Evidence of bilateral localized, but not widespread, pressure pain hypersensitivity in patients with upper extremity tendinopathy/overuse injury: a systematic review and meta-analysis.

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Abstract

Objective. The presence of altered nociceptive pain processing in patients with upper extremity tendinopathy/overuse injury is conflicting. Our aim was to compare pressure pain thresholds (PPTs) in symptomatic and distant pain-free areas between patients with upper extremity tendinopathy/overuse injury and controls.

Methods. Five databases were searched from inception to October 15, 2020. The authors selected case-control studies comparing PPTs between individuals with upper extremity tendinopathy/overuse injury and pain-free controls. Data were extracted for population, diagnosis, sample size, outcome, and type of algometer. Results were extracted by 3 reviewers. The methodological quality/risk of bias (Newcastle-Ottawa Quality Assessment Scale) and evidence level (Grading of Recommendations Assessment, Development and Evaluation approach) were assessed. Meta-analyses of symptomatic, segment-related and distant pain-free areas were compared.

Results. The search identified 807 publications with 19 studies (6 shoulder, 13 elbow) eligible for inclusion. The methodological quality ranged from fair (48%) to good (37%). Patients exhibited lower bilateral PPTs than controls at the symptomatic area (affected side: MD = −175.89 kPa [95% CI = −220.30 to −131.48 kPa]; nonaffected side: MD = −104.50 kPa [95% CI = −142.72 to −66.28 kPa]) and the segment-related area (affected side: MD = −150.63 kPa [95% CI = −212.05 to −89.21 kPa]; nonaffected side: MD = −170.34 kPa [95% CI = − 248.43 to −92.25]) than controls. No significant differences in PPTs over distant pain-free areas were observed.

Conclusion. Low to moderate quality evidence suggests bilateral hypersensitivity to pressure pain at the symptomatic and contralateral/mirror areas in patients with upper extremity tendinopathies/overuse injury. Moderate quality of evidence supports bilateral pressure pain sensitivity in the segment-related area (neck) in lateral epicondylalgia, but not in subacromial impingement syndrome. No evidence of widespread pressure pain hyperalgesia was reported.

Impact. Early identification of people with altered pain modulation could guide clinicians in treatment strategies. This review shows that there is a complex interplay between peripheral and central pain mechanisms in upper extremity tendinopathies/overuse injuries and that there likely are different subgroups of patients with upper extremity conditions.

Introduction

Tendinopathy usually occur in tendons receiving excessive or unaccustomed loads and often results in considerable pain and related-disability. Although several advances have been made, the pathophysiology of tendinopathy is not completely understood. It has been proposed that tendinopathy represents a pathological process when pain and structural changes in the tendon matrix may be present. This association between structural tendon changes with pain symptoms is a complex process.[1]

It seems that tendon related-pain is consistent with a dominant peripheral nociceptive driver since most painful tendinopathies typically present as localized pain at the tendon area;[2] however, the pathophysiological mechanisms for symptoms generation is questioned.[3] Since sustained peripheral nociception may lead to the development of altered nociceptive processing due to the plasticity of the central nervous system[4], there is controversy if tendinopathy associated pain is a peripheral or central phenomenon or both.

Identification of the predominant mechanism (eg, peripheral or central) in painful tendinopathies could be crucial since early identification of people exhibiting altered pain modulation may guide clinicians in their therapeutic strategies. In fact, preliminary evidence suggests that sensory indicators of central sensitization may be associated with greater symptoms and related-disability in musculoskeletal pain, particularly in patients with upper extremity pain.[5]

Two previous reviews have tried to determine the presence of altered nociceptive processing in tendinopathies. Heales et al reported bilateral sensory and motor deficits in people with unilateral tendinopathy, suggesting a potential involvement of the central nervous system.[6] Due to the heterogeneity in the population, a meta-analysis was only able to be performed for lateral epicondylalgia.[6] Similarly, Plinsinga et al[7] suggested the presence of central sensitization since decreased pressure pain thresholds across different tendinopathies were reported, mainly at the site of tendinopathy, as well as at remote sites; however, a meta-analysis was not conducted.[7] These previous reviews mostly compared the affected and nonaffected sides; to further confirm the presence of central sensitization, responses in distant pain-free areas (ie, widespread pain hypersensitivity) and further analyses are required. No meta-analysis has investigated widespread sensitivity changes in distant pain-free areas in patients with tendinopathy.

Since it has been suggested that sensory pain processing could be different in upper and lower extremity tendinopathies;[8] this review and meta-analysis will focus on identifying sensitization in upper extremity tendinopathies. Two previous reviews have suggested the presence of central sensitization in shoulder pain;[9,10] however, both reviews included patients with pain of different etiologies ranging from unspecific shoulder pain to hemiplegic shoulder pain.[9,10] Again, due to the heterogeneity in the diagnoses and the outcomes used, meta-analysis was not possible.

Several sensory outcomes can be used for evaluating sensitization but mechanical threshold or conditioning pain modulation are those most often used for musculoskeletal pain conditions.[11] Tendinopathy-related pain is mainly associated with potential tendon load during physical activity, which suggests that mechanical hyperalgesia seems to be the predominant impairment in this condition. Therefore, assessing pressure sensitivity would be the most appropriate quantitative sensory test to be used in individuals with tendinopathies.[12]

We aimed to report the current evidence concerning somatosensory processing in patients with upper extremity tendinopathy/overuse injury compared to healthy controls focusing on the presence of localized and widespread sensitivity to pressure pain. Therefore, the current systematic review and meta-analysis analyzes the differences in both localized and widespread pressure pain thresholds (PPTs) between individuals with upper extremity tendinopathy/overuse injury and controls.

[H1] Methods

This systematic review and meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13] We also followed similar methodology than in a previous meta-analysis published by our research group.[14] The international OPS Registry registration link is https://doi.org/10.17605/OSF.IO/B6QNJ

[H2] Data Sources and Searches

Electronic literature searches were conducted on MEDLINE, CINAHL, PubMed, Scopus, and Web of Science databases from their inception to October 15, 2020. We screened the reference lists of the papers that were identified for any other potentially eligible studies. If any info was missing, authors were contacted, if needed. Database search strategies were conducted with the assistance of an experienced science librarian.

[H3]Population: Adults (≥18 years old) with a diagnosis of upper extremity tendinopathy and no other condition altering nociceptive pain processing (eg, fibromyalgia or chronic neck pain). Due to the heterogeneity in the diagnosis, particularly in the shoulder area, we included potential diagnoses compatible with tendinopathy/overuse-related pain (eg, rotator cuff, shoulder/subacromial impingement, or supraspinatus tendinopathy).

[H3]Intervention: Not applicable. In case of the application of an intervention in people with and without tendinopathy, only baseline PPTs were included.

[H3]Comparator: A comparative group of pain-free individuals without any musculoskeletal pain condition serving as controls.

[H3]Outcomes: The primary outcome measure was PPT assessed with a pressure algometer at the symptomatic, segment-related (cervical spine), and/or distant pain-free area. The search strategy used for each database is available in Supplemental Table 1.

[H2] Selection Criteria

This systematic review and meta-analysis included cross-sectional or prospective case-control studies where at least 1 group included adults older than 18 years with any upper extremity tendinopathy and 1 pain-free control group. If clinical trials included people with and without tendinopathy were found, baseline PPTs were included. The 4 specific inclusion criteria were as follows: adults with upper extremity painful tendinopathy based on the clinical history and/or physical examination tests (since tendinopathy is a clinical diagnosis and no correlation between symptoms and tendon imaging is observed, imaging diagnosis was considered complementary); full-text report (abstracts, letters, and editorials were excluded); a control group including people who were pain free; and the study had to include PPTs assessed with an algometer as an outcome. In studies evaluating different quantitative sensory tests (eg, thermal or electrical pain thresholds), just PPT data were extracted. We excluded studies assessing mechanical sensitivity with other modalities (eg, monofilament Von-Frey); studies assessing only other quantitative sensory tests (eg, thermal/electrical thresholds); and experimentally induced tendon pain studies.

[H2] Data Extraction and Quality Assessment

Articles identified from the different databases were independently reviewed by 3 authors. After removing duplicates, titles and abstracts were screened. After, a full-text read of eligible studies was conducted by each author independently. The authors had to achieve a consensus on the included studies. If discrepancy existed between them, a fourth author participated to reach a consensus.

Population, diagnosis, sample size, outcomes, type of algometer. and results were extracted independently by 3 authors on a standardized form. A consensus on each item on the data extraction form should be achieved. No differences were observed in data extraction among authors.

Risk of bias of the studies was independently assessed by 3 authors using the Newcastle-Ottawa Quality Assessment Scale, a rating system evaluating the methodological quality of case-control/cohort studies.[15] This scale includes 3 areas: case selection (case definition, representativeness of cases, and definition and selection of controls), between-groups comparability (eg, matched or controlled for age, gender, other factors), and exposure (ascertainment for case/control groups and nonresponse rate). A maximum of 9 stars can be awarded. Studies scoring ≥7 are considered of good quality, those scoring 5 or 6 are of fair quality, and studies scoring 0 to 4 are considered of poor quality.[16] Risk of bias was also determined by 3 authors, and differences were discussed.

To evaluate the level of evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used.[17] The level of evidence was classified as high, moderate, low, or very low according to downgrading of factors such as risk of bias (Newcastle-Ottawa Quality Assessment Scale), defined as several study limitations that resulted in a substantial risk of bias across the evidence; inconsistency of the results/unexplained heterogeneity when results showed significant moderate/high heterogeneity ($I^2 > 60\%$); indirectness when the evidence was not directly comparable to the question of interest (eg, population, exposure, comparator, outcome); imprecision of the results when the studies had few participants and few events (wide CIs, as judged by the reviewers); and publication bias when funnel plots showed substantial asymmetry because studies were missing from the body of evidence and because of a statistically significant Egger test resulting in an overestimation or underestimation of true effects from exposure.[18] The level of evidence was classified as high quality when all items were negative; moderate quality when 1 item showed serious risk; low quality when 2 items showed serious risk or 1 item showed very serious risk; or very low quality when all items showed serious risk or 2 or more items showed very serious risk. Again, this process was independently performed by 3 authors, with the participation of a fourth one if disagreement appears.

[H2] Data Synthesis and Analysis

The meta-analysis was conducted using the Review Manager statistical software (RevMan version 5.3, Cochrane Collaboration) and R software 4.0 (Windows). Data synthesis was categorized by diagnosis/body area (shoulder, elbow, wrist) and by side (affected side, nonaffected side), and by assessed point (symptomatic, segment related, and distant pain free). The comparisons included affected side versus nonaffected side, affected side versus controls, and nonaffected side versus controls

We extracted the sample size, means, and SDs for each variable. When the study reported SEs or CIs, they were converted to SDs. If necessary, means and SDs were estimated from graphs with GetData Graph Digitizer v.2.26.0.20 software (Windows). When nonparametric values were presented, they were converted to means and SDs.[19] When multiple points were analyzed in the same region (eg, infraspinatus, supraspinatus, or acromion), the average of all PPTs for each area (symptomatic, segment related, or distant pain free) was calculated. Further, the mean PPTs for each area (symptomatic, segment related, or distant pain free) were pooled and compared. For studies reporting results in different tendinopathy groups, each patient group was considered separately. For studies with a single control group but different patient subtypes, we pooled data from each group of patients versus the same control group.

The between-groups mean differences and 95% CIs for each study were obtained. A random-effects model was used to determine the overall effect size by calculating the mean difference (MD) and standardized mean difference (SMD). Pressure pain thresholds were expressed in kilopascals; when other units were presented in the studies (eg, kilograms), they were converted to kilopascals.

The heterogeneity of the studies was assessed using the I^2 statistic. The Cochrane group has established the following interpretation of the I^2 statistic: 0% to 40% may not be relevant/important heterogeneity, 30% to 60% suggests moderate heterogeneity, 50% to 90% represents substantial heterogeneity, and 75% to 100% represents considerable heterogeneity.[20] Publication bias was assessed using funnel plots; if there was asymmetry and a suspicion of publication bias, the Egger test was used to detect publication bias. Publication bias was realized when 10 different studies were included in the same meta-analysis.

[H1] Results

[H2] Study Selection

The electronic search initially identified 807 studies. After removing duplicates, 165 studies remained. One hundred forty-two were excluded on examination of their titles and/or abstracts, leaving 23 articles for full-text analysis.[21-43] We excluded 4 studies after the full-text read because of no assessment of PPT,[28] lack of diagnosis,[37] and lack of a control group.[21,27] Nineteen studies were included in the review and qualitative analysis.[22,23,34–36,38–43,24–26,29–33] One study[35] was excluded from the quantitative analysis due to lack of comparability of PPTs. Eighteen studies were finally included in the quantitative meta-analysis[22,23,34,36,38–43,24–26,29–33] (Fig. 1).

[H2] Study Characteristics

The characteristics of the populations of the studies are shown in Suppl. Table 2. Six articles included patients with a diagnosis of shoulder impingement, [26,32,36,38,40,43] and 13 included patients with lateral epicondylalgia. [22,23,39,41,42,24,25,29–31,33–35] All diagnoses were based on clinical history and physical examination tests, none used imaging analysis. The total sample included 674 patients (51% women) and 489 controls (52% women). Two hundred ten patients (43% women) had shoulder impingement, and 464 patients (54% women) had lateral epicondylalgia. In 14 studies (74%), the control group was mentioned to be sex and age matched to the patient group[22,23,40–43,25,26,29,31,33,36,38,39]; in 3 studies, the control group was comparable (not truly matched) to the patient group[24,30,34]; in the remaining 2 studies,[32,35] significant differences in age between patients and controls were reported.

Ten studies (53%) used a pressure algometer from Somedic (Farsta, Sweden**),** [22–25,29,30,33,34,41,42] 4 studies (21%) used a Fisher algometer (Pain and Diagnosis and Treatment Inc, CA, USA**),** [26,31,36,38] 2 studies (10%) used a Wagner algometer (Wagner Instruments, CT, USA),[32,43] and other algometers were used in 1 study each.[35,39,40] The size of the probe surface of algometer was reported in 15 studies (74%),[22,23,39–43,24,26,29,30,32–34,36] being 1 cm^2 in all except one.[23]

Pressure pain thresholds were assessed in the symptomatic area in all studies: shoulder region in 6 studies (supraspinatus, n = 2; infraspinatus, n = 3; middle deltoid, n = 4; and acromion, n = 1) and elbow area in 12 studies (common extensor origin, n = 2; extensor carpi radialis brevis, n = 3; extensor digitorum communis, n = 1; radial head, n = 1; radial nerve, n = 2; lateral epicondyle, n = 7; and upper extremity, n = 1). In addition, the neck region was used as the segment-related area in 6 studies (upper trapezius, n = 2; levator scapulae, n = 2; and cervical spine, n = 4), whereas the lower extremity was used as distant pain-free area in 7 studies (tibialis anterior, n = 6). Suppl. Table 3 details PPTs of studies on each point.

[H2] Risk of Bias/Methodological Quality

The methodological quality scores ranged from 4 to 8 (mean = 6.25, SD = 1.0) out of a maximum of 9 stars (Suppl. Fig. 1). One study was considered of poor quality (4 stars),[35] 9 were considered of fair methodological quality (5 or 6 stars),[22,24,29,32–34,38–40] 8 were considered of good quality (7 stars), [23,26,30,36,41–43] and 1 was considered of high quality (8 stars).[31] The most frequent biases were lack of control for additional factors such as psychological aspects (eg, anxiety/depression) or ascertainment of exposure (masking assessment). Differences in star scores between reviewers were discussed and solved properly without needing arbitration. Assessment of risk of bias between reviewers showed an overall agreement of 94%. Table 1 shows the Newcastle-Ottawa Quality Assessment Scale results for each study and a summary of every item.

[H2] Pressure Pain Thresholds at the Symptomatic Area

The affected side exhibited significantly reduced PPTs at the symptomatic region (MD = −78.59 kPa [95% CI = −114.38 to −42.80 kPa], n = 1178, $z = 4.30$, $P < .001$; SMD = −0.65 [95% CI = −1.20 to −0.46]) (Fig. 2A) as compared to the contralateral nonaffected side, but with substantial heterogeneity ($I^2 = 84\%$). Significant subgroups (diagnosis) differences ($P = .02$, $I^2 = 82\%$) were observed: only individuals with lateral epicondylalgia showed significant side-to-side differences between affected and contralateral nonaffected side (MD = −93.25 kPa [95% CI = −134.13 to −52.38 kPa], n = 886, $z = 4.47$, $P < .001$; SMD = −0.83 [95% CI = −1.20 to −0.46]) (Fig. 2A). The funnel plot did not reveal asymmetry (Egger test, $P = .25$), therefore, no publication bias, in the overall PPTs side-to-side comparison was observed (Suppl. Fig. 2).

Significantly reduced PPTs at both affected (MD = −175.89 kPa [95% CI = −220.30 to −131.48 kPa], n = 1104, $z = 7.76$, $P < .001$; SMD = −1.37 [95% CI = −1.82 to −0.92]) (Fig. 2B) and nonaffected (MD = −104.50 kPa [95% CI = −142.72 to −66.28 kPa], n = 1010, $z = 5.36$, $P < .001$; SMD = −0.72 [95% CI = −1.00 to −0.45]) (Fig. 2C) sides in patients as compared to controls, with substantial heterogeneity ($I^2 > 80\%$) between studies were found. Both tendinopathy subgroups showed significantly lower PPTs bilaterally at the symptomatic area in affected (shoulder: SMD = −0.57 [95% CI = −1.02 to −0.12]; elbow: SMD = −1.75 [95% CI = −2.25 to −1.25]) and contralateral nonaffected (shoulder: SMD = −0.34 [95% CI = −0.59 to −0.09]; elbow: SMD = −0.88 [95% CI = −1.21 to −0.54]) side than controls ($P < .001$). The funnel plot showed asymmetry (Suppl. Fig 3) but the Egger test was not significant ($P = .986$) in overall PPT comparison between the affected side and controls at the symptomatic area. Also, the initial pooled effect size was an MD of −175.89 kPa, which is lower than the bias-corrected effect (MD = −197.38 [95% CI = −266.46 to −128.31], $P < .001$) reported when using the trim-and-fill procedure. Therefore, it can be assumed that there was not a risk for publication bias. For PPT comparisons between the nonaffected side and controls at the symptomatic area the funnel plot did not reveal asymmetry (Egger test, $P = .84$), no publication bias was, therefore, found (Suppl. Fig 4).

[H2] Pressure Pain Thresholds at Segment-Related Area

No significant side-to-side differences in PPTs at the cervical spine were found (MD = −10.36 kPa [95% CI = −30.26 to 9.54 kPa], n = 460, $z = 1.02$, $P = .31$) (Fig. 3A) between the affected/nonaffected sides. No heterogeneity ($I^2 = 0\%$) between studies was found.

The meta-analysis revealed significantly reduced PPTs bilaterally at the cervical spine at the affected (MD = −150.63 kPa [95% CI = −212.05 to −89.21 kPa], n = 426, $z = 4.81$, $P < .001$; SMD = −1.63 [95% CI = −2.50 to −0.76]) (Fig. 3B) and contralateral nonaffected side (MD = −170.34 kPa [95% CI = − 248.43 to −92.25], n = 352, $z = 4.28$, $P < .001$; SMD = −1.55 [95% CI = −2.52 to −0.58]) (Fig. 3C) when compared to

controls, but showing substantial heterogeneity (I^2 = 88%) between the studies. Only individuals with lateral epicondylalgia (affected side: SMD = −2.48 [95% CI = −4.17 to −0.79]; nonaffected side: SMD = −2.01 [95% CI = −3.40 to −0.62]) revealed significant reductions in PPTs bilaterally at the neck as compared to controls.

[H2] Pressure Pain Thresholds at Remote Pain-free Areas

No significant side-to-side differences in PPTs at distant pain-free area between the affected and nonaffected sides (MD = −1.63 kPa [95% CI = −69.98 to 66.72 kPa], n = 150, z = 0.05, P = .96) (Fig. 4A) were found. No heterogeneity (I^2 = 0%) between studies was observed.

Significantly reduced PPTs at the distant pain-free area on the affected side (MD = −131.48 kPa [95% CI = −221.83 to −41.13 kPa], n = 443, z = 2.85, P = .004) (Fig. 4B), but not on the nonaffected side (MD = −68.83 kPa [95% CI = −222.74 to 85.09 kPa], n = 127, z = 0.88, P = .38) (Fig. 4C) as compared to controls were reported, with substantial heterogeneity (I^2 > 70%) between studies. The subgroup analysis revealed that neither individuals with subacromial impingement syndrome nor lateral epicondylalgia separately had reduced PPTs at a distant pain-free area.

[H2] Level of Evidence

Table 2 shows the details of GRADE assessment showing risk of bias, inconsistency of the results, indirectness of evidence, imprecision of results, and high probability of publication bias. In general, the inconsistency of the results downgraded 1 or 2 levels the evidence quality in most analyses. Low to moderate quality evidence supported a bilateral reduction of PPTs at the symptomatic area in upper extremity tendinopathies as compared to controls. Moderate quality evidence also suggested a bilateral reduction of PPTs at the cervical spine (segment-related area) when compared to controls just in individuals with lateral epicondylalgia.

[H1] Discussion

[H2] Findings

This review and meta-analysis reported low to moderate quality evidence for bilateral lower PPTs (ie, hypersensitivity to pressure pain) at the symptomatic/mirror area in patients with upper extremity tendinopathy/overuse injury compared to controls. In addition, sensitivity to pressure pain was present in the cervical spine (segment-related area) in individuals with lateral epicondylalgia (moderate quality of evidence). No evidence of reduced PPTs at distant pain-free areas (ie, widespread hyperalgesia) was reported.

Identification of altered nociceptive processing in individuals with tendinopathy has previously been covered in the literature. The review by Plinsinga et al[7] suggested the presence of central sensitization; however, no quantitative analysis was conducted. Heales et al also found bilateral sensory deficits in people with unilateral tendinopathy; however, meta-analysis was only able to be performed for lateral

epicondylalgia.[6] Previous reviews have included tendinopathies of the upper and lower extremities, which should be avoided since sensory processing appears to be different.[8] This review is the most comprehensive and updated meta-analysis conducted to date analyzing differences in PPTs between patients with upper extremity tendinopathy/overuse injury and pain-free controls. We identified a total of 19 studies of fair to good methodological quality, 6 studies in patients with shoulder/subacromial impingement syndrome and 13 with lateral epicondylalgia. Previous reviews excluded shoulder impingement syndrome; however, we included this condition since it resembles symptoms highly compatible with a potential tendinopathy/overuse injury in the shoulder area.

The results support bilateral sensitisation in symptomatic and contralateral/mirror locations (ie, around the shoulder or the elbow, not directly over a tendon) in patients with shoulder/subacromial impingement (moderate to high quality evidence) or lateral epicondylalgia (low to moderate evidence). Our pooled results reported for patients with lateral epicondylalgia are similar to those previously found by Heales et al (mean PPT difference: −144.3 kPa [95% CI = −169.2 to −119.2]).[6] Bilateral pressure hyperalgesia in unilateral pain conditions would suggest the presence of bilateral sensitization changes, at least at spinal cord levels, which may explain the development of bilateral symptoms in individuals initially experiencing unilateral pain. In addition, the symptomatic area of individuals with lateral epicondylalgia exhibited larger PPTs reductions than the contralateral mirror nonaffected area, supporting the presence of localized hypersensitivity to pressure pain in the symptomatic area (peripheral sensitization). Supplementary Table 3 summarizes pooled PPTs for each point on each upper extremity tendinopathy.

The results for segment-related and distant pain-free areas were heterogeneous since the presence of reduced PPTs bilaterally in at the cervical spine (segment-related area) was only present in patients with lateral epicondylalgia (moderate evidence) but not in those with shoulder/subacromial impingement (Suppl. Table 3). Walton et al reported a minimal detectable change of 42.7 kPa for the neck area in people who were asymptomatic.[44] Between-groups differences between lateral epicondylalgia patients and controls for the neck (segment-related area) were larger than this score supporting the presence of real differences (larger than error) between this patient population and controls. The presence of pressure hyperalgesia in the segment-related area (neck) in individuals with unilateral elbow tendinopathy supports the presence of spinal cord sensitization in this population.

Finally, no significant PPT differences in distant pain-free areas were observed in either subgroup, though this was conflicted by the small number of studies analyzing distant pain-free areas PPTs in upper extremity tendinopathies/overuse injury. In addition, these findings should be considered with caution since we cannot exclude that the lack of findings were not merely due to low power analysis. These findings do not support, at this stage, the potential presence of widespread pressure hyperalgesia in upper extremity tendinopathies. These results are contrary to previous reviews suggesting the presence of altered nociceptive central processing.[6,7] However, previous reviews did not conduct a quantitative meta-analysis separating segment-related and remote asymptomatic pain-free areas; therefore, assumptions should be considered with caution at this moment.

[H2] Strengths and Limitations

Strengths of this review and meta-analysis were the rigorous methodology applied for literature search, screening for eligibility criteria, risk of bias assessment and pooling analysis of data by 3 authors. We included a total of 19 studies investigating PPTs in upper extremity tendinopathies/overuse injury, a greater number than those included in previous reviews, that only focused on lateral epicondylalgia.[6,7] Further,

studies fulfilled recommendations for the assessment of pressure algometry (eg, algometer probe size of 1 cm^2) using the mean value of 3 consecutive measures and control groups matched or at least comparable by age/gender. In fact, it has been highlighted the relevance of the inclusion of matched control group for comparison in studies including individuals with tendinopathy.[6,7]

However, some limitations are also recognized. First, it is important to consider that the diagnosis of tendinopathy was exclusively clinically done, since most studies lack of a confirmation of tendon changes by using diagnostic imaging. Similarly, any study that reported whether the control group had tendon pathology, although asymptomatic, with imaging which may affect pressure sensitivity.[45] Second, the reduced number of studies with small sample sizes identified for the shoulder could limit the generalizability of the results. In fact, shoulder impingement is considered as an overuse injury rather than a pure tendinopathy. There is a clear need for additional studies with larger sample sizes across a range of upper extremity tendinopathies. In addition, the quality of studies varied substantially; however, lack of masking or prevention of knowledge of primary exposure from influencing case ascertainment was a common problem across studies. Third, pooled data for PPTs included a variety of sites (eg, shoulder, elbow, cervical spine, hand, masseter, leg) and tissues (eg, tendon, muscle, nerve) measured; therefore, we cannot conclude that pressure pain hypersensitivity is specific of the any particular tissue (eg, tendon). Fourth, only papers published in English were included, because the majority of articles are in this language; this has probably not had a major impact on the overall findings. Finally, we only assessed PPTs as manifestation of sensitization. There are other types of measures to detect the presence of altered pain processing, such as thermal/electrical pain thresholds, conditioned pain modulation, or wind-up, which could also be assessed.

[H2] Clinical and Research Implications

The present review and meta-analysis highlight the importance of pressure pain hypersensitivity in upper extremity tendinopathies/overuse injuries as a manifestation of peripheral and spinal cord sensitization and opens several questions for future research. First, it would be important to understand that elbow and shoulder tendinopathy/overuse injury of the upper extremity exhibit different nociceptive processing. It seems that lateral epicondylalgia exhibits altered nociceptive processing at spinal levels whereas the results on the shoulder area are inconclusive. Bilateral sensory deficits in unilateral tendinopathy such as lateral epicondylalgia could benefit from therapeutic strategies addressing both extremities.

Additionally, standardized protocols for PPTs assessment would permit better identification of potential differences, if exist, between patients and pain-free controls. Second, PPTs should be analyzed separately by gender since women tend to exhibit higher sensitivity to pressure pain than men.[46] This gender distinction could lead to more solid and robust conclusions. Third, we investigated mechanical pain sensitivity since studies analyzing quantitative sensory testing in tendinopathies have mainly focused on PPTs; however, thresholds to other stimuli (eg, thermal, vibration, electrical, or conditioned pain modulation) can be also used for assessing the presence of sensitization. The German Research Network for Neuropathic Pain protocol proposes 13 measures to assess sensory profiles in chronic pain by measuring loss of sensory function, presence of allodynia, and hyperalgesia.[11] The application of the entire protocol could permit better understanding of altered pain processing in patients with upper extremity tendinopathies. Similarly, self-report patient outcomes assessing sensitization features have also been proposed and could identify some aspects not evaluated by PPTs. This could be highly relevant since self-report patient outcomes assessing sensitization manifestations, such as the Central Sensitization Inventory, have not been associated with hyperalgesia to pressure in people with shoulder pain.[47] In fact, Wheeler reported that at least 25% of patients with recalcitrant tendinopathy had central sensitization manifestations based on the Central Sensitization Inventory.[48] Futures studies including quantitative sensory tests and self-report patient outcomes assessing central sensitization manifestations are needed.

This review and meta-analysis support a complex interplay between peripheral and central pain mechanisms in upper extremity tendinopathies/overuse injuries, since it is probably that different subgroups of patients with these upper extremity conditions exist. Differences between subacromial/shoulder impingement and lateral epicondylalgia could be related to the fact that tendons differ in their roles as well as clinical features of the patients that present a particular tendinopathy/overuse injury. For instance, some tendinopathies may present with localized pain at the tendon, whereas others can exhibit spreading pain symptoms. The presence of spreading symptoms would suggest changes in nociceptive processing. Similarly, clinical features can also influence nociceptive gain, since higher levels of pain influence the central sensitisation and somatosensory alteration in musculoskeletal pain. Further, longer duration of pain symptoms may result in greater changes in the central nervous system.[4] Several studies included in this meta-analysis included patients with intensity pain levels lower than 4 of 10.[23,25,40,26,29,30,33,35,36,38,39] Clinical variables should be considered in future studies. Finally, studies investigating if altered pain processing in patients with tendinopathy who do not respond positively to treatment, and the utility of biological markers as prognostic indicators of clinical outcomes should be conducted.

[H1] Conclusions

This review and meta-analysis found low to moderate quality evidence for bilateral hypersensitivity to pressure pain at the symptomatic and contralateral/mirror area in patients with upper extremity tendinopathy/overuse injury when compared to controls. In addition, moderate quality of evidence supports that patients with lateral epicondylalgia exhibit sensitivity to pressure pain at the neck (segment-related area). No evidence of reduced widespread pressure pain hyperalgesia was observed. Current results support a complex interaction between peripheral and central mechanisms in tendinopathy/overuse injuries of the upper extremity.

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The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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Table 1.

Newcastle-Ottawa Quality Assessment Scale for Evaluating Methodological Quality/Risk of Bias

Disorder	Study	Selection				Comparability		Exposure		Score
		Adequate Case Definition	Representativeness of Cases	Selection of Controls	Definition of Controls	Controlled for Age	Controlled for Additional Factors	Ascertainment of Exposure	Same Method for Cases and Controls	
Shoulder/subacromial impingement syndrome	Hidalgo-Lozano et al[26] (2010)	★	★	★	★	★		★	★	7
	Paul et al[32] (2012)	★	★	★	★				★	5
	Coronado et al[27] (2011)		★	★	★	★	★			5
	Alburquerque-Sendin et al[36] (2013)	★	★	★	★	★		★	★	7
	Ribeiro et al[40] (2016)	★	★	★	★	★			★	6
	do Nascimento et al[43] (2020)	★	★	★	★	★	★		★	7
Lateral epicondylalgia	Slater et al[22] (2005)	★	★	★	★	★		★	★	7
	Fernández-Carnero et al[23] (2009)	★	★	★	★	★		★	★	7
	Fernández-Carnero et al[24] (2009)	★	★	★	★	★			★	6

	Fernández-de-las-Peñas et al[25] (2010)	★	★	★	★	★		★	★	7
	Ruiz-Ruiz et al[29] (2011)	★	★	★	★	★			★	6
	Lim et al[33] (2012)	★	★	★	★	★			★	6
	Coombes et al[30] (2012)	★	★	★	★	★	★		★	7
	Genc et al[31] (2012)	★	★	★	★	★	★	★	★	8
	Garnevall et al[34] (2013)	★	★	★	★	★			★	6
	Jespersen et al[35] (2013)	★	★		★				★	4
	Burns et al[39] (2016)	★	★	★	★	★			★	6
	Lim et al[41] (2017)	★	★	★	★	★	★		★	7
	Bisset et al[42] (2018)	★	★	★	★	★	★		★	7

Table 2.

GRADE Evidence Profile for Differences in Pressure Pain Thresholds Between Patients and Controls[a]

Location of Pressure Pain Threshold	**Effect by condition (No. of Studies)**	**Risk of Bias[b]**	**Inconsistency (I^2, %)[c]**	**Indirectness of Evidence[d]**	**Imprecision[e]**	**Publication Bias[f]**	**Quality of Evidence**	**MD (95% CI) in kPa**
Symptomatic area (symptomatic side vs nonsymptomatic side)	Overall effect (16)	No	Very serious (82)	No	No	No	Low	−78.59 (−114.38 to −42.80)
	Shoulder impingement (4)	No	No (0)	No	No	No	High	−24.08 (−64.49 to 16.32)
	Lateral epicondylalgia (12)	No	Very serious (84)	No	No	No	Low	−93.25 (−134.13 to −52.38)
Symptomatic area (symptomatic	Overall effect (17)	No	Very serious (88)	No	No	No	Low	−175.89 (−220.30 to −131.48)

side vs controls)								
	Shoulder impingement (6)	No	Serious (72)	No	No	No	Moderate	−93.50 (−157.47 to −29.53)
	Lateral epicondylalgia (11)	No	Very serious (89)	No	No	No	Low	−218.50 (−271.52 to −165.48)
Symptomatic area (nonsymptomatic side vs controls)	Overall effect (15)	No	Serious (77)	No	No	No	Moderate	−104.50 (−142.72 to −66.28)
	Shoulder impingement (4)	No	No (10)	No	No	No	High	−57.72 (−99.76 to −15.68)
	Lateral epicondylalgia (11)	No	Very serious (80)	No	No	No	Moderate	−120.98 (−166.93 to −75.04)
Segment-related area (symptomatic side vs nonsymptomatic side)	Overall effect (4)	No	No (0)	No	No	No	High	−10.36 (−30.26 to 9.54)
	Shoulder impingement (1)	No	No (0)	No	Yes	No	Moderate	13.07 (−89.15 to 115.29)
	Lateral epicondylalgia (3)	No	No (0)	No	No	No	High	−11.28 (−31.57 to 9.01)
Segment-related area (symptomatic side vs controls)	Overall effect (6)	No	Very serious (88)	No	No	No	Moderate	−150.63 (−212.05 to −89.21)
	Shoulder impingement (3)	No	Very serious (81)	No	Yes	No	Very low	−91.74 (−190.53 to 7.04)
	Lateral epicondylalgia (3)	No	Very serious (89)	No	No	No	Moderate	−199.77 (−278.01 to −121.52)
Segment-related area (nonsymptomatic side vs controls)	Overall effect (4)	No	Very serious (86)	No	No	No	Moderate	−170.34 (−248.43 to −92.25)
	Shoulder	No	No (0)	No	Yes	No	Moderate	−71.91 (−184.21 to

	impingement (1)							40.39)
	Lateral epicondylalgia (3)	No	Very serious (90)	No	No	No	Moderate	−194.10 (−282.34 to −105.86)
Distant pain-free area (symptomatic side vs nonsymptomatic side)	Overall effect (3)	No	No (0)	No	Yes	No	Moderate	−1.63 (−69.98 to 66.72)
	Shoulder impingement (1)	No	No (0)	No	Yes	No	Moderate	9.81 (−97.46 to 117.08)
	Lateral epicondylalgia (2)	No	No (0)	No	Yes	No	Moderate	−9.45 (−98.14 to 79.23)
Distant pain-free area (symptomatic side vs controls)	Overall effect (6)	No	Very serious (81)	No	No	No	Moderate	−131.48 (−221.83 to −41.13)
	Shoulder impingement (3)	No	Very serious (86)	No	Yes	No	Low	−132.59 (−294.88 to 29.70)
	Lateral epicondylalgia (3)	No	Very serious (80)	No	No	No	Moderate	−132.74 (−279.49 to 14.01)
Distant pain-free area (nonsymptomatic side vs controls)	Overall effect (3)	No	Serious (72)	No	Yes	No	Low	−68.83 (−222.74 to 85.09)
	Shoulder impingement (1)	No	No (0)	No	Yes	No	Low	0.00 (−107.04 to 107.04)
	Lateral epicondylalgia (2)	No	Very serious (85)	No	Yes	No	Very low	−128.91 (−439.20 to 181.39)

[a]GRADE = Grading of Recommendations Assessment, Development and Evaluation; MD = mean difference.
[b]No = most information was from results with a low risk of bias.
[c]Serious: I^2 = 40%–79%; very serious: I^2 > 80%.
[d]No indirectness of evidence was found in any study.
[e]Based on sample size.
[f]Based on funnel plots. Funnel plots for pressure pain thresholds at the symptomatic area (>10 studies) are shown in supplementary figures.

Legend of Figures

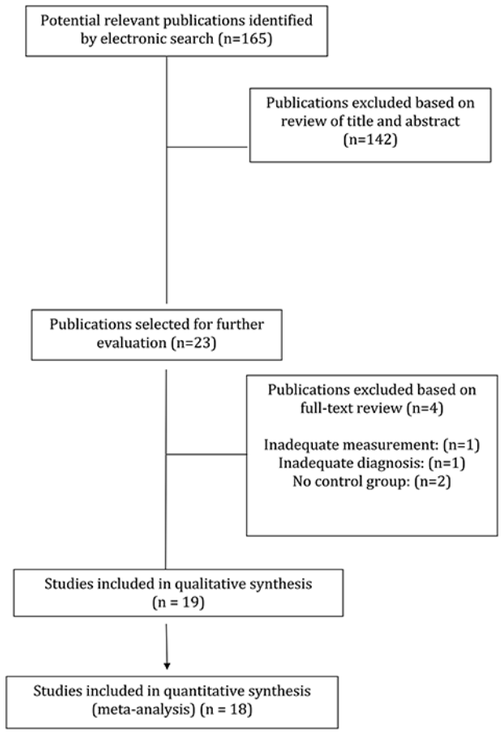


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

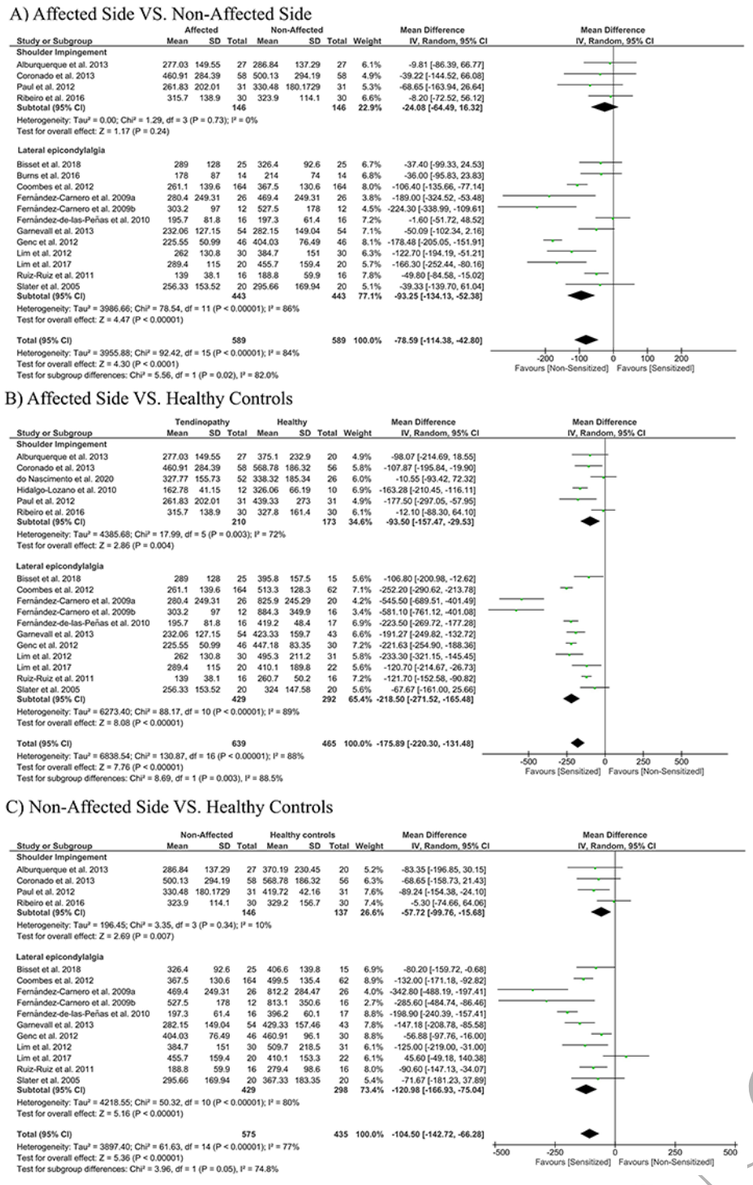
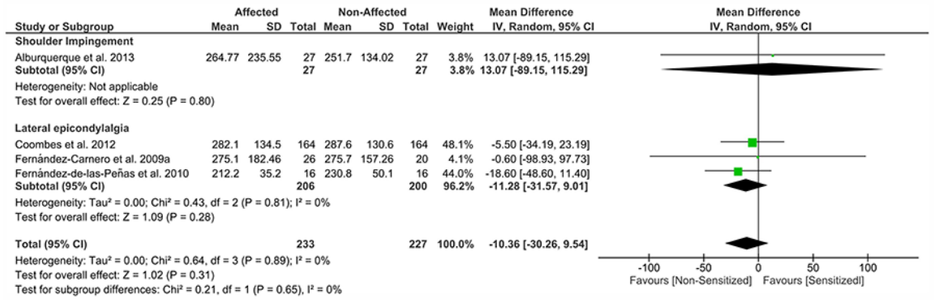
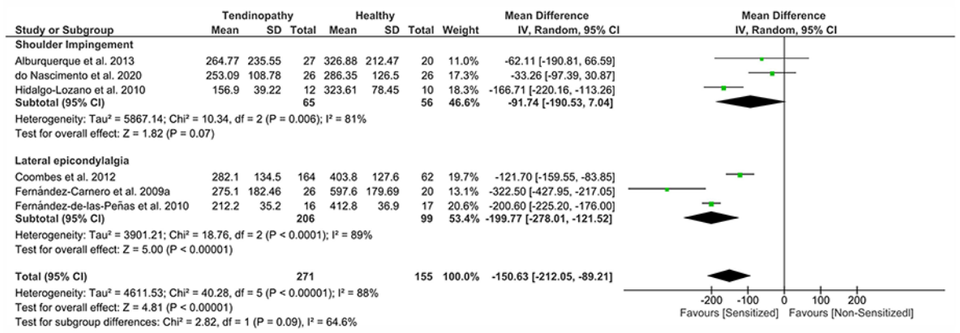


Figure 2. Summary of forest plot results for meta-analyses of pressure pain thresholds (PPTs) in the symptomatic area in patients with subacromial/shoulder impingement syndrome or lateral epicondylalgia. (A) Comparison of affected and nonaffected sides. (B) Comparison of affected side and pain-free controls. (C) Comparison of nonaffected side and pain-free controls. Negative values indicate that values for patients were lower than values for controls.

A) Affected Side VS. Non-Affected Side



B) Affected Side VS. Healthy Controls



C) Non-affected Side VS. Healthy Controls

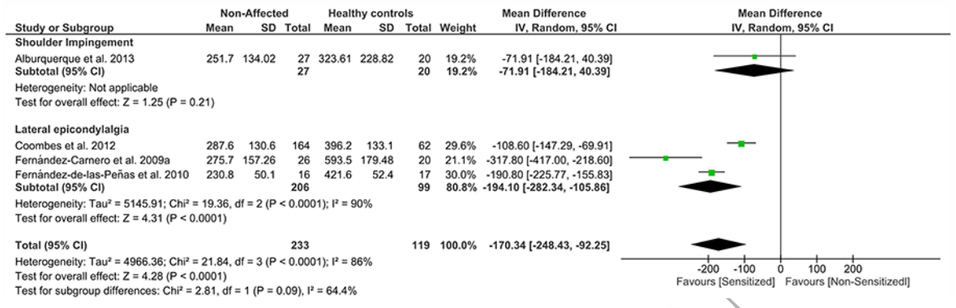
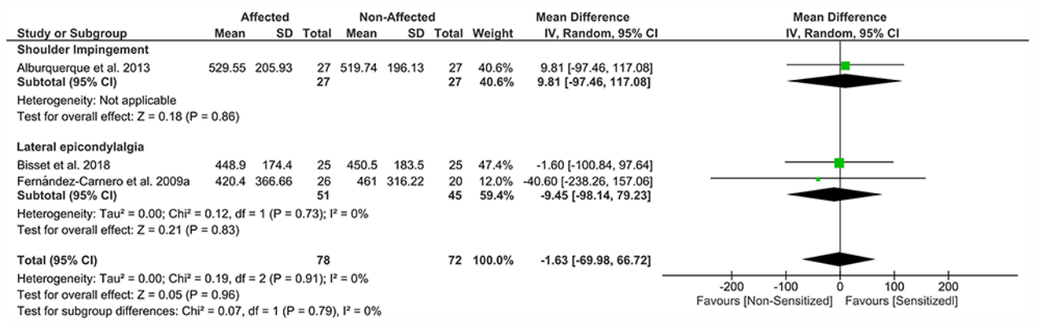
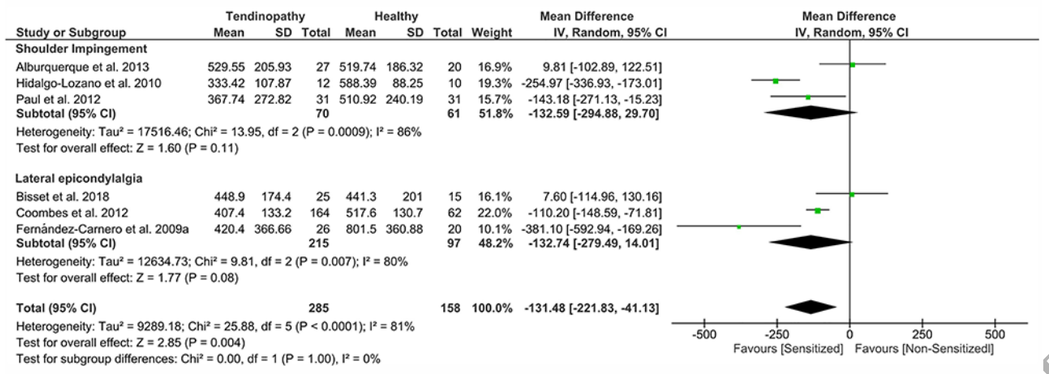


Figure 3. Summary of forest plot results for meta-analyses of pressure pain thresholds (PPTs) in the segment-related area (cervical spine) in patients with subacromial/shoulder impingement syndrome or lateral epicondylalgia. (A) Comparison of affected and nonaffected sides. (B) Comparison of affected side and pain-free controls. (C) Comparison of nonaffected side and pain-free controls. Negative values indicate that values for patients were lower than values for controls.

A) Affected Side VS. Non-Affected Side



B) Affected Side VS. Healthy Controls



C) Non-Affected Side VS. Healthy Controls

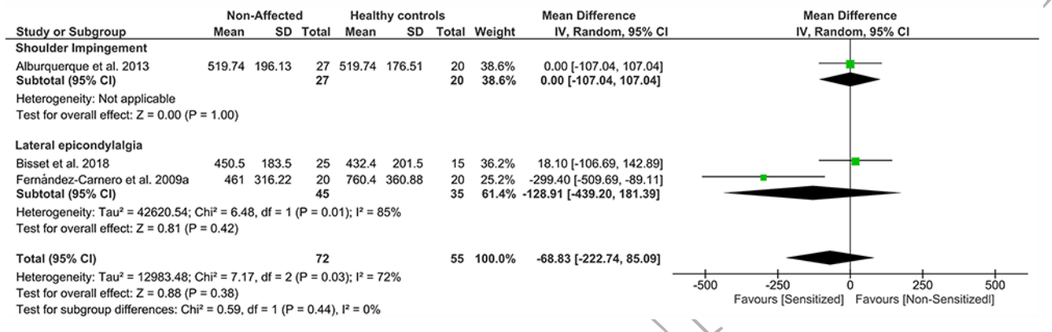


Figure 4. Summary of forest plot results for meta-analyses of pressure pain thresholds (PPTs) in distant pain-free areas in patients with subacromial/shoulder impingement syndrome or lateral epicondylalgia. (A) Comparison of affected and nonaffected sides. (B) Comparison of affected side and pain-free controls. (C) Comparison of nonaffected side and pain-free controls. Negative values indicate that values for patients were lower than values for controls.