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Original research

Do adolescents with Osgood–Schlatter display nociplastic pain manifestations compared to controls: A cross-sectional study[☆]

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ABSTRACT

Objectives: Osgood–Schlatter disease is an overuse musculoskeletal pain condition. The pain mechanism is considered nociceptive, but no studies have investigated nociplastic manifestations. This study investigated pain sensitivity and inhibition evaluated through exercise-induced hypoalgesia in adolescents with and without Osgood–Schlatter.

Design: Cross-sectional study.

Methods: Adolescents underwent a baseline assessment comprising clinical history, demographics, sports participation, and pain severity rated (0–10) during a 45-second anterior knee pain provocation test, consisting of an isometric single leg squat. Pressure pain thresholds were assessed bilaterally at the quadriceps, tibialis anterior muscle, and the patella tendon before and after a three-minute wall squat.

Results: Forty-nine adolescents (27 Osgood–Schlatter, 22 controls) were included. There were no differences in the exercise-induced hypoalgesia effect between Osgood–Schlatter and controls. Overall, an exercise-induced hypoalgesia effect was detected at the tendon only in both groups with a 48 kPa (95 % confidence interval 14 to 82) increase in pressure pain thresholds from before to after exercise. Controls had higher pressure pain thresholds at the patellar tendon (mean difference 184 kPa 95 % confidence interval 55 to 313), tibialis anterior (mean difference 139 kPa 95 % confidence interval 24 to 254), and rectus femoris (mean difference 149 kPa 95 % confidence interval 33 to 265). Higher anterior knee pain provocation severity was associated with lower exercise-induced hypoalgesia at the tendon (Pearson correlation = 0.48; $p = 0.011$) in participants with Osgood–Schlatter.

Conclusions: Adolescents with Osgood–Schlatter display increased pain sensitivity locally, proximally, and distally but similar endogenous pain modulation compared to healthy controls. Greater Osgood–Schlatter severity appears to be associated with less efficient pain inhibition during the exercise-induced hypoalgesia paradigm.

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Practical implications

- Exercise-induced hypoalgesia (EIH) is a measure for descending pain modulation that often is impaired in chronic pain patients.
- In this study patients with Osgood–Schlatter disease showed higher local, proximal, and distal pain sensitivity compared to healthy controls, but the EIH response was similar.
- Greater pain severity was associated with a lesser EIH response.

- Pain in OSD may not primarily be local, particularly in more severe longstanding cases.

1. Introduction

There is a steep rise in musculoskeletal disorders in the transition from childhood to adolescence.¹ Non-traumatic anterior knee pain includes common musculoskeletal conditions such as patellofemoral pain (PFP) and Osgood–Schlatter disease (OSD).^{2,3} Both are associated with a high level of sports-related joint loading, and impairments in quality of life, objective muscle strength, and function.^{2,3} Our recent individual participant data meta-analysis revealed that the one-year

[☆] All authors have read and approved this manuscript.

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prognosis of non-traumatic anterior knee pain in adolescents is poor, with approximately 50 % continuing to experience pain, and with limited improvements in pain and disability.⁴ Continued pain during this critical development period is concerning as it may have a longer-term impact on social, cognitive, and neurophysiological development.⁵

The underlying pain in OSD has traditionally been thought to be nociceptive, similar to other tendon problems.⁶ OSD presents as localised pain on the tibial tuberosity, which is also used to establish the diagnosis.⁷ It is common during maturation when the apophyseal cartilage is thought to be susceptible to injury.⁸ There is often evidence of cartilage swelling/fragmentation, tendon thickening, increased Doppler signal in the tendon and bone and in some cases separated ossicles.^{9–11} Nociceptive pain refers to pain arising from the altered function of pain-related sensory pathways in the periphery and central nervous system, causing increased sensitivity.¹² These nociceptive pain characteristics are seen in long-standing non-specific pain disorders but have not been evaluated in OSD, a more localised overuse pain complaint.

One paradigm used to evaluate pain inhibitory mechanisms is exercise-induced hypoalgesia (EIH).¹³ The EIH effect is an increase in pain threshold following an acute bout of exercise seen in healthy individuals, but which appears to be less efficient in chronic pain patients.¹⁴ Therefore, the aim of this study was to explore nociceptive pain mechanisms in adolescents with OSD using the EIH paradigm. We hypothesised that those with OSD would demonstrate nociceptive pain profiles encompassing lower pressure pain thresholds at the tendon, tibialis anterior, and rectus femoris and impaired EIH compared to controls without pain. A secondary aim was to examine if the degree of EIH was associated with pain severity in adolescents with OSD. We hypothesised that those with greater OSD severity would have a diminished EIH effect.

2. Methods

This study was designed as a cross-sectional study and included adolescents with Osgood–Schlatter disease and matched controls recruited from the same sports teams (e.g., football, handball, badminton) and age groups. The research was undertaken in accordance with the Declaration of Helsinki. The study was approved by the research ethics committee of the Northern Denmark Region (N-20200001). Parental/guardian informed written consent was provided by the appropriate custody holder, as well as participant consent, prior to any study-related procedures being undertaken. Data were stored and processed in alignment with the General Data Protection Regulation (GDPR) guidelines.

The present investigation was conducted as part of a larger investigation of ACute and CUMulative LOAding in adolescents with OSD (ACCULOAD). The ACCULOAD study consists of one session consisting of a clinical examination, ultrasound scan, and evaluation of pain aggravating activities, is followed by two weeks of prospective pain and activity monitoring, in addition to the measures reported here, and is reported in detail elsewhere. To ensure no carry-over effects of the pain aggravating activities, a minimum of 15-minutes of wash-out was given to each participant prior to conducting the EIH paradigm (Fig. 1 Experimental design). Several studies have shown that ≥ 15 minutes of rest after exercise is sufficient to wash out any analgesic effects from an acute bout of isometric exercise.^{13,15}

Potentially eligible participants were recruited from the community by disseminating information about the project through local sports clubs, through flyers distributed in clubs, on social media, and through our professional network. Participants with OSD were eligible for inclusion if they were aged 8–18 years old and diagnosed with OSD. Diagnosis was based on clinical history and localised pain at the tibial tuberosity provoked by palpation, resisted knee extension, and other knee loading activities such as jumping and running that provoked pain. Participants were excluded from the OSD group if they had a history of other types of knee pain or knee surgery, pain emerging from the hip or back, habitual patellar subluxations or clinical suspicion of meniscal injuries, or any conditions or chronic illnesses that affect tendon properties.

Controls were recruited from the same sports, sex, and age range and matched at a group level (1:1 matching was not conducted due to unequal sample sizes). Controls were eligible for inclusion, providing that they had no current musculoskeletal or pain conditions, based on self-reported history. Exclusion criteria for controls included previous history of self-reported knee symptoms, or other chronic illness (e.g., diabetes, autoimmune diseases).

The baseline assessment included clinical examination and self-report questionnaires. Questionnaires included participant demographics, self-reported symptoms (including pain intensity, duration, and frequency), and sports participation. Self-reported knee function was captured using the Knee Injury and Osteoarthritis Outcomes Score (KOOS)¹⁶ Child version, and health related quality of life using the youth version of the EuroQol five dimensions, with 3 levels (EQ. 5D 3L youth).¹⁷ The anterior knee pain provocation (AKPP) test was used to assess pain severity in response to knee loading.¹⁸ Participants performed a single leg squat (on their most symptomatic knee) to around 60° of knee flexion and were instructed to hold this position for 45 s. After completion, participants

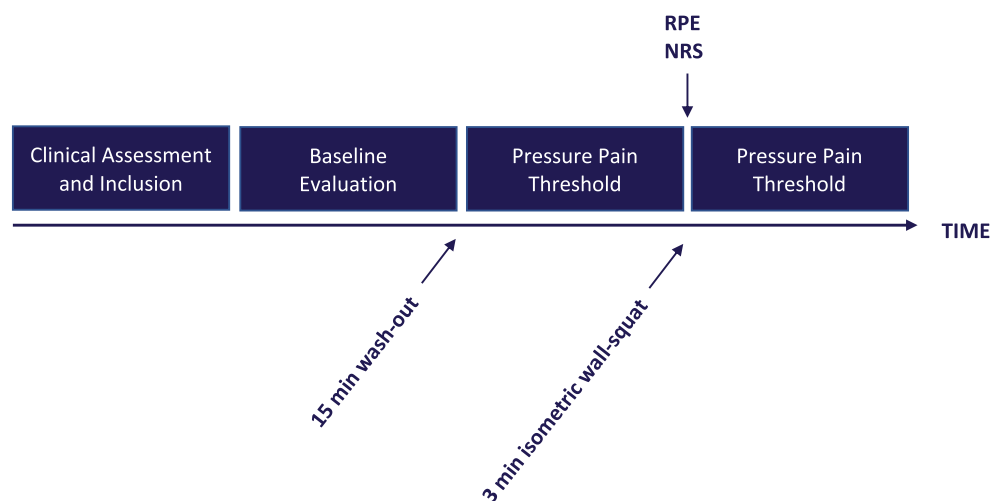


Fig. 1. Experimental design.

Schematic view of the experimental design used in this study. Rate of perceived exertion (RPE). Numerical rating scale (NRS).

rated their pain on an 11-point numeric pain rating scale ranging from 0 (no pain) to 10 (worst pain imaginable).

The EIH paradigm (outlined below) was conducted by a trained assessor with extensive experience in performing manual pressure algometry, exercise testing, and delivering information to adolescents (KDL). All experimental procedures were first piloted in young adolescents with and without OSD prior to testing to ensure comprehension of instructions and procedures, and ensure participants were comfortable with procedures invoking pain. Instructions regarding pain thresholds were standardised and followed pre-determined age appropriate instructions as we have previously used in this age group.^{19,20}

Pressure pain thresholds were measured using a manual handheld pressure algometer (Somedic Sales AB, Horby, Sweden) with a stimulation area of 1 cm². All measures were conducted with the participant seated comfortably on a plinth, with their legs over the side.

With the algometer probe placed perpendicular to the skin at the assessment site, force was increased at a rate of 30 kPa/s. Participants were instructed to push the button on a handheld device when the pressure sensation changed at the first onset/sensation of pain, and the test was stopped, and the pressure recorded.^{19,21}

A predetermined order was used for the pressure pain thresholds (PPTs) before and following exercises as follows; PPTs on the test limb at the mid-portion patellar tendon,^{22,23} muscle belly of the tibialis anterior,^{19,21,22} and the rectus femoris (at a site measured as 15 cm proximal from the basis of patella), followed by PPTs on the contralateral limb in the same order. For participants with OSD, the test limb was the painful knee (or most painful in the case of bilateral pain), and in controls, the test limb was randomly assigned. The PPT measurements were repeated in the same order immediately following the isometric exercise (detailed below) to determine EIH.

All participants were asked to perform a three-minute isometric wall squat exercise.²⁴ Participants began in a standing position with their back flat against the wall, feet shoulder-width apart, and hands by their sides. Participants then lowered themselves until they reached approximately 100° of knee flexion. This position was maintained for a maximum of 3 min, or until muscular fatigue. Immediately following the wall squat, participants rated the pain intensity from 0 to 10 on the numeric rating scale (NRS), where 0 was defined as “no pain” and 10 as the “worst imaginable pain”. Furthermore, participants rated their perceived exertion (RPE) on a Borg CR 10 scale³ ranging from 0 to 10, with 0 defined as “no exertion at all” and 10 as “maximal exertion”.

Descriptive data (participants' characteristics) are presented as mean and standard deviation (SD), or median and inter-quartile range (IQR) as appropriate. Inferential statistics are presented as the point estimate with associated 95 % confidence intervals (95 % CI). *t*-Tests were used to examine differences between OSD and controls in pain intensity and RPE during the wall-squat test. Potential differences between groups in PPTs at the tendon, tibialis anterior, and rectus femoris were assessed using mixed between- and within-subject analysis of variance (ANOVA). The group (OSD versus controls) was the independent factor, with time (pre versus post exercise) and limb (test versus contra-lateral limb) included as within subjects repeated factors. To investigate the association between pain in response to knee loading and degree of EIH, we conducted Pearson correlation on the EIH effect (EIH effect = PPT at the patellar tendon post exercise – PPT at the patellar tendon pre-exercise) and pain during the AKPP test.

3. Results

This study included 27 participants with OSD (Supplementary material 1) and 22 pain-free controls. Participants from the OSD and control groups were comparable in terms of age, BMI, gender, and sports participation (see Table 1). Fifty-six percent (N = 15) of participants with OSD had bilateral pain. Clinical characteristics are displayed in Table 2.

Table 1
Participant descriptives.

	OSD	Control
Sex (% female)	44 %	50 %
Age (years)	13.0 (1.5)	13.4 (1.4)
BMI ^a	18.2 (2.9)	18.9 (2.4)
Sports participation (hours per week) ^a	2 (2 to 3)	3 (2 to 4)
Sports participation (times per week) ^a	3 (2 to 4)	5 (2 to 4)

Data are displayed as mean (SD) unless denoted.

^a Median (inter-quartile range).

The OSD group had significantly higher ratings for both pain intensity (mean difference 1.9 95 % CI 0.6 to 3.2) and RPE (mean difference 0.8 95 % CI 0.1 to 1.6) during the wall squat.

Overall, there was no statistically significant interaction between group (OSD versus control) and time (pre versus post wall squat at the patellar tendon (F = 1.46 (1,47) p > 0.05), tibialis anterior (F = 0.30 (1,47); p > 0.05) or rectus femoris (F = 1.06 (1,47) p > 0.05); Fig. 2), indicating that there may be no differences in EIH response between OSD and controls. Overall, an EIH effect was detected at the patellar tendon only with an increase in PPTs, increasing 48 kPa (95 % CI 14 to 82) from before to after isometric exercise (Fig. 2). No EIH effect was observed at the tibialis anterior (mean PPT difference 13 kPa 95 % CI –20 to 46) or rectus femoris (mean PPT difference –27 kPa 95 % CI –61 to 6).

There was a significant main effect of group (OSD versus controls) for PPTs (Fig. 3). Controls had significantly higher PPTs compared to OSD at the patellar tendon (mean difference 184 kPa 95 % CI 55 to 313), tibialis anterior (mean difference 139 kPa 95 % CI 24 to 254), and rectus femoris (mean difference 149 kPa 95 % CI 33 to 265).

The effect of limb (test versus contra) was not different between OSD and controls (i.e. there was no significant interaction between the ‘test’ and contralateral limb, and group status (OSD versus control, Fig. 4). Overall, there was a significant main effect of limb at the patellar tendon with PPTs 41 (95 % CI 0.4 to 83) kPa lower on the ‘test’ limb on average.

In those with OSD, there was a moderate negative association between pain severity as documented by the AKPP test and the EIH effect at the patellar tendon (Pearson correlation = 0.48; p = 0.011), indicating those with greater pain severity experienced a decreased EIH response at the patella tendon.

4. Discussion

To our knowledge, this is the first study to investigate pain mechanisms in adolescents with OSD, a localised condition at the tibial tuberosity seen during musculoskeletal development. This cross-sectional study found that adolescents with OSD displayed increased pressure

Table 2
Participant characteristics.

	OSD	Control
Worst pain past week (0–100) ^a	68 (50 to 74)	NA
Pain duration (months)	12 (6 to 24)	NA
Pain frequency N (%)		
Rarely	2 (7.7 %)	NA
Monthly	2 (7.7 %)	NA
Weekly	5 (19.2 %)	NA
Several times per week	9 (34.6 %)	NA
Almost daily	8 (30.8 %)	NA
KOOS scores		
KOOS-Child Pain	67.6 (15)	94.3 (7.3)
KOOS-Child Symptom	72.1 (15.0)	92.2 (7.9)
KOOS-Child ADL	83.2 (13.8)	97.9 (3.71)
KOOS-Child Sport/Rec	60.1 (17)	93.8 (9.2)
KOOS-Child QOL	56.9 (12.4)	93.4 (10.3)
Baseline AKPP pain score (0–10) ^a	7.0 (5.5 to 8)	0.0 (0.0 to 2.3)

Data are displayed as mean (SD) unless denoted.

KOOS: Knee injury Osteoarthritis Outcome Score; AKPP: anterior knee pain provocation test.

^a Median (inter-quartile range).

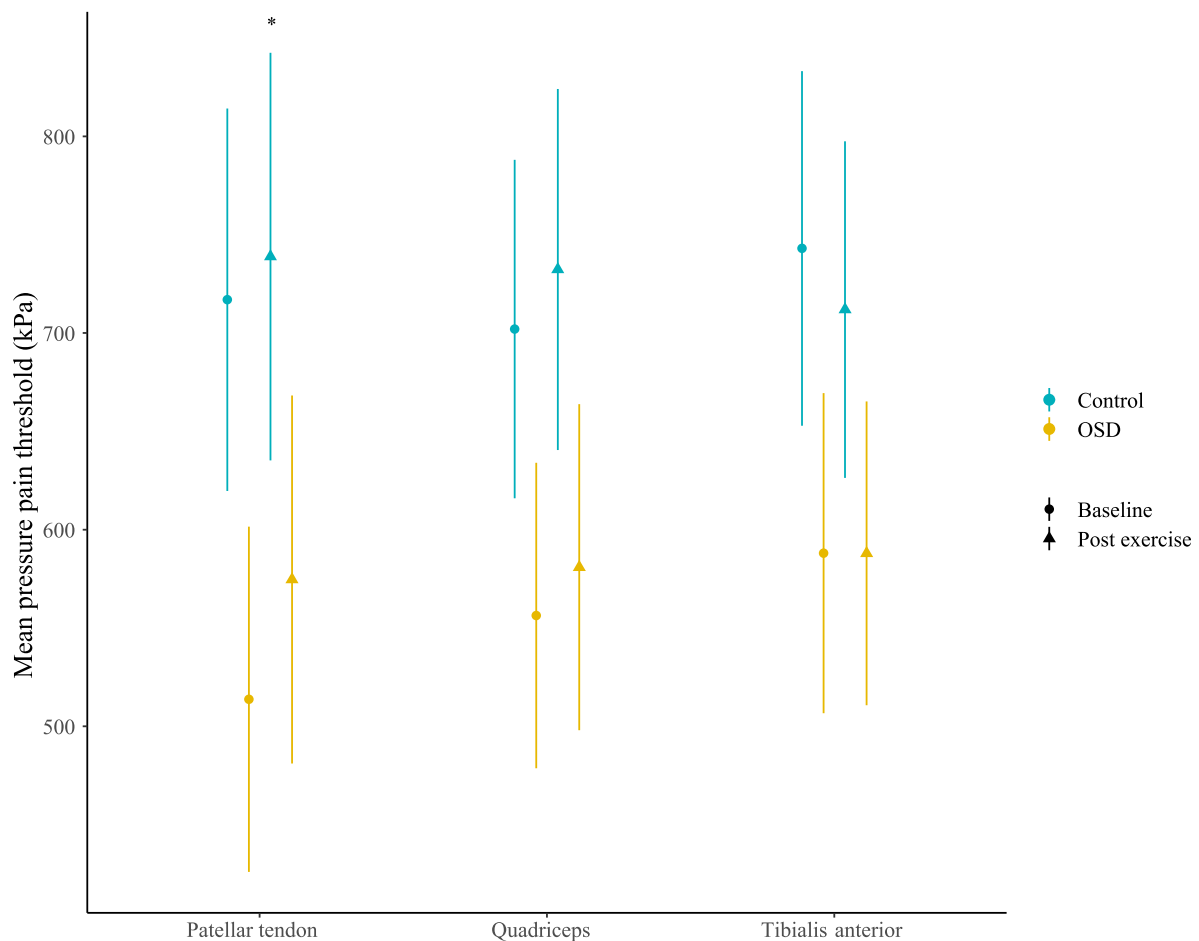


Fig. 2. Pressure pain threshold before and after wall-sit, exercise-induced hypoalgesia.

Mean (95% confidence interval) pressure pain thresholds (PPTs) for adolescents with Osgood–Schlatter disease (OSD, $n = 27$) and matched controls ($n = 22$) before and after the wall-sit test. PPTs significantly increase post exercise at the patellar tendon only. * indicates significant difference from baseline at this site (for OSD and controls combined).

pain sensitivity locally, distally, and proximally compared to controls. Adolescents with OSD display similar endogenous pain modulation as their peers without pain. Overall, there was an EIH effect detected at the patellar tendon in these adolescents. An EIH effect was not detected at the other sites. There was a negative correlation between the degree of the EIH effect and pain severity during a functional pain provoking task in adolescents with OSD. This indicates that adolescents with greater OSD related pain severity have less efficient pain inhibition.

OSD was originally described as a traction apophysitis of the tibial tuberosity, caused by repeated tensile loading via the quadriceps onto the apophyseal cartilage of the tibial tuberosity, resulting in avulsion of segments of the anterior cartilage and bone. In addition, changes in the surrounding soft tissues of the patellar tendon and infrapatellar bursa are part of OSD classifications.^{8,9,25} Up to this point, OSD related pain has primarily been characterised as a nociceptive pain condition, with the literature focusing mainly on the local pathology.¹¹

The current investigation found a lack of differences in the EIH effect between OSD and controls. However, participants with OSD had increased pain sensitivity not only locally at the tendon, which would be expected, but also distally at the tibialis anterior and proximally on the quadriceps. This distal spreading hyperalgesia is considered a surrogate for pro-nociceptive central mechanisms.²⁶ The decreased PPTs observed at the rectus femoris may relate to the quadriceps involvement in OSD. The aetiology is thought to relate to activities associated with high loading of the tendon through the quadriceps, such as kicking, running, and jumping.^{2,25,27} Previous studies have found reduced flexibility^{2,24,26} and alterations in the mechanical properties of the

quadriceps musculotendinous unit,^{27,28} which may play a role in OSD and explain the findings in the current study.

Quantitative sensory testing has been used to evaluate nociceptive mechanisms in adolescents with other musculoskeletal pain conditions (primarily PFP).^{19,20} PFP is similar to OSD in that it is considered an overuse pain condition. Like many non-specific pain conditions, PFP is characterised by clinical and psychophysical characteristics indicating altered pain processing, suggesting nociplastic pain. Our research indicates that young adolescents (aged 10–14) with PFP and older adolescents with a history of PFP demonstrate more facilitated temporal summation of pain, impaired pain modulation, and localised and widespread hyperalgesia compared to controls.^{19,21} These studies used the conditioned pain modulation (CPM) paradigm to investigate pain modulation. Both CPM and EIH are thought to be indicators of the pain facilitatory and inhibitory system and have previously been shown to be correlated.¹³

In contrast, we did not find evidence of impaired anti-nociceptive mechanisms in adolescents with OSD when using the EIH paradigm. This highlights a potential difference in the underlying mechanisms. Traditionally, overload is considered an important factor in the development of pain in PFP and OSD. Both have been associated with sports specialisation (thought to be due to the repetitive nature of single sport actions²⁹). However, PFP contrasts to OSD as it is considered a non-specific ‘diagnosis of exclusion’ when no other observable pathology can be detected. Adolescents with PFP are often characterised by pain in multiple locations, and spreading pain which may be attributable to (or a cause of) the nociplastic characteristics of this pain complaint.²¹

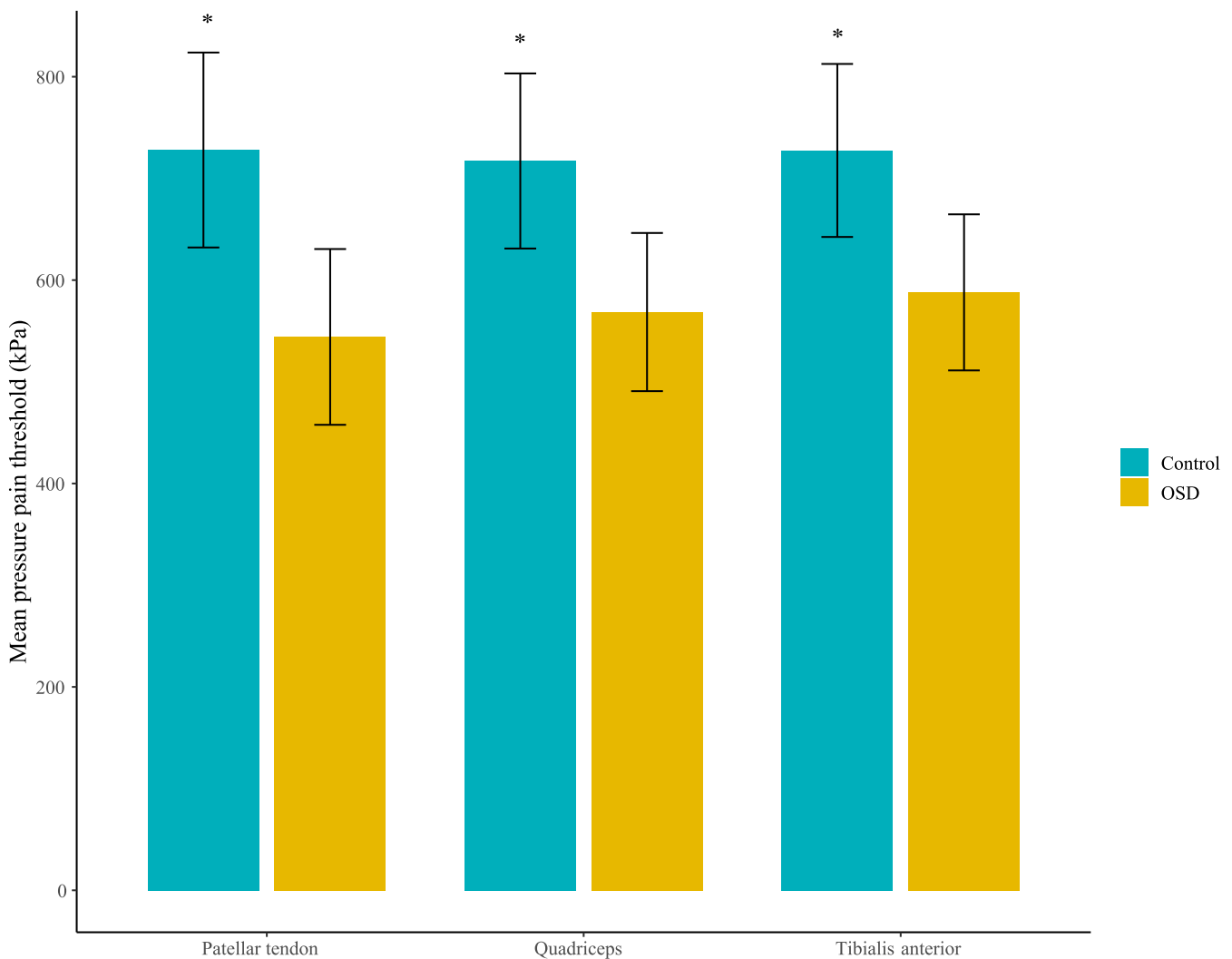


Fig. 3. Pressure pain thresholds between Osgood–Schlatter disease and matched controls. Mean (95 % confidence interval) pressure pain thresholds (PPTs) in adolescents with Osgood–Schlatter disease compared to matched controls. * indicates significant difference from OSD at this site.

From unpublished data based on our previously published prospective study of OSD,¹⁰ participants did not present with patterns of pain spreading which may support the more localised nature of this condition.

As mentioned previously, OSD and patellar tendinopathy share many similar traits as the involvement of the distal patellar tendon in OSD has been documented by many studies. Imaging in OSD shows thickening of the distal part of the patellar tendon and increased Doppler signal.^{8–10} This is similar to what is observed more proximally in patellar tendinopathy, making the comparison between quantitative sensory assessments in OSD and patellar tendinopathy particularly interesting to understand the similarities and differences in the pathophysiology. Studies evaluating tendinopathy have demonstrated mixed results, with some studies showing primarily peripheral manifestations⁶ and others showing more widespread/central nociplastic manifestations.³⁰ Plinsinga et al. recently found that athletes with patellar tendinopathy demonstrated widespread hyperalgesia but found no evidence of EIH in either the athletes with patellar tendinopathy or controls.³⁰ In our study, we found an EIH-effect in both groups (OSD and controls), but only at the patellar tendon. The small EIH effect observed in our study (13 % increase in PPTs at the tendon and 8 % at the tibialis anterior) may relate to the age of the participants as there is a developmental component to pain inhibitory mechanisms.³¹ Younger adolescents do not display the same inhibitory responses as older adolescents, indicating that the descending control manifests during adolescence. Therefore, as OSD is

related to the maturation of the tibial tuberosity and thus presents in early adolescence, it is likely these mechanisms are not yet fully mature in this group. This is similar to studies on CPM in young adolescents, which found a smaller CPM effect in adolescents compared to what is detected in young adults using the same methods.¹⁹ At present, it is unclear what longstanding pain does to the maturing pain system during this critical developmental period. One notable difference is that the studies on tendinopathy have been conducted in adults.

This study includes a few limitations. Firstly, there was no blinding of the assessor to group status (OSD versus control). To minimise expectations for participants, participants were given neutral information regarding the exercise, and not informed of the hypothesis to ensure a non-biased response. Finally, we did not include a remote location on the upper limb.

We identified an increased pain sensitivity among young adolescents suffering from what was previously considered a localised pain complaint when compared to controls. This was not just locally, at the site of OSD but proximally and distally indicating nociplastic pain characteristics in addition to nociceptive pain. This may have implications for understanding why some cases of adolescents with OSD persist for years. Adolescents with OSD had similar EIH, but the degree of EIH was associated with pain severity, indicating pain modulation is linked to the pain experience in adolescents with OSD.

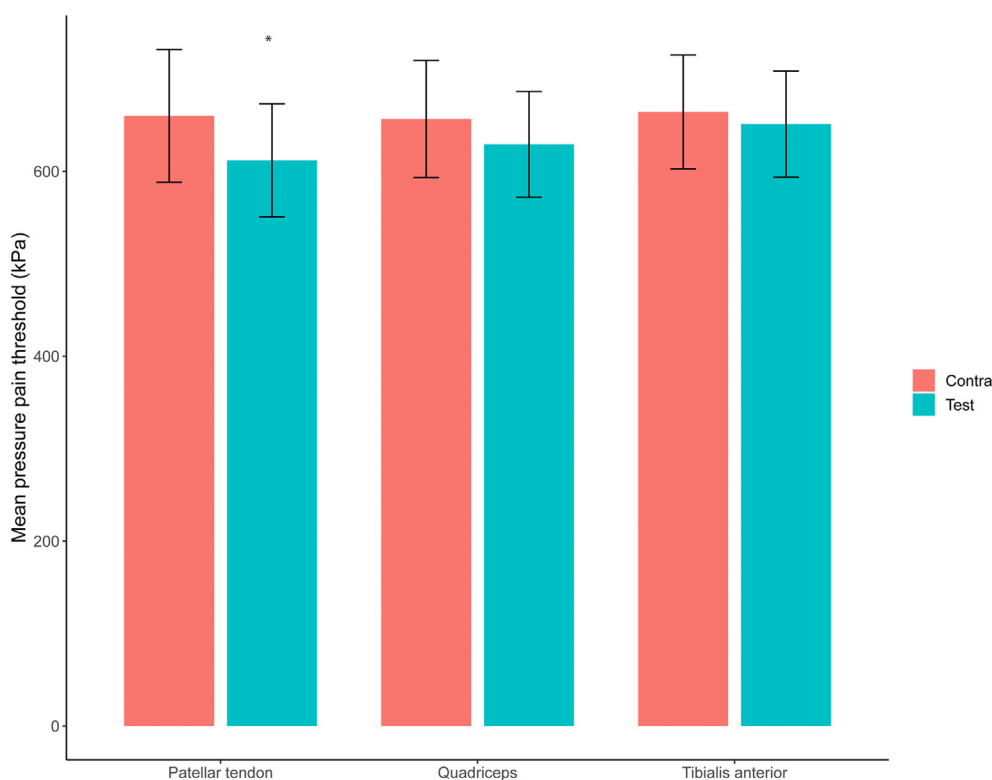


Fig. 4. Comparison between test limb and contralateral limb.

Overall mean (95 % confidence interval) pressure pain thresholds (PPTs) for the test limb (not stratified by group OSD versus control) and contralateral limb. * indicates significant difference.

5. Conclusions

This study demonstrates that adolescents diagnosed with OSD, and healthy controls experience similar local and remote endogenous pain responses to an acute bout of exercise. However, we observed that higher levels of pain severity were associated with lower pain inhibition. Adolescents with the most severe and long-standing symptoms showed nociplastic changes. This may change current perception from primarily a nociceptive condition. This may have implications for management and expanding the treatment approach in those with most severe and long-standing symptoms.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jsams.2023.05.005>.

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Confirmation of ethical compliance

The research was undertaken in accordance with the Declaration of Helsinki. The study was approved by the research ethics committee of the Northern Denmark Region (N-20200001). Parental/guardian informed written consent was provided by the appropriate custody holder, as well as participant consent, prior to any study related procedures being undertaken. Data were stored and processed in alignment with the General Data Protection Regulation (GDPR) guidelines.

CRedit authorship contribution statement

Kristian Damgaard Lyng: Conceptualization, Methodology, Investigation, Writing – original draft, Visualization. **Line Bay Sørensen:**

Conceptualization, Methodology, Writing – review & editing. **Jens Lykkegaard Olesen:** Conceptualization, Methodology, Writing – review & editing. **Michael Skovdal Rathleff:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Sinead Holden:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization, Supervision, Project administration, Funding acquisition.

Data availability

Researchers interested in the data from this study may contact the principal investigator, Sinéad Holden, siho@hst.aau.dk @Sinead_Holden.

Declaration of interest statement

The funder had no role in the study design, analysis, or interpretation of the data. Otherwise, the authors have no conflicts to declare.

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