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Original Research Article

Female Adults with Patellofemoral Pain Are Characterized by Widespread Hyperalgesia, Which Is Not Affected Immediately by Patellofemoral Joint Loading

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Abstract

Objective. Compare pressure pain thresholds (PPTs) at the knee and a site remote to the knee in female adults with patellofemoral pain (PFP) to pain-free controls before and after a patellofemoral joint (PFJ) loading protocol designed to aggravate symptoms.

Design. Cross-sectional study

Setting. Participants were recruited via advertisements in fitness centers, public places for physical activity and universities.

Subjects. Thirty-eight females with patellofemoral pain, and 33 female pain-free controls.

Methods. All participant performed a novel PFJ loading protocol involving stair negotiation with an extra load equivalent 35% of body mass. PPTs and current knee pain (measured on a visual analogue scale) was assessed before and after the loading protocol. PPTs were measured at four sites around the knee and one remote site on the upper contralateral limb.

Results. Females with PFP demonstrated significantly lower PPTs locally and remote to the knee, both before and after the PFJ loading protocol when compared to control group. Following the loading protocol, PPTs at knee were significantly reduced by 0.54 kgf (95%CI = 0.33; 0.74) for quadriceps tendon, 0.38 kgf (95%CI = 0.14; 0.63) for medial patella, and 0.44 kgf (95%CI = 0.18; 0.69) for lateral patella. No significant change in PPT remote to the knee was observed – 0.10 kgf (95%CI = −0.04; 0.24).

Conclusions. Female adults with PFP have local and widespread hyperalgesia compared to pain free controls. A novel loading protocol designed to aggravate symptoms, lowers the PPTs locally at the knee but has no effect on PPT on the upper contralateral limb. This suggests widespread hyperalgesia is not affected by acute symptom aggravation.

Key Words. Patellofemoral Pain Syndrome; Central Nervous System Sensitization; Hypersensitivity Immediate; Pain Threshold; Visual Analogue Pain Scale

Introduction

Patellofemoral pain (PFP) is defined as idiopathic anterior knee pain, with symptoms aggravated by activities such as stair negotiation and squatting that load the patellofemoral joint (PFJ) [1–3]. The estimated prevalence of PFP among females aged 18–35 years is 13% [4] and is 2.23 times more common than in males [5]. Symptoms often lead to reduced participation in sports and daily activities, and a large number of individuals with PFP have recurrent or chronic pain, which may increase the risk of developing osteoarthritis in later life [6,7].

Previous research investigating deficits in individuals with PFP have mostly focused on biomechanics and reported small differences in the way that patients move compared to pain free controls [8–10]. However, it is unclear whether these small, observed differences are the cause of pain, or alternatively, pain itself is responsible for driving (perhaps by compensatory mechanisms) them [11]. Regardless, pain is a cortical experience and the single most important symptom for the patient. Other factors such as fear of pain and recurrence or chronicity can amplify the pain experience for the patient [11]. The amplification of signaling in the central nervous system that elicits an increased response to a stimulus is called central sensitization [12]. The presence of sensitization results in hyperalgesia, which is defined by the International Association for the Study of Pain (IASP) as "an increased response to a stimulus which is normally painful," e.g., intense pain following a mechanical stimulus [13,14]. Local and widespread hyperalgesia are usually measured by pressure pain threshold (PPT) [13,15,16].

At present, there is only one study that has investigated local and widespread hyperalgesia among patients with PFP [15]. Rathleff et al. [15] reported significantly lower PPTs at the knee and a site on the lower limb in adolescents with long-standing PFP compared to pain free adolescents. This suggests that adolescent females with PFP have local and widespread hyperalgesia. At present, there does not appear to be any evaluation of PPTs or possible presence of widespread hyperalgesia in adults with PFP. Addressing this knowledge gap in the PFP evidence-base may prove important as it may demonstrate a need to change the current treatment focus from a biomechanically and strength targeted perspective to include components aimed at pain neuroscience education. Treatment strategies including intensive pain neuroscience education and exercise therapy [17] might improve outcomes and reduce the risk of long-standing pain [18].

Previous findings suggest that the degree of local and widespread hyperalgesia correlate with clinical pain ratings, measured by visual analogue scale (VAS) [19]. Although, PFP symptoms such as pain are intermittent and variable [2], it is unclear if PPT measures have the same variability. Understanding potential variability of PPT measures in PFP has important implications when attempting to quantify local and widespread hyperalgesia in individuals with PFP. Stair negotiation is often used to evaluate the reliability of symptoms and to identify abnormal movement patterns indicative of PFP [9,20,21]. Additionally, stair negotiation with an external extra load will further increase the PFJ stress, and consequently, may arouse the symptoms in individuals with PFP [22,23]. Therefore, this is a relevant functional task to measure potential changes in local and widespread hyperalgesia that may result from an acute aggravation of knee pain.

The aim of this study was to evaluate local PPTs at the knee and remote to the knee in female adults with PFP compared to pain-free controls before and after a PFJ loading protocol. It was hypothesized that: 1) patients with PFP would have lower PPTs local at the knee and remote on the upper limb compared to controls; and 2) patients with PFP will have a significant reduction in both local and remote PPTs after the PFJ loading protocol, but there would be no change in PPT measures among pain free controls.

Methods

This study is reported according to STROBE guideline recommendations, and uses a cross-sectional design comparing adult patients with PFP to a pain free control group. Seventy-one females aged 18 to 30 years were recruited, consisting of two groups, PFP (PFPG; $N = 38$) and control (CG; $N = 33$). An upper limit of 30 years was chosen to reduce the risk of including someone with PFJ osteoarthritis. Participants were recruited in the west region of Sao Paulo state—Brazil, via advertisements in fitness centers, public places for physical activity and universities, between June and November 2014. The study was approved by the Local Ethics Committee and each participant gave written informed consent prior to participation. The sample size was calculated on the basis of previous studies [24,25]. Using $\text{alpha} \leq 0.05$, and an expected difference between groups of at least 25% on the PPT measurements with a common standard deviation of 0.80kgf [15]. A minimum of 25 individuals per group was estimated to be needed to ensure 80% power.

Diagnosis of PFP was completed following consensus from two experienced clinicians (>5 years' experience) and based on definitions used in previous studies [21,26]. The inclusion criteria were: 1) symptoms of insidious onset and duration of at least 3 months; 2) anterior knee pain during at least two of the following activities: prolonged sitting, squatting, kneeling, running, climbing stairs, and jumping; 3) worst pain level in the previous month at least 3 cm on a 10 cm VAS; and 4) three or more positive clinical signs in the following tests: Clarke's sign, McConnell test, Noble compression, Waldron test and patellar pain on palpation. Prospective participants were required to fulfill all four requirements to be included in the PFPG. To be included the CG participants could not present any signs or symptoms of PFP or other musculoskeletal conditions. 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. Those who had received oral steroids, opiate treatment, acupuncture, physiotherapy or any other treatment for pain during the preceding 6 months were also excluded from this study.

Measurements

Pressure pain thresholds were measured using a handheld pressure algometer (Wagner FPX^{TM} 25, Greenwich, CT, USA) with a probe of 1cm^2. Units were measured as kilogram-force (kgf) and the graduation was given by 0.01 kgf.

All measurements were performed by the same trained rater to apply a pressure rate of 0.50 kgf/s [25]. All evaluations were performed with individuals in a standardized position, supine with slightly flexed knees (approximately 20°) supported by a cushion under the popliteal fossa [24,27]. Four sites in the patellar region were selected for PPT testing: quadriceps tendon (QT), medial patella (MP), lateral patella (LP), and patellar tendon (PT) [28]; and on an upper limb (UL) remote site, the lesser tubercle of the humerus (Figure 1) [29]. PPT was measured twice at each site with a 30-second period between testing [30], and the average was used for analysis [15,24,27]. Participants were instructed to indicate when the sensation changed from a sensation of pressure to the first sensation of pain.

Prior to the PPT measurements, all individuals were asked to rate their knee pain on a 10 cm VAS. In this scale, the ends were defined by no pain and worst perceived pain [3,27,31].

Procedures

Pain VAS and PPT data were collected before and after a PFJ loading protocol. The PFJ loading protocol involves a stair case with seven steps, where the participants performed 15 repetitions of stair ascent and descent with 35% external load of the subject's body mass [23], carried in a backpack. A metronome was used at 96 steps/minute to standardize the rhythm of stair negotiation [32,33]. For the reliability analysis, measurements were completed on two separated days, with an interval of 2 to 7 days, at the same period of the day. PPT measurements were performed in the same manner both days, with PPT being measured twice at each site and the average being used for analysis [15,24,27] both before and after the PFJ loading protocol. Participants were advised to avoid taking medications during and between the assessments, as well as changing common habits and physical activity levels.

Figure 1 A = Represents the knee position with slightly flexion and the four sites in the patellar region selected for PPT testing; B = the remote site; C and D = examples of the PPT testing.

Reliability

For PFPG, all PPT measures showed satisfactory reliability assessed by the intraclass correlation coefficient (2,k) values ranging between 0.72 to 0.80 for PT and UL respectively before the PFJ loading protocol. The reliability values increased after PFJ loading protocol ranging between 0.79 to 0.86 for UL and QT respectively. The reliability for VAS measures was 0.79 and 0.76 before and after PFJ loading protocol, respectively. The intraclass correlation coefficient (ICC), standard error of measurement (SEM) and the minimal detectable change with a confidence level of 95% (MDC_{95}) for both groups are presented in Table 1. In order to clarify the SEM's

Table 1 $ICC_{2,2}$ with 95% confidence intervals, SEM and MDC_{95} values of the algometer and VAS measures

Before PFJ loading protocol	CG			PFPG		
	$ICC_{2,2}$ (95% CI)	SEM(%)	MDC_{95}	$ICC_{2,2}$ (95% CI)	SEM(%)	MDC_{95}
QT	0.84 (0.69; 0.92)	0.33 (6.4)	0.91	0.77 (0.05; 0.91)	0.54 (13.4)	1.50
MP	0.89 (0.78; 0.94)	0.19 (3.6)	0.53	0.78 (0.23; 0.91)	0.51 (12.3)	1.41
LP	0.81 (0.62; 0.90)	0.24 (4.6)	0.67	0.76 (0.34; 0.89)	0.56 (13.1)	1.55
PT	0.79 (0.58; 0.90)	0.18 (3.4)	0.50	0.72 (0.10; 0.89)	0.55 (12.5)	1.52
UL	0.84 (0.65; 0.92)	0.57 (15.7)	1.58	0.80 (0.57; 0.90)	0.41 (16.0)	1.14
VAS	NA	NA	NA	0.79 (0.58; 0.89)	0.93 (93.0)	2.58
After PFJ loading protocol						
QT	0.92 (0.84; 0.96)	0.32 (6.4)	0.89	0.86 (0.52; 0.94)	0.47 (14.1)	1.30
MP	0.86 (0.71; 0.93)	0.25 (4.8)	0.69	0.84 (0.68; 0.95)	0.54 (15.0)	1.50
LP	0.77 (0.53; 0.88)	0.29 (5.6)	0.80	0.82 (0.61; 0.91)	0.55 (14.7)	1.52
PT	0.74 (0.47; 0.87)	0.23 (4.3)	0.64	0.85 (0.71; 0.92)	0.54 (13.8)	1.50
UL	0.93 (0.85; 0.96)	0.46 (12.9)	1.28	0.79 (0.59; 0.90)	0.42 (17.4)	1.16
VAS	NA	NA	NA	0.76 (0.54; 0.88)	1.41 (39.8)	3.91

PFJ = patellofemoral joint; CG = control group; PFPG = patellofemoral pain group; QT = quadriceps tendon; MP = medial patella; LP = lateral patella; PT = patellar tendon; UL = upper limb; VAS = visual analogue scale; ICC = intraclass correlation coefficient; 95% CI = confidence interval; SEM = standard error of the measurement; MDC_{95} = minimal detectable change (95% confidence interval); NA = not applied.
VAS does not present ICC, SEM and MDC_{95} values for the CG in any condition, because there was no variance in the data of individuals in this group.

interpretation, the values are also expressed as a percentage of the mean.

Statistical Analysis

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.

Due to high values of reliability, data used for subsequent analyses were from first day of data collection (this day was randomly chosen). For each dependent variable (PPTs and VAS), a two-way mixed model analysis of variance (ANOVA) was run with the between factor being group (PFPG and CG) and the within factor with repeated measures being before and after the PFJ loading protocol. Bonferroni's *post hoc* test was performed for multiple pairwise comparisons where appropriate. The data reported from ANOVA were the F values (with degrees of freedom), partial eta squared (as a measure of effect size) and *P* values. The guidelines [34] for interpreting the eta squared are: 0.01 = small effect, 0.06 = moderate effect, 0.14 = large effect.

Table 2 Characteristics of participants

	PFPG	CG	*P* value
Age (years)	21.6±2.6	22.4±3.5	0.153
Height (m)	1.64±0.06	1.65±0.10	0.275
Body mass (kg)	61.89±9.91	62.34±10.63	0.702
Symptoms duration (years)	5.19±3.84	–	

PFPG = patellofemoral pain group; CG = control group.
The values are showed in mean ± standard deviation.

Results

The comparison of the demographics characteristics between groups indicated no differences for age, height or body mass (Table 2). A significant group by appraisal (before and after) interaction was observed for three PPTs measures: QT ($F_{1,69}=12.731$; $\eta^2=0.156$; $P=0.001$), MP ($F_{1,69}=7.399$; $\eta^2=0.097$; $P=0.008$) and LP ($F_{1,69}=10.488$; $\eta^2=0.132$; $P=0.002$); and VAS ($F_{1,69}=48.046$; $\eta^2=0.410$; $P<0.001$). The *post hoc* analysis using Bonferroni correction revealed that there were differences between the PFPG and CG in all measures before and after the PFJ loading protocol (Figure 2). The mean difference between CG and PFPG for PPTs at the knee (QT, MP, LP and PT) and PPTs remote at the knee (UL) are showed in Table 3.

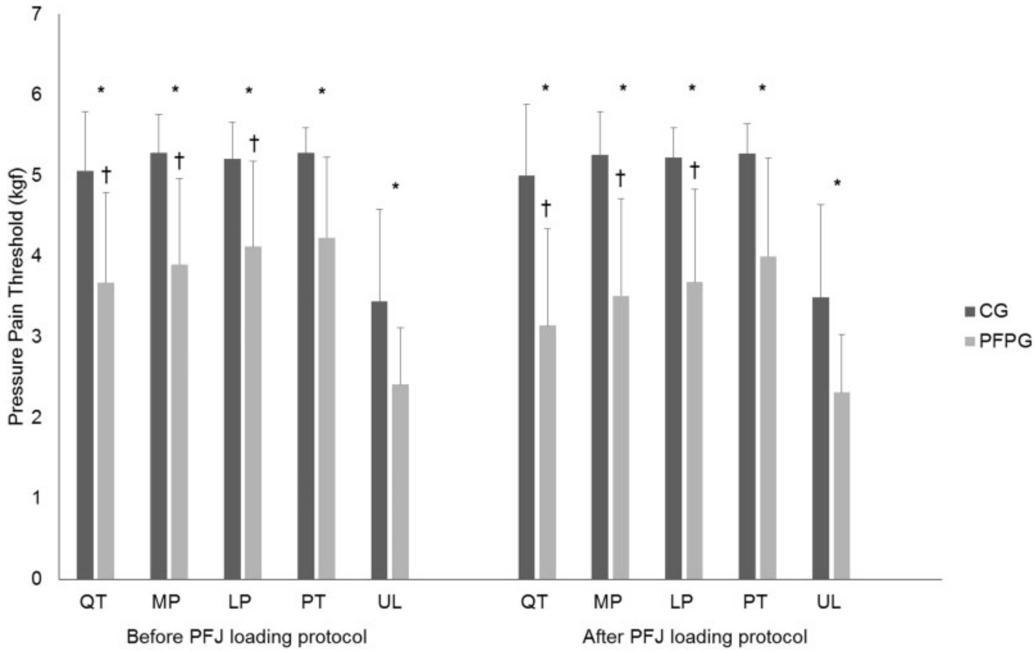

Figure 2 CG = control group; PFPG = patellofemoral pain group; QT = quadriceps tendon; MP = medial patella; LP = lateral patella; PT = patellar tendon; UL = upper limb; PFJ = patellofemoral joint.
*statistical significance comparing CG vs PFPG before PFJ loading protocol or CG and PFPG after PFJ loading protocol
†statistical significance comparing each group individually before vs after PFJ loading protocol.

Table 3 Mean difference between control group and PFP group in two conditions

	Before PFJ loading protocol		After PFJ loading protocol	
	Mean difference (95% IC)	*P* value	Mean difference (95% IC)	*P* value
QT	1.39 (0.95; 1.83)	<0.001	1.87 (1.36; 2.37)	<0.001
MP	1.39 (1.00; 1.77)	<0.001	1.75 (1.32; 2.18)	<0.001
LP	1.09 (0.71; 1.46)	<0.001	1.54 (1.14; 1.93)	<0.001
PT	1.05 (0.71; 1.39)	<0.001	1.27 (0.85; 1.69)	<0.001
UL	1.03 (0.57; 1.49)	<0.001	1.18 (0.72; 1.65)	<0.001
VAS	−1.03 (−1.66; −0.40)	0.002	−3.39 (−4.19; −2.60)	<0.001

PFJ = patellofemoral joint; QT = quadriceps tendon; MP = medial patella; LP = lateral patella; PT = patellar tendon; UL = upper limb; VAS = visual analogue scale.
The PPT values are showed in kilogram-force (kgf) and VAS measure is in centimeter (cm).

Comparisons between the two conditions (before and after the PFJ loading protocol) for PFPG resulted in significant reductions in PPTs 0.54kgf (95% CI = 0.33; 0.74; $P < 0.001$) for QT, 0.38kgf (95% CI= 0.14; 0.63; $P = 0.003$) for MP and 0.44kgf (95% CI = 0.18; 0.69; $P = 0.001$) for LP (Figure 2); and a significant increase in pain VAS −2.37cm (95% CI = −2.98; −1.76; $P < 0.001$) (Figure 3). The distal site (UL) did not present any significant difference in PPT following the PFJ loading protocol for either group ($P > 0.142$).

Discussion

Findings from this study show that female adults with PFP have lower PPTs locally at the knee, and on the contra-lateral upper limb, suggesting widespread

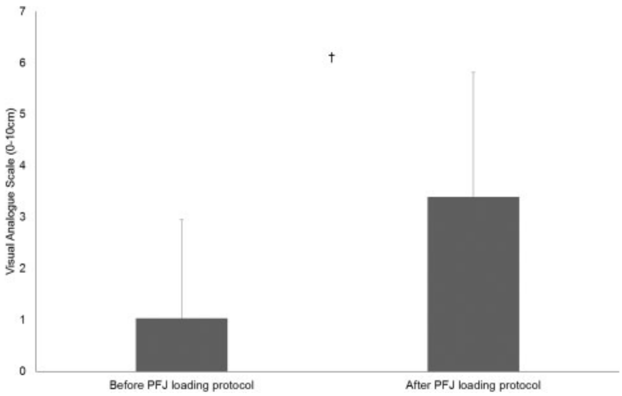

Figure 3 †-statistical significance comparing PFPG before vs after PFJ loading protocol. There is no CG value because in both conditions they reported no pain on visual analogue scale.

hyperalgesia. After completing a novel PFJ loading protocol designed to aggravate symptoms, female adults with PFP had a reduction in PPTs locally at the knee, but had no change in PPTs on the contralateral upper limb. This suggests that acute aggravation of knee pain in female adults with PFP increases local but not widespread hyperalgesia. Pain free controls showed no change in PPTs after the loading protocol.

The reliability analysis (ICC, SEM and MDC_{95}) used in this study provides insight into the reliability of both PPT and pain VAS measures. Previous studies have reported high reliability values of PPTs measured using an algometer [24,25,35]. Consistent with these findings, PPT measures in this study presented high to very high ICC values (0.72 to 0.93), small values of SEM (3.14% to 17.4%) and MDC_{95} (0.50 to 1.55). However, VAS measures seem to be even more reliable after the PFJ loading protocol, as there was a 53.2% reduction in the SEM after the protocol. In addition, our findings reinforce the need of individuals with PFP to perform a PFJ loading protocol before assessments of PPTs. After such protocol, the between group differences were higher than the respective MDCs, the same did not occur before the PFJ loading protocol. In other words, the PFJ loading protocol seems to be able to reproduce symptoms in females with PFP, but does not cause pain or hyperalgesia in asymptomatic controls. This highlights the potential importance of using such protocol to gain insight into possible physiological or biomechanical differences in the presence of pain.

Reduced PPTs in female adults with PFP found in this study are consistent with those reported by Rathleff et al. [15] for female adolescents with PFP. There are no previous studies published on adults with PFP to compare our findings. However, consistent with our findings, PPTs have been reported to be lower both local and remote to the knee in individuals with knee osteoarthritis [29,36,37]. This indicates potentially similar pain processing impairments in these two common chronic knee pain conditions.

As expected, the PFPG presented higher values for pain VAS measures compared to CG participants, with an average pain VAS of 1.03 ± 1.92 in the PFPG. However, 24 of the 38 participants in the PFPG had no pain prior to the PFJ loading protocol, reinforcing the assumption that pain is an intermittent symptom in females with PFP [2]. Following the PFJ loading protocol mean pain VAS increased to 3.39 ± 2.42 in the PFPG, and all participants reported pain. In accordance with Crossley and colleagues (2004), this mean difference is clinically important, with changes greater than 2 cm are considered clinically important in individuals with PFP [38]. This highlights the potential importance of using the loading protocol to gain insight into changes in self-reported pain and central pain processing after an increase in symptoms. According to Cohen [34], all variables which presented significant group by appraisal interaction had medium to large effects (from 0.097 to 0.410). This considerable effect size values demonstrate the clinical importance of the between groups differences.

The PFJ loading protocol used in this study resulted in reductions in PPTs locally at the PFJ in the PFPG, suggesting that symptom aggravation may generate a local hyperalgesia responses (primary hyperalgesia), where local receptors and nociceptive fibers (A delta and C) are involved [12,39]. Interestingly, PPTs were not significantly reduced remote to the knee (i.e., in the upper limb) in either group as a result of the PFJ loading protocol, indicating symptom aggravation does not acutely increase activity of the dorsal horn neuron, which is thought to be responsible for widespread hyperalgesia or central sensitization [12,39]. However, lower PPTs remote to the knee in the PFPG compared to the CG at baseline highlight that alterations do occur in the presence of chronic or persistent pain. Further research is needed to determine the frequency and severity of pain aggravation, which may lead to signs of widespread hyperalgesia in individuals with PFP.

The key consideration moving forward is whether PPTs can be increased following successful rehabilitation. A recent study [40], pointed to increased local PPT measures and trends towards increases at tibialis anterior muscle in adolescents with PFP, who deemed themselves recovered after 3 months of treatment. It is well established the presence of local and widespread hyperalgesia in patients with knee osteoarthritis. As knee osteoarthritis has been speculatively considered a progression of PFP [6,7], findings from this population may provide valuable insight into the management of PFP. Specifically, upper body exercise completed by patients with knee osteoarthritis resulted in an increase in PPTs at upper limb and knee [41]. Moreover, after 12 weeks of supervised exercise therapy, patients with knee osteoarthritis have shown a reduction on local and widespread hyperalgesia [42], indicating a similar approach could be beneficial in PFP.

Study Limitations and Future Directions

We evaluated females in the age group most affected by PFP, limiting extrapolation of findings to males with PFP, or older patients with PFP. Other limitations of this study were that the assessor who collected PPT measures was not blinded to group (PFP vs. control), which may bias our findings and we did not evaluate cultural background of the participants nor comorbid conditions which could affect results, as presented in a previous study [43]. The widespread hyperalgesia found in females with PFP in this study suggests an impaired conditioned pain modulation and changes in central pain processing. Further research is now needed to evaluate how this widespread hyperalgesia might contribute to ongoing pain in PFP, and how best to treat it.

Clinical Implications

The presence of widespread hyperalgesia in patients with PFP may have important implications to exercise prescription aimed at improving symptom management. Importantly, addressing these deficits may require innovative and non-mechanical approaches to treatment. A number of considerations have been previously recommended to address hyperalgesia associated with chronic musculoskeletal pain [17,44]. These include a conservative approach when prescribing initial exercise loads; cautious progression of load to prevent symptom flaring, including exercises that targeted towards non-painful areas of the body (e.g., upper limbs); and only allowing small increases in pain during and shortly following exercise, but avoiding increased pain intensity over time [17,44]. Further research is now needed to determine the effectiveness of these and other approaches aimed at addressing the presence of widespread hyperalgesia in individuals with PFP.

Conclusion

Lower PPTs in both the knee and contra-lateral upper limb in female adults with PFP suggest local and widespread hyperalgesia. Importantly, addressing these deficits may require innovative and non-mechanical approaches to treatment. The patellofemoral joint loading protocol decreased PPTs locally but not remote to the knee in patients with PFP. This finding indicates that symptom aggravation may not acutely affect central pain processing.

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