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Local and widespread hyperalgesia in female runners with patellofemoral pain are influenced by running volume

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Objectives: To compare pressure pain threshold (PPT) around the knee (local hyperalgesia) and at a site remote to the knee (widespread hyperalgesia) between female runners with and without patellofemoral pain (PFP); and to evaluate the relationship between running volume, self-reported knee function and PPT measures.

Design: Cross-sectional study.

Methods: Twenty female runners with PFP and twenty pain-free female runners participated in the study. PPTs were measured using a handheld pressure algometer at four sites in the patellar region: quadriceps tendon, medial patella, lateral patella and patellar tendon; and on the contralateral upper limb. Additionally, all participants were asked to report their average weekly
running volume in a typical month and answer the anterior knee pain scale (AKPS) questionnaire.

**Results:** For all sites, female runners with PFP presented lower PPT measures in comparison with control group (P<0.017). There were negative correlations between AKPS and running volume (ρ= -0.88; P<0.001) and between all PPTs and the running volume in the PFP group with correlation (ρ) values ranging between -0.46 and -0.70 (P<0.022). There were positive correlations between all PPTs and AKPS with correlation (ρ) value from 0.50 to 0.69 (P<0.030).

**Conclusion:** Lower PPTs locally and remote to the knee in female runners with PFP indicate the presence of local and widespread hyperalgesia. Additionally, this hyperalgesia, which is related to self-reported knee function, appears to be increased by greater running volumes. Development and evaluation of non-mechanical interventions for the management of running-related PFP in females may be needed to address this apparent hyperalgesia.

**Keywords:** Patellofemoral joint; Anterior knee pain; Hyperalgesia secondary; Athlete; Knee; Pain.
Introduction

Running is a very common and popular form of exercise due its low cost and ease of access. However, there is a high incidence of lower extremity injuries among runners, with estimates reaching as high as 79%, with the knee being the most commonly affected site\(^1\). Patellofemoral pain (PFP) is the most common running-related knee injury\(^2\), and is particularly common in females aged 18-35, with an estimated prevalence being 13%\(^3\). Symptoms often become chronic and may reduce sports and daily activity participation, with chronicity associated with PFP also thought to increase the risk of developing osteoarthritis in later life\(^4\).

A recent systematic review with meta-analysis\(^5\) reported that athletes had higher pain thresholds when measured using a variety of methods, including pressure pain threshold (PPT)\(^6\), in comparison with normally active controls. This may be protective against hyperalgesia\(^7\) associated with conditions such as PFP\(^8,9\). Moreover, Hoffman and colleagues\(^10\) reported that greater running volume per week leads to reduced pressure pain perception compared with smaller running volumes. These findings indicate higher PPT relate to more active runners without pathology\(^5,10\).

Although higher physical activity levels appear to protect against pain sensitization in uninjured runners, it is unclear if this same relationship exists in injured runners. It is well established that females with PFP present local and widespread hyperalgesia\(^8,9\) measured by PPT. However, PPTs in female runners with PFP are yet to be evaluated in the literature. Therefore, it is unclear whether high levels of activity (i.e. running volume) in female runners with PFP provides protection against pain sensitivity, has no effect on sensitization, or in fact increases sensitization in the presence of pathology. The latter is highly plausible since sensitization and hyperalgesia are thought to be contributed by the persistent presence of pain and symptoms\(^11\), which is frequently aggravated by running in PFP\(^12\). If true, this may have particularly important implications for the management of PFP, including the possible need to
incorporate pain neuroscience education alongside current evidence based biomechanical and strength targeted treatments in female runners with PFP\textsuperscript{13,14}.

The aims of this study were to (i) compare PPTs around the knee (local hyperalgesia) and at a site remote to the knee (widespread hyperalgesia) between female runners with and without PFP; and (ii) evaluate correlations between running volume (i.e. number of kilometers run per week), self-reported knee function and PPT measures in female runners with and without PFP. Due to impaired endogenous pain inhibitory mechanism previously reported in females with PFP\textsuperscript{15} we hypothesized that female runners with PFP would also (i) present with lower PPTs compared to female runners without PFP; and (ii) running volume would be negatively correlated with PPTs and self-reported knee function would be positively correlated with PPTs in female runners with PFP.

**Methods**

Reporting of this cross-sectional study is in accordance to STROBE guideline recommendations. Twenty female runners with PFP (PFP group - PFPG) aged 18-35 and twenty asymptomatic female runners (Control group - CG) were recruited via advertisements in fitness centres and public places for physical activity, between September 2015 and February 2016. All participants had been running at least 15 km per week prior to enrolment for the minimum period of six months\textsuperscript{16}. Power calculations for this study were performed based on a pilot data (n = 8 for each group). Conservatively, we chose the PPT of patellar tendon, because it was the variable with higher standard deviation and lower detectable difference. Sample size was determined on the basis of predicted power to detect a difference of 1.27kgf (SD 1.22) in PPT of patellar tendon between groups, considering an $\alpha$ level of .05 and a power of 80\%. Based on the calculations performed with SamplePower software a minimum sample size of 14 participants per group was indicated.
Runners with PFP were included if they had (1) symptoms of insidious onset and duration of at least 3 months; (2) anterior knee pain during at least 2 of the following activities: prolonged sitting, squatting, kneeling, climbing stairs, and jumping; (3) anterior knee pain during running; and (4) worst pain level in the previous month at least 3cm on a 10cm VAS. To be included in the CG participants could not present any signs, symptoms or historical of PFP or other current musculoskeletal injury. Exclusion criteria for both groups were: events of patellar subluxation or dislocation, lower limb inflammatory process, lower limb surgery, patellar tendon or meniscus tears, bursitis, ligament tears or the presence of neurological diseases. The inclusion and exclusion criteria were verified following consensus from two experienced clinical physiotherapists (> 5 years’ experience). The study was approved by the Local Ethics Committee and each participant gave written informed consent prior to participation. The participants included were asked to avoid pain medications on the day of their evaluation (none of the participants reported use of any medications).

PPTs were measured using a handheld pressure algometer (Wagner FPX™ 25, Greenwich, CT, USA) with a probe of 1cm² placed perpendicular to the skin. Participants were instructed to indicate when the sensation changed from a sensation of pressure to the first sensation of pain.

All measurements were performed in the same period of the day and by the same trained rater to a pressure rate of 0.50kgf/s. The assessor was blinded concerning groups. All evaluations were performed with participants in a standardized position, supine with slightly flexed knees at 20°. For PFPG, we evaluated the symptomatic knee and for CG, we chose the knee of the dominant leg. Four sites in the patellar region were selected to investigate local hyperalgesia: quadriceps tendon (QT), medial patella (MP), lateral patella (LP) and patellar tendon (PT); and on a contralateral upper limb (UL) to reflect widespread hyperalgesia (the lesser tubercle of the humerus). PPT was measured twice at each site with a 30-second period between testing, and the average was used for analysis.
Half of the participants (Ten female runners with PFP and ten asymptomatic female runners) were invited to return at the lab for repeat the evaluation with an interval of 2 to 7 days of the first evaluation to calculate the intra-rater reliability using the intraclass correlation coefficient (ICC2,k) with a confidence interval of 95%, standard error of measurement (SEM) and the minimal detectable change with a confidence level of 95% (MDC95) for PPT measures. All PPT measures demonstrated satisfactory reliability with ICC values ranging between 0.79 to 0.93 for CG (UL and PT, respectively) and 0.67 to 0.91 for PFPG (UL and QT, respectively). Additionally, the measures presented values of SEM ranging between 1.1% to 22.7% and values of MDC95 ranging between 0.17 to 2.27 (Supplementary material).

Prior to the PPT measurements, all participants were asked to rate their worst knee pain intensity during the last 4 weeks, and current pain measured on a 0–10 visual analogue scale (VAS). Additionally, symptom duration (months), self-reported knee function (Anterior Knee Pain Scale – AKPS) and running volume (number of kilometers run per week in a typical month) were recorded. The AKPS is a 13-item questionnaire that evaluates subjective symptoms and functional limitations associated with PFP. The questionnaire score ranges from 0 to 100, with the maximum total score of 100 indicating no disability. This tool has been validated for subjects with PFP and has been reported to demonstrate high test–retest reliability22.

All analyses were performed using Statistical Package for the Social Sciences software program (version 18.0, SPSS, INC., Chicago, IL) with an a priori level of significance of 0.05. Normality and variance homogeneity of data were tested using the Shapiro-Wilk and Levene tests, respectively. Data for normally distributed variables were reported as mean (SD) and for non-normally distributed variables were reported as median (interquartile range).

Independent t-tests were used to compare the characteristics including age, height, body mass and running volume of the participants between groups. Due to non-normal distribution of data, the Mann-Whitney U test was used to assess the group differences for each dependent variable (PPTs and VAS). The data reported were the U, z, p and effect size (r) values. Besides,
Spearman correlation coefficients were used to correlate PPTs with running volume and self-reported knee function.

Results

No differences between groups for age, height, body mass and weekly running distance were identified; the AKPS scores were lower in the PFPG (Table 1). For all sites, the PFPG had lower PPT measures in comparison with CG: QT (U= 71; z= -3.639; P< 0.001; r= -0.58), MP (U= 118.5; z= -2.392; P= 0.017; r= -0.38), LP (U= 51; z= -4.171; P< 0.001; r= -0.66); PT (U= 100.5; z= -2.885; P= 0.004; r= -0.46) and UL (U= 93; z= -3.005; P= 0.002; r= -0.48) (Figure 1).

There were negative correlations between self-reported knee function and running volume in the PFPG (ρ= -0.88; P<0.001) and among all PPT measures and the running volume per week in the PFPG, indicating lower PPTs were associated with higher running volumes. The correlations for PFPG were: QT (ρ= -0.56; P= 0.006), MP (ρ= -0.70; P< 0.001), LP (ρ= -0.46; P= 0.020), PT (ρ= -0.46; P= 0.022), UL (ρ= -0.48; P= 0.015). There were positive correlations among PPT measures and self-reported knee function in the PFPG, indicating lower PPTs were associated with poorer knee function. The correlations for PFPG were: QT (ρ= 0.52; P= 0.030), MP (ρ= 0.69; P= 0.003), LP (ρ= 0.52; P= 0.028), PT (ρ= 0.50; P= 0.034), UL (ρ= 0.52; P= 0.028). No significant correlations were identified in the CG (p > 0.213). Figure 2 depicts all significant correlations found in the PFPG.

Discussion

Female runners diagnosed with PFP, in this study, presented with lower PPTs locally and remote to the knee when compared with asymptomatic female runners, indicating the presence of local and widespread hyperalgesia. Lower PPTs were also associated with poorer
self-reported knee function and greater running volume in the PFPG. Put together, these findings highlight the potential importance of load management to control symptoms and reduce hyperalgesia in female runners with PFP.

Previous studies comparing PPTs in females with PFP and asymptomatics have reported mean differences of 1.56kgf (range= 0.83 to 2.19) around the knee and 1.45kgf (range= 0.80 to 2.44) at a remote site to the knee. Findings from our study of female runners with PFP are comparable, with differences of 1.38kgf and 1.53kgf, locally and remote to the knee, respectively. Based on these findings, it appears that similar hyperalgesia deficits may exist in both running and non-running female PFP populations, indicating the potential need for non-mechanical interventions such as pain neuroscience education in both populations.

According to our hypothesis, similar reductions in PPTs found in female runners with PFP to those in more general PFP populations indicate exercise induced analgesia is lost in the presence of pathology. This apparent exercise induced analgesia represented by higher PPTs is thought to be facilitated by activation of the endogenous opioid system. Based on findings of this study, it appears that this potentially protective mechanism against hyperalgesia in asymptomatic runners may be impaired in female runners with PFP, not just locally, but also remote to the knee.

Greater running volume was also found to be associated with local and remote hyperalgesia, and also with poorer self-reported knee function in female runners with PFP in this study, which is contrary to previous findings reported in asymptomatic runners. This widespread hyperalgesia, consistent with other research on this topic in including thermal, tactile and vibration thresholds in individuals with PFP, may point to the possible presence of central sensitization, characterized by malfunctioning of descending pain inhibitory pathways and subsequent dysfunctional endogenous analgesic control. This malfunctioning of descending pain inhibitory pathways associated with a chronic overstressing of the endogenous...
opioid system by heightened activation levels, during high intensity exercises, may eventually result in exhaustion over time. Such exhaustion may result in disinhibition of pain processing\textsuperscript{7}.

Activities that load patellofemoral joint during weight bearing on a flexed knee as stair climbing and running are responsible to aggravate the PFP symptoms\textsuperscript{12}. Our findings demonstrated that presence of hyperalgesia is associated with poorer self-reported knee function, which was also associated with higher weekly running volumes. In other words, greater running volume may lead to poorer self-reported knee function and hyperalgesia. According to Dye and colleagues\textsuperscript{27}, altered pain perception in individuals with PFP with certain loading activities can therefore be viewed as an overt biologic indicator that the joint is being loaded out of its envelope of function (load acceptance capacity of the joint). Consideration of this possible phenomenon may have important implications for management, with the potential need to monitor and control running volume and activity levels in the presence of PFP in order to manage hyperalgesia effectively. Further research is needed to develop and evaluate interventions in this regard.

Some limitations of this study should be acknowledged: (i) we evaluated females in the age group most affected by PFP, limiting extrapolation of findings to males with PFP, or older participants with PFP; (ii) PPTs were not evaluated immediately following a bout of running, preventing us establishing the acute effects of exercise on the endogenous analgesic control and potential influence on widespread hyperalgesia; (iii) we did not evaluate a non-running female population with PFP, and therefore cannot determine if there are differences between runners and non-runners with PFP; however, it could be further explored in future studies; (iv) the power calculation was performed using PPT of the patella tendon as in our pilot data it was the site we found the smallest difference between groups with the greatest standard deviation. However, it may be a possible bias for between groups difference in other sites.

Previous research evaluating potential deficits in runners with PFP have tended to focus on mechanical variables such as kinematics, kinetics and muscle function\textsuperscript{28,29}. As a result, the
majority of the current research and subsequent evidence base for managing runners with PFP has been focused on addressing these mechanical deficits\textsuperscript{13,30}. However, findings from our study indicate that female runners with PFP may also require non-mechanical interventions in order to focus on components aimed at pain neuroscience education\textsuperscript{14}. The relationship between greater running volume and hyperalgesia also indicates that education and guidance to decrease loading within a joint’s current diminished envelope of function\textsuperscript{27} may also be vitally important to tackling this non-mechanical phenomenon. A number of considerations have been previously recommended to address CS associated with chronic musculoskeletal pain\textsuperscript{14,24}. These include a conservative approach when prescribing initial exercise loads; cautious progression of load to prevent symptom flaring, including exercise of non-painful areas of the body (e.g. upper limbs); and allowing only small increases in pain during and shortly following exercise, but avoiding increased pain intensity over time\textsuperscript{14,24}. Further research to develop and evaluate interventions related to addressing hyperalgesia, and providing education on training load and activity modification are needed.

**Conclusion**

Lower PPTs locally and remote to the knee in female runners with PFP indicate the presence of local and widespread hyperalgesia in this common patient presentation. Additionally, this hyperalgesia appears to be increased by greater running volumes and associated with poorer self-reported knee function. Put together these findings highlight the need to further develop and evaluate non-mechanical interventions including load management to treat running-related PFP in females.

**Practical Implications**

- Female runners with patellofemoral pain presented signs of local and widespread hyperalgesia. Additionally, greater running volume and poorer self-reported function were found
to be associated with increased local and widespread hyperalgesia in female runners with patellofemoral pain.

- The relationship between greater running volume and hyperalgesia also indicates that education and guidance to maintain runners with PFP in their envelope of function may also be vitally important to tackling this non-mechanical phenomenon.

- A conservative approach with cautious progression of load to prevent symptom flaring and avoiding increased pain intensity over time is encouraged to manage this disorder.

- Female runners with PFP may also require non-mechanical interventions in order to address potential pain neuroscience deficits.

Acknowledgments

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References


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Figure Legends

Figure 1. Box-plots of the PPT measures for CG and PFPG. Abbreviation: CG – control group; PFPG – patellofemoral pain group; QT - quadriceps tendon; MP - medial patella; LP – lateral patella; PT – patellar tendon; UL – upper limb; * - represents statistical difference between groups.

Figure 2. A) Correlation graphs for PPT (pressure pain threshold) measures and running volume per week for PFPG (patellofemoral pain group). B) Correlation graphs for PPT measures and self-reported knee function by Anterior Knee Pain Scale (AKPS). C) Correlation graph for AKPS and running volume per week.
Fig 1
Fig 2
Table 1. Characteristics of participants

<table>
<thead>
<tr>
<th></th>
<th>CG</th>
<th>PFPG</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.00 (5.58)</td>
<td>25.62 (4.05)</td>
<td>0.518</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.62 (0.04)</td>
<td>1.63 (0.06)</td>
<td>0.444</td>
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<tr>
<td>Body mass (kg)</td>
<td>60.00 (7.35)</td>
<td>58.33 (6.89)</td>
<td>0.662</td>
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<tr>
<td>Weekly running distance (km)</td>
<td>20.75 (4.17)</td>
<td>19.75 (4.47)</td>
<td>0.591</td>
</tr>
</tbody>
</table>

**VAS**

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<tr>
<th></th>
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<tbody>
<tr>
<td>Previous month</td>
<td>0 (0)</td>
<td>4.81 (1.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>During evaluation</td>
<td>0 (0)</td>
<td>1.15 (1.50)</td>
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<tr>
<td>Symptoms duration (months)</td>
<td>NA</td>
<td>37.69 (49.31)</td>
<td>NA</td>
</tr>
<tr>
<td>AKPS</td>
<td>100.0 (0)</td>
<td>80.45 (4.55)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: CG – control group; PFPG – patellofemoral pain group; VAS – visual analogue scale; AKPS – anterior knee pain scale; NA – Not applicable. The values are showed in mean (standard deviation).