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European Journal of Pain

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

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Abstract:	<p>Background</p> <p>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.</p> <p>Methods</p> <p>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]).</p> <p>Results</p> <p>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 rate of VAS increase over repeated stimulations was not significantly affected by exercise. The CPM-effect was reduced after both types of exercise ($P < 0.001$).</p> <p>Conclusion</p> <p>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.</p>

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

3

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5

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12 Technology, Aalborg University

13 **Running head:** Acute effect of exercises on patellofemoral pain

14 **Original article for:** Eur J Pain

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

26

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29 knee exercises help improve treatment outcomes. This study compared the acute effect of hip
30 versus knee exercise on anti-nociceptive and pro-nociceptive mechanisms in young females
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48 observed following both hip and knee exercise as well as decreased conditioned pain
49 modulation, potentially indicating an attenuated ability from exercise to inhibit pain.

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55 INTRODUCTION

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

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

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

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

88 The aim of the current study was to investigate the acute effect of a hip exercise *versus* a knee
89 exercise on local and widespread pain sensitivity in young female adults with PFP. A
90 secondary aim was to compare their effects on anti- and pro- nociception (CPM and TSP
91 respectively). It was hypothesised that 1) the hip exercise would have a greater EIH effect
92 compared to the knee exercise, and 2) the knee exercise would induce more self-reported pain
93 during the exercise 3) the hip exercise would reduce the gain of temporal summation of pain
94 and reduce conditioned pain modulation to a greater extent compared to the knee exercise.
95

96 **METHOD**

97 *Participants*

98 This randomized crossover study was conducted at the Center for General Practice at Aalborg
99 University in Aalborg, Denmark. Reporting of the study follows the CONSORT guidelines
100 for randomized trials of Non-pharmacologic Treatment (Boutron et al., 2008). Ethical
101 approval was obtained from the local ethics committee in the North Denmark Region (N-
102 20160058). All participants received oral and written information before providing informed
103 consent to enter the study. The study was pre-registered at Clinicaltrials.gov (NCT03054701)
104 before the first subject was enrolled. The current study was imbedded within a larger cross-
105 sectional study comparing pain sensitivity in young adults with current PFP, to those
106 recovered from PFP and pain free controls (Clinicaltrial.gov, NCT03051412) (Holden et al.,
107 2018).

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

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

121 current study.

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

136

137 *Protocol*

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

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

158

159 *Handheld pressure algometry*

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

170

171 *Computer-controlled cuff algometry*

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

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

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

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

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

212

213 *Exercises-induced hypoalgesia*

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

220 repetitions only. This was established prior to each exercise during familiarisation, by using
221 elastic bands with different thickness. After the training, the load was selected, participants
222 performed three sets of 12 repetitions with a 120-s break between each set, for both the hip
223 and the knee exercise. The concentric and the eccentric phase had a duration of 3 seconds,
224 with a 2-second isometric phase in between. There was no rest between repetitions. The pace
225 was maintained by a metronome (Metronom: Tempo Lite, 3.9.2 retrieved from AppStore).
226 Full description of the exercises can be found online in [supplementary material S1](#).
227 The EIH response was quantified by evaluating PPTs, cPDTs and cPTTs immediately before
228 and after each exercise condition (hip or knee exercise). An increase in thresholds (assessed
229 by subtraction) would indicate a positive EIH response.
230 During both hip and knee exercise sessions, participants rated pain on a 0 to 10 numeric rating
231 scale (NRS) where 0 indicated “no pain” and 10 indicating “worst possible pain”. This was
232 done before, and immediately after each three exercise set. The NRS is applicable for
233 quantifying pain in patients with chronic conditions and a change of 2 points in the NRS is
234 considered clinically meaningful (Hawker et al., 2011).

235

236

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

238

239 *Statistical analyses*

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

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

252 EIH-effect. In cases of significant interaction, post-hoc comparison was done using Fisher's
253 least significant difference (LSD).
254 Assessing the effect of the hip and the knee exercise on knee pain during exercise, all sessions
255 which lead to a clinically meaningful increase of two NRS points or more from before to after
256 exercise (pain flare) were identified and compared with Chi² statistics.
257 As an explorative analysis it was tested if those participants with the highest pain NRS score
258 at baseline had a larger EIH response (based on handheld PPTs). In an additional analysis we
259 also tested the association between baseline CPM effect and the EIH effect. These analyses
260 were done using Pearson' correlations.

262 **RESULTS**

263 *Participants*

264 Thirty participants were recruited for the study and data was collected between March 7 and
265 May 17, 2017. One rated her worst knee pain during last week as less than 3 on the NRS on
266 the test day and was excluded from the study before undergoing baseline testing. Twenty-nine
267 females [age: median 23 years (range 21-24)]; BMI (body weight in kilos divided by height in
268 meters squared); median 23 kg/m² (range 17-32 kg/m²) who had experienced knee pain for a
269 median duration of 8 years (range 5-12 years) participated and were included in the analysis.
270 Participants pain characteristics were as follows (based on available data from 28/29
271 participants); worst pain during last week (median: 7, range: 3-9), average pain during last
272 week (median: 4, range: 1.5-8) and pain intensity at the time of inclusion (median: 2, range 0-
273 7). There was no evidence of a carry-over effect or an effect of the order of exercises.

274 *Knee pressure pain threshold (primary analysis)*

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

278 *Distant pressure pain threshold (secondary analyses)*

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

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

285 *Cuff pressure pain sensitivity (secondary analyses)*

286 There was no significant interaction of time and exercise on cPDT ($F(1,28)=0.046$; $p=0.833$)
287 but a main effect of time ($F(1,28)=32.161$; $p=0.001$) was found for the cPDT (Table 1; mean:
288 4.9 kPa; 95% CI: 3.1-6.7) indicating the EIH response was independent of the type of
289 exercise. In contrast, a significant time * exercise interaction was found for the cPTTs
290 ($F(1,28)=8.556$; $p=0.007$) reflecting a significant EIH response which was dependant of the
291 exercise paradigm. Post-hoc test revealed an increase in cPTT following the knee exercise
292 (Table 1; mean: 6.8 kPa; 95% CI: 4.4-9.1) which was larger compared to the hip exercise
293 (Table 1; mean: 2.6 kPa; 95% CI: 0.8-4.5; LSD: $p<0.001$) (Fig. 2).

294

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

296

297 *Temporal summation of pain*

298 Data from the first stimulus was excluded for 3 participants before the hip exercise and 5
299 participants before the knee exercise as they did not rate the first stimulus. In these cases
300 VAS-I was calculated as the average of the interval between the 2 and the 4 stimuli.

301 There was no significant main effect of time ($F(1,28)=0.224$; $p=0.432$). There was also no
302 significant time * exercise interaction on the TSP-effect (i.e. VAS II minus VAS I)
303 ($F(1,28)=1.2$; $p=0.28$).

304 There was a significant time* exercise interaction for VAS-I (Table 1; $F(1,28)=9.7$; $p=0.004$)
305 and VAS-II scores ($F(1,28)=7.71$; $p=0.01$). Post hoc test showed that VAS I was increased
306 after hip exercise (mean: 1.1 cm; 95% CI: 0.7-1.6; $p<0.001$) but not knee exercise (mean: 0.0
307 cm; 95% CI: -0.5-0.5). VAS-II was also increased following hip exercise (mean: 1.3 cm; 95%
308 CI: 0.7-2.0; $p<0.001$) but not significantly after the knee exercise (mean: -0.3 cm; 95% CI: -
309 1.0-0.4). Despite no change in the TSP effect, this indicates an upward shift of VAS ratings
310 after hip exercises (Fig. 3).

311

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

313

314 *Conditioned pain modulation*

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

321 *Exercise-induced pain*

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

325 *Explorative analyses*

326 There was no association between the clinical pain experienced at baseline pain (measured as
327 NRS scores on the day of inclusion) and the change in EIH assessed at the centre of patella
328 for either the hip exercise ($r(28)=0.178$; $p=0.365$) or the knee exercise ($r(28)=0.006$;
329 $p=0.975$).

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

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

334

335 **DISCUSSION**

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

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

344 *Exercise induced hypoalgesia*

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

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

365 *Pain modulation after exercise*

366 It is possible that EIH and CPM may act through some of the same shared mechanisms as
367 individuals with a greater CPM effect also experience greater EIH response (Lemley et al.,
368 2015; Stolzman & Bement, 2016). In patients, those with the lowest CPM effect also have a
369 decreased EIH response (Fingleton, Smart, & Doody, 2017). However, other studies have
370 found that CPM and EIH are either weakly or not correlated (Vaegter et al., 2014; Vaegter,
371 Handberg, Jørgensen, Kinly, & Graven-Nielsen, 2015b). In our data, we also found in the
372 exploratory correlation, that baseline CPM and EIH were positively correlated (i.e. those with
373 the highest CPM response also had the highest EIH response). Until recently, little was known

374 how CPM behaves in response to exercise, and if exercise could potentially ‘boost’ or
375 ‘dampen’ the CPM effect. The current findings of a decreased CPM effect after exercise
376 corresponds with a recent study demonstrating that CPM is decreased subsequent to exercise
377 (Alsouhibani et al., 2018). Gajsar et al., 2018 suggested that if CPM and EIH share similar
378 descending pain inhibitory mechanisms, further subsequent CPM effect may not be possible
379 due to a ceiling effect (Gajsar et al., 2018). As the effect of CPM is thought to last less than
380 10 minutes (Kennedy et al., 2016) , it is unclear if this could have had an influence the current
381 study design. The decreased CPM following exercise in our study corroborates with findings
382 from healthy controls and highlight the need for further research.

383 *Exercised-induced pain*

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

388 *Strengths and limitations*

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

404

405 **CONCLUSION**

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

411

412 **Author contributions**

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

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563

564

565 Figure ledges

566

567 **Fig 1:** Flowchart of study protocol.

568

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

571

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

575

576 Ledge for Table 1

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

578

579 Footnotes for Table 1

580 (a) Data from 27 participants were used.

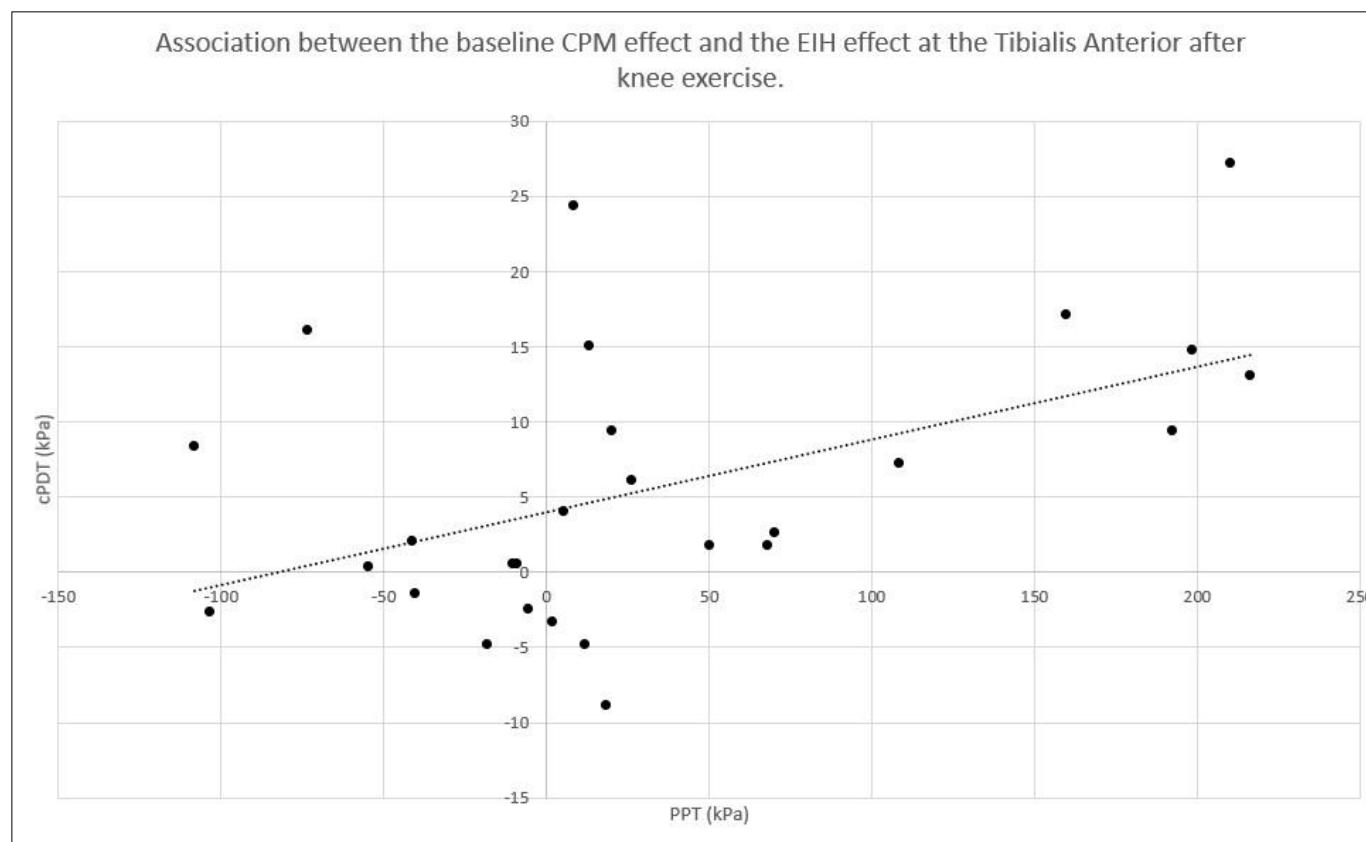
581 (b) P-values are provided by repeat measures ANOVA.

582

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.