. Participants pain characteristics were as follows (based on available data from 28/29 participants); worst pain during last week (median: 7, range: 3-9), average pain during last week (median: 4, range: 1.5-8) and pain intensity at the time of inclusion (median: 2, range 0-7). There was no evidence of a carry-over effect or an effect of the order of exercises.

Knee pressure pain threshold (primary analysis)

There was no main effect of time (Table 1; $F(1,28)=0.017$; $p=0.898$) (pre *versus* post exercise) on PPTs at the centre of patella. Further, there were no significant time * exercise interaction for PPTs at the centre of patella ($F(1,28)=0.465$; $p=0.501$).

Distant pressure pain threshold (secondary analyses)

A significant effect of time ($F(1,28)=12.256$; $p=0.002$) was detected at the tibialis anterior muscle (Table 1; mean: 33.5 kPa; 95% CI: 13.9-53.1), indicating an EIH response at this location, which was independent of exercise paradigm. Moreover, no significant main effect of time ($F(1,28)=0.012$; $p=0.912$) was detected at the contralateral elbow. There was no

significant interaction between time and exercise for PPTs at the tibialis anterior muscle (F(1,28)=0.001; p=0.972) or the contralateral elbow (F(1,28)=0.260; p=0.614).

Cuff pressure pain sensitivity (secondary analyses)

The was no significant interaction of time and exercise on cPDT (F(1,28)=0.046; p=0.833) but a main effect of time (F(1,28)=32.161; p=0.001) was found for the cPDT (Table 1; mean: 4.9 kPa; 95% CI: 3.1-6.7) indicating the EIH response was independent of the type of exercise. In contrast, a significant time * exercise interaction was found for the cPTTs (F(1,28)=8.556; p=0.007) reflecting a significant EIH response which was dependant of the exercise paradigm. Post-hoc test revealed an increase in cPTT following the knee exercise (Table 1; mean: 6.8 kPa; 95% CI: 4.4-9.1) which was larger compared to the hip exercise (Table 1; mean: 2.6 kPa; 95% CI: 0.8-4.5; LSD: p<0.001) (Fig. 2).

***** Fig. 2. HERE*****

Temporal summation of pain

Data from the first stimulus was excluded for 3 participants before the hip exercise and 5 participants before the knee exercise as they did not rate the first stimulus. In these cases VAS-I was calculated as the average of the interval between the 2 and the 4 stimuli.
There was no significant main effect of time (F(1,28)=0.224; p=0.432). There was also no significant time * exercise interaction on the TSP-effect (i.e. VAS II minus VAS I) (F(1,28)=1.2; p=0.28).

There was a significant time* exercise interaction for VAS-I (Table 1; F(1,28)=9.7; p=0.004) and VAS-II scores (F(1,28)=7.71; p=0.01). Post hoc test showed that VAS I was increased after hip exercise (mean: 1.1 cm; 95% CI: 0.7-1.6; p<0.001)) but not knee exercise (mean: 0.0 cm; 95% CI: -0.5-0.5). VAS-II was also increased following hip exercise (mean: 1.3 cm; 95% CI: 0.7-2.0;p<0.001) but not significantly after the knee exercise (mean: -0.3 cm; 95% CI: -1.0-0.4). Despite no change in the TSP effect, this indicates an upward shift of VAS ratings after hip exercises (Fig. 3).

***** Fig. 3 HERE*****

Conditioned pain modulation

Two participants reached 100 kPa on both the leg most affected by PFP and the contralateral leg and were therefore excluded from the analysis. There was a significant main effect of time on CPM-effect assessed by cPDT ($F(1,26)=13.900$; $p=0.001$), with a significant decrease in the CPM-effect post exercise, independent of exercise paradigm. There was no significant time * exercise interaction on the CPM-effect evaluated as cPDT ($F(1,26) = 0.002$: $p=0.961$). CPM before and after exercise can be found in Table 1.

Exercise-induced pain

Pain flares (i.e. change greater than or equal to 2 NRS points) occurred 10 times during the hip exercise and 16 times during the knee exercise, which was not significantly different ($\chi^2(1) = 1.357$, $p=0.244$).

Explorative analyses

There was no association between the clinical pain experienced at baseline ~~pain~~ (measured as NRS scores on the day of inclusion) and the change in EIH assessed at the centre of patella for either the hip exercise ($r(28)=0.178$; $p=0.365$) or the knee exercise ($r(28)=0.006$; $p=0.975$).

There was a significant positive association of moderate strength between baseline CPM prior to the knee exercise and the EIH response at the tibialis anterior following the knee exercise ($r(27)=0.494$; $p=0.009$) (see supplementary material S2).

***** Table 1 HERE*****

DISCUSSION

Contrary to the main hypothesis, there was no superior effect of hip exercises on PPT at the patella compared to the knee exercise. There were no significant change in PPT at the patellar following either of the two exercises. Overall, an EIH was detected on PPT at the tibialis anterior muscle and cPDT, with no differences between exercise. No EIH effect was detected at the contralateral elbow. Furthermore, the knee exercise resulted in a significantly greater EIH effect evaluated by cPTT. Neither exercise type successfully modulated TSP-effect, but

VAS pain scores during the paradigm (VAS I and VAS II) was significantly greater after hip exercises. CPM was decreased following both types of exercise.

Exercise induced hypoalgesia

It was hypothesized that the hip exercise would lead to a larger acute EIH response because previous research has shown upper-body exercises (e.g. chest press and lat pulldown) have an EIH response in individuals with knee OA, whereas lower-body exercises (e.g. leg press and calf raise) does not (Burrows et al., 2014). Contrary to the hypothesis, there was a difference between exercises for one outcome only (pain tolerance (cPTT)) which knee extension exercise was more effective in modulating. This could be due to the fact that EIH has the greater response closest to the site of exercising muscles (Alsouhibani et al., 2018; Vaegter et al., 2014). Surprisingly, the hip abduction exercise increased VAS ratings during the temporal summation of pain paradigm. This is surprising as EIH is presumed to be centrally mediated and can reduce TSP (Vaegter et al., 2015a), which did not occur in our study.

Additionally, in the current study the EIH effect detected was small and not consistent across outcomes. The magnitude of the EIH effect has recently been shown to be diminished when evaluated after a CPM paradigm (Gajsar et al., 2018) which may have influenced the possibility to detect EIH in the current study. Further, it is unknown if patients have a similar EIH response, as the majority of research has been on healthy individuals (Koltyn.F, 2000). Chronic pain patients demonstrate increased pain sensitivity which has also been associated with an inefficient EIH (Vaegter et al., 2016). This may be important, and could have influenced the EIH effect as the current study included participants with long-standing pain. This is speculative as no healthy controls were included, but the protocol was piloted on healthy participants which successfully induced analgesia.

Pain modulation after exercise

It is possible that EIH and CPM may act through some of the same shared mechanisms as individuals with a greater CPM effect also experience greater EIH response (Lemley et al., 2015; Stolzman & Bement, 2016). In patients, those with the lowest CPM effect also have a decreased EIH response (Fingleton, Smart, & Doody, 2017). However, other studies have found that CPM and EIH are either weakly or not correlated (Vaegter et al., 2014; Vaegter, Handberg, Jørgensen, Kinly, & Graven-Nielsen, 2015b). In our data, we also found in the exploratory correlation, that baseline CPM and EIH were positively correlated (i.e. those with the highest CPM response also had the highest EIH response). Until recently, little was known

how CPM behaves in response to exercise, and if exercise could potentially 'boost' or 'dampen' the CPM effect. The current findings of a decreased CPM effect after exercise corresponds with a recent study demonstrating that CPM is decreased subsequent to exercise (Alsouhibani et al., 2018). Gajsar et al., 2018 suggested that if CPM and EIH share similar descending pain inhibitory mechanisms, further subsequent CPM effect may not be possible due to a ceiling effect (Gajsar et al., 2018). As the effect of CPM is thought to last less than 10 minutes (Kennedy et al., 2016) , it is unclear if this could have had an influence the current study design.The decreased CPM following exercise in our study corroborates with findings from healthy controls and highlight the need for further research.

Exercised-induced pain

Overall pain ratings during the repeated cuff stimulation paradigm (VAS I and VAS II) were systematically increased following the hip exercise. It remains to be investigated whether or not these findings are specific to people with PFP or how hip exercise increase pain in this population.

Strengths and limitations

The randomized design, being pre-registered with a blinded assessor and participants, being blinded to study hypothesis are significant strengths of the study. Further, recruitment of participants from a population-based cohort increase the generalizability of the findings in the study. It should however be noted that only females were included. A potential limitation to the design is that participants performed both the exercises on the same day. Although EIH and CPM may share underlying mechanisms for inhibition of pain, the effect of these mechanisms seems to decline following a certain amount of inhibition as the EIH response was found to be affected by CPM and vice versa (Gajsar et al., 2018). Therefore, it is unclear if a greater EIH effect would have been detected if CPM had not been conducted prior to the exercises. Finally, the study population were particularly chronic, reporting a long pain duration (median 8 years). Multiple studies have found that ongoing peripheral input (Graven-Nielsen et al., 2015; Laursen, Graven-Nielsen, Jensen, & Arendt-Nielsen, 1997) and pain duration (Arendt-Nielsen et al., 2014), may influence pain sensitivity and modulatory characteristics, meaning the results may not be generalisable to patients with a shorter duration of pain.

CONCLUSION

Contrary to the main hypothesis, there was no superior effect of hip exercises on pain pressure thresholds at the patella compared to the knee exercise. The knee exercise had a greater effect on pressure tolerance threshold, and hip exercise increased pain ratings for temporal summation of the pain paradigm. Future studies need to investigate the effects of cumulative exposure to exercises on quantitative sensoriy testing in a similar population.

Author contributions

All authors contributed to the conceptualication and continiues development of the study as well as providing intellectual contributions regarding content. C.L.S., M.S.R. and S.H. contributed to the analysis, interpretation of data and drafting of the manuscript. All authors discussed the results and commented on and approved the final manuscript.

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Figure ledges

Fig 1: Flowchart of study protocol.

Fig. 2: Mean (+95%CI) cuff pain tolerance thresholds (cPTT) values pre (solid bars) and post (grey bars) hip and knee exercise. Significant different (*, $p<0.05$).

Fig. 3: Mean responses (95% confidence interval, N=29) for the visual analogue scale (VAS) scores related with the 10 cuff pressure stimuli during testing of temporal summation of pain before (grey line) and after (solid line) the hip exercise (a) and knee exercise (b).

Ledge for Table 1

Table 1: Quantitative sensory testing presented with means and 95% confidence intervals.

Footnotes for Table 1

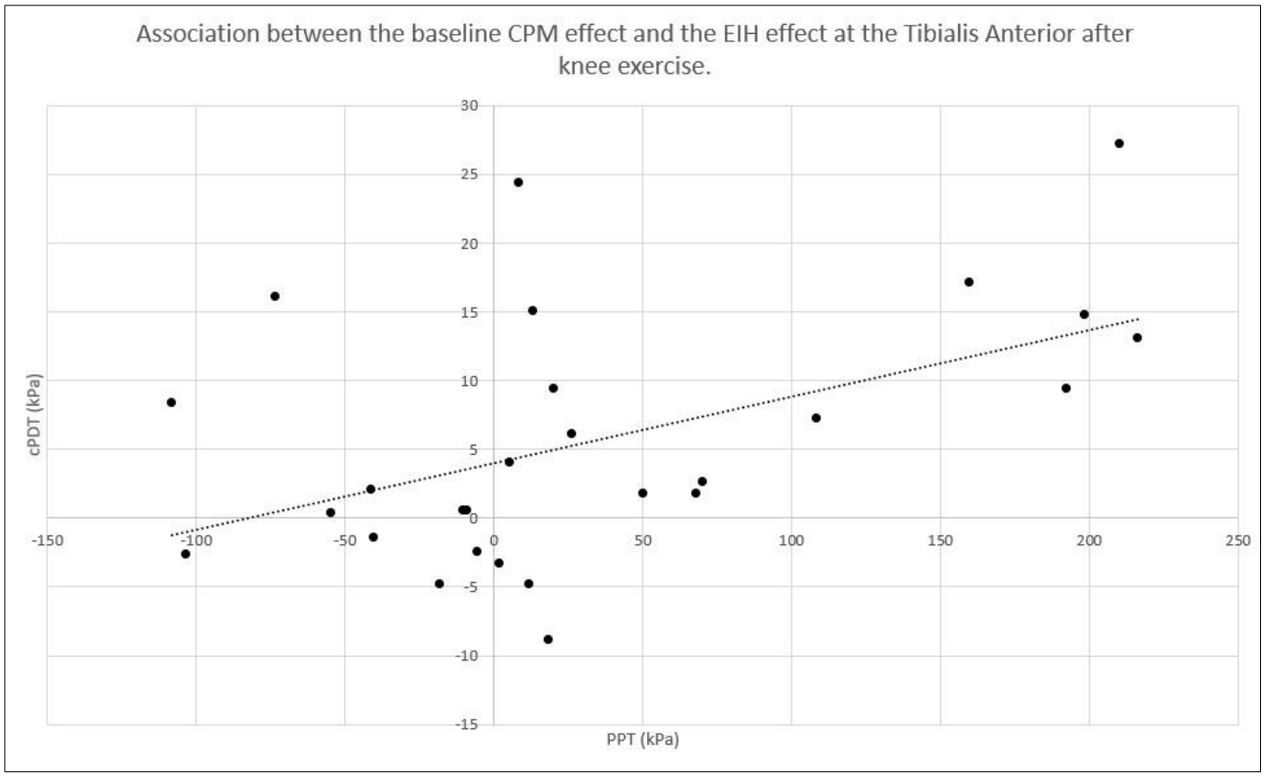
(a) Data from 27 participants were used.
(b) P-values are provided by repeat measures ANOVA.

Table 1 Quantitative sensory testing

Handheld PPTs (kPa)	Before Hip exercise	After Hip exercise	Before Knee exercise	After Knee exercise	p-value (b)	
					Time x exercise	Time
Centre of patella	410 (95%CI: 340-480)	420 (95%CI: 346-494)	419 (95%CI: 348-489)	412 (95%CI: 339-485)	0.501	0.898
M. Tibialis Anterior	375 (95%CI: 297-453)	408 (95%CI: 327-488)	384 (95%CI: 307-462)	418 (95%CI: 331-505)	0.972	0.002
Contralateral Elbow	380 (95%CI: 319-441)	375 (95%CI: 316-435)	389 (95%CI: 325-452)	396 (95%CI: 330-462)	0.614	0.912
cPDT (kPa)	24.1 (95%CI: 19.1-29.1)	28.8 (95%CI: 23.8-33.9)	25.6 (95%CI: 21.1-30.1)	30.6 (95%CI: 24.9-36.5)	0.833	0.001
cPTTs (kPa)	51.9 (95%CI: 44.9-58.8)	54.5 (95%CI: 47.6-61.4)	45.1 (95%CI: 38.5-51.7)	51.9 (95%CI: 44.9-58.8)	0.007	0.001
CPM (absolute change in cPDT) (a)	5.3 (95%CI: 3.1-7.6)	1.9 (95%CI: -1.6-5.2)	5.6 (95%CI: 2.0-9.2)	2.1 (95%CI: -0.7-4.9)	0.961	0.001
TSP (VAS II-VAS I)	1.2 (95%CI: 0.7-1.8)	1.4 (95%CI: 1.0-1.8)	1.6 (95%CI: 1.1-2.0)	1.2 (95%CI: 0.8-1.8)	0.281	0.640
VAS-I	4.2 (95%CI: 3.4-5.0)	5.3 (95%CI: 4.6-6.1)	4.8 (95%CI: 4.1-5.6)	4.8 (95%CI: 4.1-5.6)	0.004	0.001
VAS-II	5.4 (95%CI: 4.4-6.4)	6.7 (95%CI: 6.0-7.5)	6.4 (95%CI: 5.5-7.3)	6.1 (95%CI: 5.2-7.0)	0.01	0.005

Supplementary material S2 - Explorative analyses

There was a significant positive association of moderate strength between baseline CPM prior to the knee exercise and the EIH response at the tibialis anterior following the knee exercise ($r(27)=0.494$; $p=0.009$).



The CPM effect is presented as cuff pain detection thresholds (cPDT) and EIH as pressure pain thresholds (PPT). The dotted line represents the tendency of the association.