Evidence of nervous system sensitization in commonly presenting and persistent painful tendinopathies: a systematic review

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Study Design: Systematic review

Objectives: Elucidate if there is sensitization of the nervous system in those with persistent rotator cuff (shoulder), lateral elbow, patellar, and Achilles tendinopathies.

Background: Tendinopathy can be difficult to treat and persistent intractable pain and dysfunction frequent. It is hypothesized that induction or maintenance of persistent pain in tendinopathy is at least in part based on changes in the nervous system.

Methods: Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were followed. Relevant articles were identified through a computerized search in Embase, PubMed, and Web of Science followed by a manual search of reference lists of retained articles. To be eligible, studies had to include quantitative sensory testing (QST) and evaluate individuals diagnosed with a persistent tendinopathy of the rotator cuff (shoulder), lateral elbow, patellar, or Achilles tendon. Methodological quality assessment was evaluated with the Newcastle-Ottawa Scale.

Results: In total, 16 full-text articles met the criteria for inclusion, of which the majority were case-control studies with heterogeneous methodological quality. No studies on Achilles tendinopathy were found. Mechanical algometry was the predominant QST used. Lowered pressure pain threshold was observed across different tendinopathies at the site of tendinopathy as well as at other sites, with the latter being suggestive of central sensitization.

Conclusion: Although more research on sensory abnormalities is warranted, it appears likely that there is an association between persistent tendon pain and sensitization of the nervous system. This evidence is primarily from studies of upper limb tendinopathy and caution should be exercised with inference to lower limb tendinopathy.

Key words: athletic injuries, central sensitization, chronic pain, pain threshold

INTRODUCTION

Patellar tendinopathy in volleyball, Achilles tendinopathy in runners, lateral epicondyle tendinopathy in racket sports, and shoulder impingement syndrome in swimmers are examples of some of the most common persistent overuse-type musculoskeletal injuries in sports.[23,25,31,41] Tendinopathy is a generic descriptor of a clinical presentation of tendon pain with assumed accompanying pathological changes within the tendon.[33,41] The challenge with tendinopathy is that pain at the tendon, especially persistent pain, does not always correlate with pathological changes in tendon[34] and histologic studies consistently show either absent or minimal inflammation.[3,4]

Local tendon damage or inflammation (as identified on imaging or biopsy) induced nociception cannot be regarded as the only plausible reason for persistent tendinopathies. Recently, altered somatosensory perceptions (ie, sensitization of the nervous system) has been proposed as an alternative or complementary mechanism underlying persistent tendon pain.[12,41,42,52] Sensitization of the nervous system, both peripherally and centrally, in response to nociceptive input or inflammation can be protective and helpful in the short term. In cases where the tendon pain has persisted, this sensitization of the nervous system might be maladaptive and therefore contribute to persistent pain and possible disability.[12,54]

Sensitization can be characterized as either mechanical or thermal sensory gain, with the former likely being more relevant in painful tendinopathy.[44] Sensory gain in tendinopathy refers to pain on loading of the tendon during activities such as athletic training/practice or performance that are normally not painful when performed within the person's physiological limits. For example, a decline squat[61] loads the tendon within physiological limits in the normal tendon, but in patellar tendinopathy it is most likely symptomatic (ie, painful). An

increased pain sensitivity with a nociceptive stimulus is termed hyperalgesia and with mechanical stimuli it is known as mechanical hyperalgesia. Pain from a non-nociceptive stimulus, such as a light touch, is called allodynia.

A way to evaluate and systematically measure the extent of sensitization in mechanically induced pain is by quantitative sensory testing (QST).[43,44] QST, which entails measurement of participants responses to standardized thermal and mechanical stimuli, is used to assess perceptual functioning of somatosensory modalities that correspond with large fiber function (Ab), small fiber function (C, Ad) and the central nervous system pathways.[6,20,43,54] The cause or underlying mechanism of sensitization may lie along the sensory pathway; from the peripheral receptor to the highest cortical regions in the brain.[20] Central nervous system sensitization might be implied by findings of differences in QST results between those with tendinopathy and asymptomatic controls at sites remote from the tendinopathy.[22] In the last decennia convincing evidence has shown that central and peripheral sensitization underlies persisting pain states such as chronic whiplash, low back pain, fibromyalgia, irritable bowel syndrome, and several other pain states.[38,60] This finding has clinical implications for the treatment of these patient groups.

There has been a growing recognition of the role of the nervous system in contributing to musculoskeletal pain, including tendinopathies.[22,52] The finding that sensitization might play a role in the maintenance of pain with tendinopathies might therefore also be of importance for treatment in sports medicine. Until now tendinopathy research has largely focused on the tendon pathology locally as opposed to other system(s). The goal of this systematic review was to elucidate evidence of sensitization of the nervous system in commonly presenting persistent tendinopathies of the rotator cuff (shoulder), lateral elbow, patellar, and Achilles

tendons.

METHODS

Study design

The current paper encompassed a systematic review that follows the PRISMA guidelines for the reporting of systematic reviews and meta-analysis,[21,36] which provided the basis for a narrative on the application of revealed findings in clinical and research practice.

Search strategy

A computerized search was conducted in April 2014 to identify relevant articles concerning the research topic. PubMed, Embase, and WebofScience databases were searched. The search term consisted of the following keywords and MeSH terms: "Central Nervous System sensitization", "hyperalgesia", "pain threshold", sensitization, hyperalgesia, hypersensitivity, algometry, hyperexcitability, neural inhibition, altered pain threshold, central pain physiopathology, nociception, pain modulation, pain processing, neuropathic pain, allodynia, somatosensory profile, pain pressure threshold AND "athletic injuries", "tendinopathy", "tennis elbow", overuse injuries, jumpers knee, jumper's knee, patellar tendin*, epicondylitis lateralis, tennis elbow, Achilles tendin*, impingement. The construct of the search strategy reflects the aim of evaluating sensitization of the nervous system in relation to pain perception in studies of specific tendinopathies of the shoulder, elbow, patella and Achilles. Both the keywords and MESH terms are presented in **TABLE 1**. After the computerized search, literature lists of all selected articles were manually checked for additional literature.

Study selection

The authors MLP and CPW independently screened each paper to select the potentially relevant studies from titles, abstracts, and keywords, before retrieval of the full-text article and full-text analysis. Hereafter, full-text articles were assessed for eligibility, which was also independently done by reviewers MLP and MSB. To be eligible, an article had to meet the following criteria: (1) participants of the study had to be diagnosed with a persistent tendinopathy of the shoulder, elbow, patella, or Achilles, which was defined by the average pain duration of the study population being 3 months or longer; (2) studied somatosensory modalities; (3) presented in English; (4) participants older than 18 years of age; and (5) full-text reports, and not abstracts, letters, or editorials. If any of the 5 inclusion criteria were not fulfilled, the article was excluded. Disagreements were resolved through consensus. Articles were categorized as per study design (case report/cross sectional/case-control study/longitudinal study/randomized control trial).

Study quality

Quality assessment of cohort (cross sectional) studies, case-control studies, and case series was performed independently by 2 researchers MLP and MSB using the Newcastle-Ottawa Scale (**TABLE 2**).[53] The Newcastle-Ottawa Scale uses a star rating system to judge quality based on case selection, comparability of cases and controls, and exposure. Case selection considers case definition, representativeness of cases, definition, and selection of controls. Comparability of cases and controls examines comparability on the basis of the design or analysis, whereas exposure deals with ascertainment of exposure, same method of ascertainment for cases and controls, and non-response rate (refusing to participate in the study). A total of 9 stars can be awarded for every quality assessment.[53] The Newcastle-Ottawa Scale has different quality assessments for both case-control and cohort studies; the former being used in this systematic review to assess cross sectional studies. After rating the

articles, results of both researchers were compared and differences were discussed. In case of disagreement, articles were screened a second time and the point of disagreement was discussed. When consensus could not be reached, a third researcher CPW arbitrated a consensus decision.

Data extraction

Data extraction was done by MLP and CPW, with all investigators being consulted on any issues encountered. Data extracted were: study design, population characteristics (age, sex), tendinopathy location and its duration, the measurement tools used and details thereof, and a summary of main outcomes reported by the authors. Authors were contacted if there was insufficient detail in the paper. Papers were examined for any QSTs that included mechanical or thermal stimuli.

Data analysis

Meta-analysis was to be performed, but there was substantial heterogeneity between location of tendinopathy, which rendered it inappropriate. Data are presented as point estimates of effect (eg, mean differences and 95% confidence intervals) between data from the unaffected side in the tendinopathy group compared to the healthy control, as this provides a clear indication of widespread sensitization.

RESULTS

Study selection

The search strategy retrieved 328 studies, from which 28 full-text articles were assessed and 16 included for review after screening to determine eligibility (**FIGURE**). No studies including participants with Achilles tendinopathy were eligible for inclusion. In total 16

studies were included; 1 case series and 15 case control studies.

Methodological quality

Sixteen studies were scored for their methodological quality; scores are presented in **TABLE 2**. Consensus was reached for all items after the second round of interrater comparison. The low score of the case series was due to the questions about the absence of controls.[30] Case control studies often lost points as a result of an inappropriate control of confounders or not providing information about the non-response rate (eg, refusing to participate in the study). Selective reporting about the non-response rate within studies could have biased the cumulative evidence.

Participants

Details of included studies, including participant characteristics, measurement tools, and main outcomes are presented in **TABLE 3**. A total of 537 participants were included across all studies, consisting of both female (49.5%) and male (50.5%) participants with a mean age 41.8 years (**TABLE 3**). The duration of participants' tendinopathies ranged from 2–240 months. Only one study specifically included athletes as the participant group.[55]

Lateral epicondyle tendinopathy was the most studied tendinopathy (10/16 studies),[11,14,15,16,17,28,30,32,45,47] followed by shoulder tendinopathy (4/16),[2,19,24,40] and patellar tendinopathy (2/16, **TABLE 3**).[55,56] Except for lateral epicondyle tendinopathy meta-analysis was not possible.

Measures used

Ten studies (10/16) measured only pressure pain thresholds (PPT).[2,14,15,17,24,28,32,40,47,56] Two

studies (2/16) used thermal and pressure stimuli,[11,45] one study (1/16) a combination of thermal, pressure, and vibration stimuli,[15] and another study (1/16) used a combination of thermal, pressure, and punctate pressure (**TABLE 3**).[30] One study used the full German Research Network on Neuropathic Pain QST.[55] This protocol consists of 7 different tests that measure 13 parameters,[20] covering nociceptive thermal (cold and warm) detection thresholds (CDT and WDT respectively), paradoxical heat sensations, thermal (cold and heat) pain thresholds (CPT and HPT respectively), mechanical detection and pain thresholds and sensitivity, tests for wind-up ratio and dynamic mechanical allodynia, vibration detection thresholds, as well as PPT.[43] One study used the nociceptive flexion reflex as a direct measure of spinal cord excitability.[32] The nociceptive flexion reflex measures the amount of noxious electrical cutaneous stimulation that is required to elicit a motor response.[32]

Fifteen studies (15/16) measured PPT. Rate of pressure application differed between 20 and 98 kPa/s and the inter-test interval varied from 30 seconds to 5 minutes. The average of 3 measures was mostly used as the indicator of PPT,[2,11,14,15,16,17,24,28,32,40,45,47,55] but a 2 trial protocol was also used.[30,56]

Five studies (5/16) measured thermal pain thresholds (eg, HPT and CPT) with a baseline temperature of 30°C or 32°C with a change of 1°C/s.[11,15,30,45,55] The maximal cut-off temperature was 50°C, whereas the minimum cut-out temperature differed between 4.5°C and 5°C (**TABLE 3**). Sites for thermal stimuli were measured bilaterally either over one[11] or 12 points at the lateral elbow.[45]

The site of measurement was either the participants reported most painful spot[30,56] on the tendon or a standardized spot.[2,11,14,15,16,17,19,24,28,32,40,49,55] Additionally, several studies

described the use of standardized spots in remote areas[2,11,15,16,17,24,30,40,45,47] to measure widespread sensitivity (**TABLE 3**). For the 2 studies that used the most painful spot, one study used PPT as measure[56] and the other used CDT, WDT, CPT, HPT, light touch perception threshold, and PPT as measures.[30]

Outcomes from the included studies

Decreased mechanical pain thresholds (ie PPT, inferring mechanical hyperalgesia) was reported in all studies, with pressure algometry being the predominant tool used (15/16). Greater mechanical hyperalgesia at sites a distance from the participants' reported site of the tendon pain was found in studies of lateral epicondyle tendinopathy[11,14,15,16,17,28,45] and shoulder impingement syndrome.[24,40] Standardized sites over the tibialis anterior muscle, C6-C7 facet joint, contralateral elbow, and wrist were used as remote sites for lateral epicondyle tendinopathy, whereas only tibialis anterior was used in shoulder impingement syndrome.

Of the five (5/16) studies measuring thermal stimuli (ie, CPT and HPT), one was studying patellar tendinopathy and 4 studied lateral epicondyle tendinopathy. For lateral epicondyle tendinopathy, 2 reported heat hyperalgesia (ie, HPT) in the contralateral elbow compared to healthy controls.[11,45] One reported both heat and cold hyperalgesia (ie, HPT and CPT respectively) in the contralateral elbow.[45] The other study only found cold hyperalgesia in the contralateral elbow, but only in a more severe sub-group of participants with worse pain and disability as identified through the Patient Rated Tennis Elbow Evaluation (PRTEE) questionnaire.[11] The more severe sub-group also exhibited reduced heat pain thresholds at the affected side compared to controls.[11]

Detection thresholds did not feature greatly in studies (3/16).[15,30,55] One study did not find differences in light touch perception thresholds in the local pain area and the area of pain referral compared to the corresponding homologous contralateral area.[30] In 2 other studies that compared tendinopathy to healthy controls, one reported a higher sensitivity to vibration detection in athletes with patellar tendinopathy,[55] whereas the other did not find differences in lateral epicondyle tendinopathy.[15]

DISCUSSION

We identified 16 studies that satisfied our selection criteria in terms of our goal to elucidate evidence of nervous system sensitization in individuals with persistent tendinopathies of the rotator cuff (shoulder, n = 4), lateral epicondyle (n = 10), and patellar tendons (n = 2). There was no study related to Achilles tendinopathy meeting the inclusion criteria. All except the case series[29] used a healthy control group as comparison, but were cross sectional in nature and so it is difficult to determine causality between tendinopathy and measures of sensitization. Measurements of QST are increasingly used in studies of pain and are well described.[43,44] Mechanical and thermal pain threshold testing predominated. In synopsis, the most reported evidence for sensitization were mechanical hyperalgesia, locally and in area's at a distance from the involved tendon. This mechanical hyperalgesia has also been reported in chronic pain states that are not tendinopathies,[13,26] and in a previous systematic review on lateral epicondyle tendinopathy.[22]

Most studies used tests of mechanical hyperalgesia, which requires, as all QST measures, the participant to consciously decide on a (pain) threshold. Lim et al[32] used a nociceptive flexion reflex protocol that does not require such a decision by the participant and showed evidence of spinal cord excitability in lateral epicondyle tendinopathy compared to healthy controls.[50]

Collectively the data on widespread mechanical hyperalgesia and nociceptive flexion reflex might be suggestive of centrally mediated hyper excitability underlying mechanisms of chronic tendon pain.[58]

There appears a characteristic feature of sensitization emerging from the literature on persistent tendinopathies that might have promise clinically in determining prognosis and possibly guiding treatments. For example, a study by Coombes et al[11] demonstrated significant cold hyperalgesia in the affected and unaffected side of a group with severe lateral epicondyle tendinopathy, compared to those with moderate to mild forms of the tendinopathy and healthy controls. This might have clinical importance and utility because a different study[10] showed that cold pain threshold was significantly predictive of pain and disability status on PRTEE 12 months later (R^2, *9%* at 12 months, 35% at 8 weeks) and along with PPT and sex significantly predicted mechanical hyperalgesia at 12 months follow up (R^2, *52%*). These findings of possible predictive capacity of thermal QST in tendinopathies appear to have parallels with similar reports of QST being able to predict outcomes following treatment (eg, surgery) for a range of conditions (including osteoarthritis[35]).[1,57,59] They are also somewhat analogous with studies showing thermal and mechanical QST data differentiate severity in participants with conditions such as knee osteoarthritis,[18] non-specific low back pain,[39] whiplash associated disorder,[49] and chronic musculoskeletal pain.[48] Further research is required to better understand possible roles for QST as prognostic and treatment guiding tools in tendinopathy.

This review has identified a small number of QST studies in tendinopathy that are cross sectional in nature, which do not allow us to make any definitive statements on their implications to clinical practice or likely underlying mechanisms. Nevertheless, it is tempting

to speculate that there might be a role for PPT and CPT (as outlined above) testing in the clinical context. For example, PPT has moderate to good inter- and intra-rater reliability[8,27,37,56] and could be considered in quantifying palpation findings at the affected tendon on clinical examination. PPT might also prove to have a role in diagnosis, with a preliminary study of Kregel et al[29] showing that there was 96.5% positive predictive value in identifying tendinopathy in patients with patellar tendinopathy from asymptomatic tendons in control participants. These data form the basis for planning and the conduct of rigorous testing before implementation.

Tendinopathy is typically characterized as an adverse response to mechanical loading (eg, pain and reduced performance on decline squat in patellar tendinopathy, grip in lateral epicondyle tendinopathy). It might be that the peripheral and central mechanism(s) in persistent tendinopathy is analogous to that underlying temporal summation of pain with repeated PPT in knee osteoarthritis[5] and that of repetition-induced summation of pain with a physical low back pain aggravating task (ie, bending and lifting) in chronic low back pain.[51] While peripheral sensitization will likely involve changes in local milieu within the tendon[9] (see Scott et al[46] in this issue) any central sensitization will plausibly involve to varying degrees psychosocial factors (stress, cognitions, peer pressure, fear of pain) and behavioral factors (behaviors and beliefs that lead to overuse, overtraining, inadequate adaptation periods), as is evident in other chronic pain syndromes.[7,51,52] New treatment strategies might evolve from further research investigating the interaction and influences of behavioral (including loading behaviors), psychosocial factors, and the process of sensitization in persistent tendinopathies.

Although there appears evidence for central sensitization in tendinopathy, several limitations ought to be considered and more research is warranted on several topics. Foremost is the lack of studies on lower limb tendinopathies, with only 2 studies of patellar tendinopathy included[55,56] and none of Achilles tendinopathy. This underpins the importance of the need for more research in activity-related (sports) injuries like patellar and Achilles tendinopathy. Then there is the possible risk of bias concerning methodology, such as in the blinding of assessors to the participants' condition, which was only reported in 5 studies[2,14,16,17,24] and the non-response rate (eg, refusing to participate in the study) not being reported in any study. Finally, heterogeneity in the type of participants (non-athletes or retired athletes versus athletes), and duration of pain (2-260 months) also needs to be considered further.

CONCLUSION

In summary, it would appear that tendinopathy exhibits mechanical hyperalgesia that is widespread and indicative of central sensitization. This evidence is predominantly from upper limb conditions, with additional lower limb studies being needed. The underlying mechanism(s) and prognostic value of bilateral cold hyperalgesia in unilateral tendinopathy shown in 1 cohort requires evaluation in future research.

KEY POINTS

Findings: Presence of widespread mechanical hyperalgesia in persistent tendinopathies implies that there is an underlying nervous system sensitization. These findings of nervous system sensitization underpin the need for more comprehensive sensory testing research in tendinopathy.

Implications: The likely role of the nervous system contributing to pain and disability in persistent tendinopathies should be considered during diagnostics and for devising

management strategies in clinical practice. Accordingly, diagnosis and treatment should go beyond focusing on the tendon locally to consider possible central nervous system mechanisms.

Caution: Predominant representation of upper limb tendinopathies, especially lateral epicondyle tendinopathy, requires caution when drawing inferences to other tendinopathies, especially in the lower limb.

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507 **TABLE 1.** Systematic Literature Search.

Entry terms	
Central Nervous System sensitization [Mesh]	AND athletic Injuries [Mesh]
OR hyperalgesia [Mesh]	OR tendinopathy [Mesh]
OR pain Threshold* [Mesh]	OR tennis Elbow [Mesh]
OR sensitization [tw]	OR overuse injuries [tw]
OR hyperalgesia [tw]	OR jumpers knee [tw]
OR hypersensitivity [tw]	OR jumper's knee [tw]
OR algometry [tw]	OR patellar tendin* [tw]
OR hyperexcitability [tw]	OR epicondylitis lateralis [tw]
OR neural inhibition [tw]	OR tennis elbow [tw]
OR altered pain threshold* [tw]	OR Achilles tendin* [tw]
OR central pain physiopathology [tw]	OR impingement [tw]
OR nociception [tw]	
OR pain modulation [tw]	
OR pain processing [tw]	
OR neuropathic pain [tw]	
OR allodynia [tw]	
OR somatosensory profile* [tw]	
OR pain pressure threshold* [tw]	

508 * Both singular and plural keywords.

509 Abbreviations: Mesh, hierarchical structured medical terms; tw, text word, only searching for text words.

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TABLE 2. Quality ratings using NOS Scale of reviewed papers (n = 16). Listed in descending order of quality rating.

Study	Criteria*								Score
	S1: Adequate case definition	S2: Representativeness of cases	S3: Selection of Controls	S4: Definition of Controls	Ca: Controlled for age	Cb: Controlled for …	E1: Ascertainment of exposure	E2: Same method case & control	(/9)(%)
Fernandez-Carnero[16]	★	★	★	★	★	★	★	★	8 (89)
Alburqueque- Sendin[2]	★	★		★	★	★	★	★	7 (78)
Coombes[11]	★	★	★	★	★	★		★	7 (78)
Fernandez-Carnero[14]	★	★	★	★		★	★	★	7 (78)
Fernández-de-las-Peñas[17]	★	★	★	★		★	★	★	7 (78)
Hidalgo-Lozano[24]	★	★	★	★		★	★	★	7 (78)
Ruiz-Ruize[45]	★	★	★	★	★	★		★	7 (78)
Lim[32]	★	★	★	★	★	★		★	7 (78)
Slater[47]	★	★	★	★	★	★		★	7 (78)
Fernandez-Carnero[15]	★	★	★	★		★		★	6 (67)
Paul[40]	★	★	★	★			★	★	6 (67)
Van Wilgen[55]	★	★	★	★		★		★	6 (67)
Gwilyim[19]	★	★		★				★	4 (44)
Jespersen[28]	★	★		★		★			4 (44)
Leffler[30†]	★	★							2 (22)
Van Wilgen[56†]			★	★					2 (22)

*Criteria E3; non response rate was not applicable to any of the studies.

‡Criteria Cb; other controlled additional factors.

†Case series; no controls included.

527 **TABLE3.** Characteristics of included studies.

Author	Study design	Age (yr)	N Sex (M/F)	Tendinopathy	Duration	Measurement details and tools used	Main outcomes
Alburqueque-Sendin[2]	Case control	35.6 ± 12.1 (30.8-40.4)	13M; 14F	Shoulder impingement syndrome (SIS)	44.3 ± 54.0 (23.0-65.7) months	Pressure algometer (kg/cm2): bilaterally over the upper trapezius, infraspinatus, supraspinatus, middle deltoid, levator scapulae, serratus anterior, articular pillar of C5-C6 zygapophyseal joint, and tibialis anterior (order randomized). The mean of 3 trials (30-s rest in between) was used for data analysis.	Differences between involved and uninvolved sites of participants with SIS and higher differences between both sites of the SIS group and dominant site of controls although with significant difference only in the supraspinatus PPT. SMD for PPT in the unaffected side compared to healthy controls was 0.55 (95%CI: -0.03, 1.14) in the trapezius, 0.57 (95% CI: -0.02, 1.16) in the infraspinatus, 0.62 (95% CI: 0.02, 1.21) in the supraspinatus, 0.327 (95% CI: -0.26, 0.91) in the middle deltoid, 0.48 (95% CI: -0.11, 1.06) in the levator scapulae, and 0.22 (95% CI: -0.36, 0.80) in the serratus anterior.
Coombes[11]	Case control including participants from a RCT	49.6 ± 9.0	101M; 63F	Lateral epicondyle tendinopathy (LET)	24.8 ± 30.8 weeks	Digital pressure algometer (applied rate 40 kPa/s): bilaterally at lateral epicondyle, C6-C7 facet joints, and left tibialis anterior muscle. Thermal stimuli: bilateral heat and cold pain thresholds (baseline temperature 30°C, rate of increase or decrease 1°C). The mean of 3 trials (20-s rest in between) was used for data analysis.	Bilateral cold hyperalgesia and unilateral heat hyperalgesia were evident in severe LET in comparison to controls. SMD for PPT in the unaffected elbow compared to healthy controls was 0.88 (95% CI: 0.69, 1.3), 0.4 (95%CI: 0.11, 0.70) for HPT, and 0.62 (95% CI: 0.32, 0.92) for CPT. All participant groups demonstrated bilateral and widespread mechanical hyperalgesia relative to controls.
Fernandez-Carnero[14]	Case control	39 ± 14 (18-62)	8M; 12F	Lateral epicondyle tendinopathy	1 ± 0.5 (0.5-3) years	Pressure algometer (kg/cm2): lateral epicondyle on the symptomatic site in participants, dominant site in controls. The mean of 3 trials (30-s rest in between) was used for data analysis.	Lower PPT and larger referred pain patterns suggest that peripheral and central sensitization exists in LET.

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Table 3: (Continued)

Author	Study design	Age (yr)	N Sex (M/F)	Tendinopathy	Duration	Measurement details and tools used	Main outcomes
Fernandez-Carnero[15]	Case control	47 ± 10 (34-56)	6M; 6F	Lateral epicondyle tendinopathy	25 ± 16 (10-52) months	Vibrameter: frequency of 120Hz. Thermal stimuli: heat and cold pain thresholds (baseline temperature 30°C, rate of increase or decrease 1°C). The mean of 3 trials (5-s rest in between) was calculated and used for further analysis. Pressure algometer (applied rate 30kPa/s): 3 measurements (30-s rest in between) were taken and the mean was used for further analysis. All tests were bilaterally and randomly assessed over the lateral epicondyle and in the dorso-lateral aspect of the wrist in both participants and controls.	Participants with unilateral LET exhibit reductions in PPT on the affected site compared to the unaffected site and compared to controls. No differences were found in cold and heat pain, cold- and warm-detection thresholds and vibration-detection thresholds on the affected site compared to the unaffected site and compared to controls. SMD for PPT in the unaffected elbow compared to healthy controls was 0.95 (95% CI: 0.16, 1.75), 0.0 (95%CI: -0.75, 0.75) for HPT, and 0.34 (95% CI: -0.41, 1.09) for CPT.
Fernandez-Carnero[16]	Case control	43 ± 10 (25-63)	10M; 16F	Lateral epicondyle tendinopathy	20.3 (95% CI: 11.3, -29.2) months	Pressure algometer (applied rate 30kPa/s): bilaterally over the median, radial, and ulnar nerve, the articular pillar of C5-C6 zygapophyseal joint, the lateral epicondyle, and the tibialis anterior muscle. The mean of 3 trials (30-s rest in between) was used for data analysis.	PPT was significantly decreased bilaterally in participants with LET than healthy controls. PPTs over the measured points was negatively related to current elbow pain intensity. SMD for PPT in the unaffected elbow compared to healthy controls was 1.29 (95% CI: 0.64, 1.93), 1.26 (95% CI: 0.62, 1.91) in the median nerve, 1.37 (95% CI: 0.72, 2.03) in the radial nerve, and 1.26 (95% CI: 0.62, 1.91) in the ulnar nerve.
Fernández-de-las-Peñas[17]	Case control	43 ± 7 (34-55)	0M; 16F	Lateral epicondyle tendinopathy	1.8 ± 1.2 (95% CI: 0.8, -2.8) years	Pressure algometer (applied rate 30kPa/s): bilaterally over the median, ulnar, and radial nerve trunks and the articular pillar of C5-6 zygapophyseal joint (order randomized). The mean of 3 trials (30-s rest in between) was used for data analysis.	Lower PPT suggests that bilateral mechanical nerve pain hypersensitivity is related to specific and particular nerve trunks in women with either unilateral LET. SMD for PPT in the unaffected side compared to healthy controls was 2.86 (95% CI: 1.86, 3.87) in the median nerve, 3.20 (95% CI: 2.13, 4.26) in the radial nerve, and 2.27 (95% CI: 1.38, 3.17) in the ulnar nerve.

Table 3: (Continued)

Author	Study design	Age (yr)	N Sex (M/F)	Tendinopathy	Duration	Measurement details and tools used	Main outcomes
Gwilyim[19]	Case control	55.0 (42-60)	7M; 10F	Shoulder impingement syndrome	41.9 (10-240) months	Punctate sharpness threshold as described by the QST protocol of Rolke et al[44]: bilaterally at shoulders over the deltoid insertion. The mean of 5 trials was used for data analysis.	Participants experienced referred pain radiating down the arm and had significant hyperalgesia to punctate stimulus of the skin compared to controls.
Hidalgo-Lozano[24]	Case control	25 ± 9 (20-38)	7M; 5F	Shoulder impingement	8.5 (95% CI: 5, –12) months	Pressure algometer (kg/cm2): unilaterally over the levator scapulae, supraspinatus, infraspinatus, pectoralis major, biceps, and tibialis anterior muscles (order randomized). The mean of 3 trials (30-s rest in between) was used for data analysis.	Participants showed a significant lower PPT in all muscles when compared to controls.
Jespersen[28]	Case control	43 ± 10.6 range 39	0M; 22F	Lateral epicondyle tendinopathy	5.6 ± 3.2 months	Pressure algometer: both arms and in controls dominant arm only (applied rate: 1.0 kPa/s). The mean of 3 trials was used for data analysis.	In LET compared with controls the PPT and tolerance were on average reduced by 31%(NS) and 18%(NS) on the lower arm and by 32% and 22% on the lower leg.
Leffler[30]	Case series	45.4 (38–62)	2M; 8F	Lateral epicondyle tendinopathy	5.9 (2–12) months	Thermal stimuli: heat and cold pain thresholds (baseline temperature 30°C, rate of increase or decrease respectively 2°C and 3°C). Pressure algometer (applied rate 50kPa/s): the mean of 2 trials was used for data analysis. Von Frey fibers: applied in descending order of magnitude to assess the level at which the sensation disappeared, and in ascending order to assess the level at which the sensation reappeared. All tests were bilaterally assessed at the local pain area and in the area of pain referral.	No significant differences were found between cold- and warmth perception thresholds, cold- and heat pain thresholds, PPTs and light touch perception thresholds in the local pain area and the area of pain referral compared to the corresponding homologous contralateral area.
Lim[32]	Case control	52.24 ± 9.35	21M; 9F	Lateral epicondyle tendinopathy	20.7 ± 35.3 months	Nociceptive flexion reflex Pressure algometer (applied rate 40kPa/s): triplicate recordings were taken bilaterally and the mean value was recorded.	Within the LET group, there was no statistically significant correlation between nociceptive flexion reflex and PPT over the affected site (P = .263). There were significant differences in NFR threshold between the control and LET with or without a positive neurodynamic test (P <.01). SMD for PPT in the unaffected elbow compared to healthy controls was 0.66 (95% CI: 0.15, 1.18).

Table 3: (Continued)

Author	Study design	Age (yr)	N Sex (M/F)	Tendinopathy	Duration	Measurement details and tools used	Main outcomes
Paul[40]	Case control	51.7 ± 10.0	15M; 16F	Shoulder impingement syndrome	At least 6 months	Pressure algometer (kg/cm2): bilaterally over the middle deltoid and unilateral over the tibialis anterior (unaffected/nondominant arm). The mean of 3 trials (30-s rest in between) was used for data analysis.	Participants with SIS had significantly lower PPTs than did controls at all locations. Controls had a higher PPT at their affected shoulder than did those with SIS, higher PPT at their nonaffected shoulder, and higher PPT at their contralateral tibialis anterior.
Ruiz-Ruize[45]	Case control	45 ± 8 (32-58)	6M; 10F	Lateral epicondyle tendinopathy	19.2 ± 6 .8 (95% CI: 1.0, – 2.9) years	Pressure algometer (applied rate 30kPa/s): bilaterally over a 3 x 4 matrix on the elbow. The mean of 3 trials (30-s rest in between) was used for data analysis. Thermal stimuli: bilateral heat and cold pain thresholds (baseline temperature 32°C, rate of increase or decrease 1°C). The mean of 3 trials (10-s rest in between) was used for data analysis.	Topographical pressure and thermal pain sensitivity maps revealed bilaterally reduced PPT in participants with strictly unilateral LET. SMD for PPT in the unaffected elbow compared to healthy controls was 0.76 (95% CI: 0.04, 1.48), 0.59 (95%CI: -0.12, 1.30) for CPT, and 0.72 (95% CI: 0.00, 1.44) for HPT.
Slater[47]	Case control	48.25 (34–65)	10M; 10F	Lateral epicondyle tendinopathy	6.5 ± 1.1 months	Pressure algometer (applied rate 30kPa/s): assessed bilaterally over the common extensor origin at the lateral epicondyle, the belly of the extensor carpi radialis brevis muscle, and the radial head bilaterally. The mean of 3 trials (30-s rest in between) was used for data analysis.	Participants showed significant mechanical hyperalgesia at common extensor origin in both sore and control arms compared with healthy controls ($P < .04$). PPT at the common extensor origin in the sore arm and arms allocated for DOMS was lower than for the control arms in both participants and healthy controls ($P < .001$). SMD for PPT in the unaffected elbow compared to healthy controls was 0.50 (95% CI: -0.17, 1.17), 0.37 (95% CI: 0.29, 1.03) in the extensor carpi radialis brevis, and 0.27 (95% CI: -0.40, 0.93) in the radial head.

Table 3: (Continued)

Author	Study design	Age (yr)	N Sex (M/F)	Tendinopathy	Duration	Measurement details and tools used	Main outcomes
van Wilgen[55]	Case control	23.3 ± 3.57	12M; 0F	Patellar tendinopathy	30 (6-120) months	QST described by Rolke et al[44] : over the patellar tendon directly distal to the apex of the patella in participants and controls. The mean of 5 trials was used for data analysis.	The Mechanical Pain Threshold for the injured athletes was significantly more sensitive to the applied stimuli than for controls (P = .04). Furthermore, Vibration Disappearance Threshold was also more sensitive to the applied stimuli in injured athletes than the controls (P = .01).
van Wilgen[56]	Case control	23.1 (18-35)	53M; 49F	Patellar tendinopathy	Not mentioned	Pressure algometer: bilaterally over the tendon directly distal of the patella apex in the asymptomatic participants, most painful spot in participants. The mean of 2 trials was calculated and used for data analysis.	The PPT of asymptomatic participants differs significantly (P < .001) from athletes with a diagnosis of patellar tendinopathy.

Abbreviations: CI, confidence interval; CPT, cold pain threshold; CTS, carpal tunnel syndrome; DOMS, delayed onset muscle soreness; HPT, heat pain threshold; LET, lateral epicondyle tendinopathy; NS, non-significant; PFPS, patellar femoral pain syndrome; PPT, pressure pain threshold; QST, quantitative sensory testing; RCT, randomized controlled trial; SIS, shoulder impingement syndrome; SMD, standard mean difference.

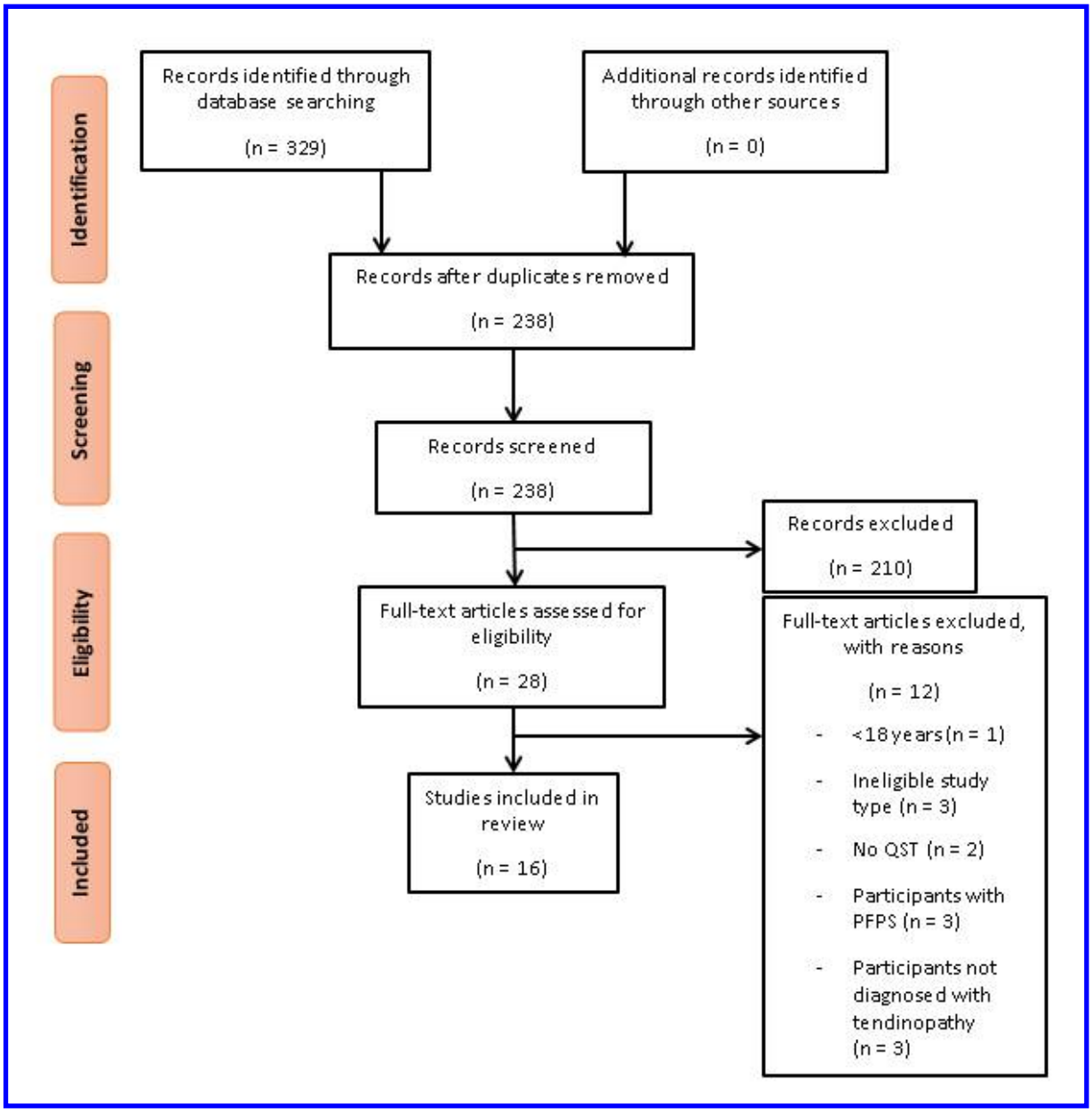

FIGURE. PRISMA flowchart of study selection process. Abbreviations: PFPS, patellofemoral pain syndrome; QST, Quantitative Sensory Testing).

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5,6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7,8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7,8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7,8

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7,8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	none done
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9 & 31
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	26-30
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	26-30
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	26-30
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	none done
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14,15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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