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Thermal hyperalgesia distinguishes those with severe pain and disability in unilateral lateral epicondylalgia

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Abstract:	Objectives To evaluate if sensory, motor and psychological factors are different in severe lateral epicondylalgia compared to less severe cases and control. Methods 164 patients with unilateral lateral epicondylalgia and 62 healthy control participants of comparable age and sex underwent the following testing: quantitative sensory testing (pressure, thermal pain thresholds), pain-free grip, quality of life (EuroQol) and psychological (HADS, Tampa). Cluster analysis classified patients into mild, moderate or severe subgroups using the Patient Rated Tennis Elbow Evaluation (PRTEE). Data were then evaluated to determine differences between control and lateral epicondylalgia subgroups. Results Bilateral cold hyperalgesia (affected elbow, standardised mean difference (SMD): 1.14, P=0.000; unaffected elbow SMD: 0.94, P=0.000) and unilateral heat hyperalgesia (SMD -1.06, P=0.001) were evident in severe lateral epicondylalgia in comparison to healthy controls. All patient groups regardless of severity demonstrated bilateral and widespread mechanical hyperalgesia relative to controls (P<0.003), however only those with moderate and severe symptoms showed large differences (SMD>0.8) at all sites. Quality of life was significantly poorer in patients with severe symptoms, while anxiety, depression and kinesiophobia did not differ between subgroups. Discussion Lateral epicondylalgia patients presenting with severe pain and disability could be distinguished by hypersensitivity to thermal stimuli, notably bilateral cold hyperalgesia. Findings might implicate a combination of central, peripheral and sympathetic nervous system processes and may help explain the poorer outcomes found in this subpopulation.

Thermal hyperalgesia distinguishes those with severe pain and disability in unilateral lateral epicondylalgia

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Abstract

Objectives To evaluate if sensory, motor and psychological factors are different in severe lateral epicondylalgia compared to less severe cases and control.

Methods 164 patients with unilateral lateral epicondylalgia and 62 healthy control participants of comparable age and sex underwent the following testing: quantitative sensory testing (pressure, thermal pain thresholds), pain-free grip, quality of life (EuroQol) and psychological (HADS, Tampa). Cluster analysis classified patients into mild, moderate or severe subgroups using the Patient Rated Tennis Elbow Evaluation (PRTEE). Data were then evaluated to determine differences between control and lateral epicondylalgia subgroups.

Results Bilateral cold hyperalgesia (affected elbow, standardised mean difference (SMD): 1.14, P=0.000; unaffected elbow SMD: 0.94, P=0.000) and unilateral heat hyperalgesia (SMD -1.06, P=0.001) were evident in severe lateral epicondylalgia in comparison to healthy controls. All patient groups regardless of severity demonstrated bilateral and widespread mechanical hyperalgesia relative to controls ($P<0.003$), however only those with moderate and severe symptoms showed large differences ($SMD>0.8$) at all sites. Quality of life was significantly poorer in patients with severe symptoms, while anxiety, depression and kinesiophobia did not differ between subgroups.

Discussion Lateral epicondylalgia patients presenting with severe pain and disability could be distinguished by hypersensitivity to thermal stimuli, notably bilateral cold hyperalgesia. Findings may implicate a combination of central, peripheral and sympathetic nervous system processes and may help explain the poorer outcomes found in this subpopulation.

Keywords / Phrases: tennis elbow, hyperalgesia, depression, quality of life, kinesiophobia.

Introduction

Lateral epicondylalgia (LE) or tennis elbow affects up to 3% of the population with peak incidence occurring between 40-50 years of age.[1, 2] For the majority of sufferers, LE is self-limiting, with an average duration of a typical episode between six months and two years.[3] However, in two recent randomised controlled trials, 10 and 17% of people adopting a wait-and-see policy failed to report successful outcomes after one year.[4, 5] Furthermore, it has been estimated that between 5 and 10% of patients develop chronic symptoms and eventually undergo surgery.[6, 7] High pain and disability at baseline is one of the few consistently reported indicators of poorer long term outcome after conservative[3, 8, 9] and surgical treatment of LE.[10] For this reason, it might be valuable to identify other features that differentiate those individuals with higher pain and disability from those with lesser symptoms.

The relative simplicity of the clinical presentation of LE belies the complexity of its underlying aetiological processes. The mechanisms of pain and disability are likely multifactorial, involving an interaction of local tendon pathophysiological changes, motor impairment, nociceptive system mechanisms[11] and possibly psychological factors.[12] Motor impairment is widespread in the affected upper limb,{Alizadehkhaiyat, 2007 #17}{Coombes, 2011 #1344} with consistent evidence of markedly reduced pain-free grip strength being the strongest feature.[24, 25] Nociceptive system impairments in LE as measured through quantitative sensory testing have identified sensory alterations, but little is known about the distinct patterns of these changes in those who have high levels of pain and disability. A number of studies have shown that bilateral mechanical hyperalgesia exists in LE,[13-15] while a nascent body of research has explored thermal hyperalgesia.[15-18] Recently Ruiz-Ruiz et al[16] reported bilateral thermal hyperalgesia in a group of 16 LE participants, whereas other authors[19] have previously proposed that a subgroup of patients with severe LE exhibit cold

hyperalgesia. Cold hyperalgesia is emerging as an important factor in other musculoskeletal disorders such as whiplash associated disorders, with evidence that it can differentiate subgroups and help predict poor recovery over and above that of baseline pain and disability.[20, 21] In addition, Huge et al identified bilateral cold and heat hyperalgesia in acute complex regional pain syndrome (CRPS), and incomplete recovery of cold pain thresholds in chronic CRPS in comparison to healthy controls.[22] There is a growing interest in possible psychological factors being associated with chronic musculoskeletal conditions, for example, fear avoidance has been implicated.[23] Preliminary evidence of higher levels of depression and anxiety, which was correlated with pain and disability, has been identified in a small study of LE (n=16), prompting a need for further evaluation of psychological factors in LE.

The aim of this cross-sectional study was to identify whether sensory, motor and psychological factors can distinguish the subgroup of LE patients with higher pain and disability from those with lesser symptoms and a healthy control population. Comprehensive analysis might provide novel insights into the pathophysiology of the disease and mechanisms underlying delayed recovery found in patients with high baseline pain.

Methods

Patients and control participants

165 participants with LE meeting the following criteria for a randomised controlled trial[26] were recruited: unilateral elbow pain over the lateral epicondyle for longer than six weeks and aggravated by a combination of palpation, gripping and resisted wrist and/or finger

extension. Participants were excluded if they had other upper limb conditions, such as, cervicogenic, radiohumeral or neurological, or experienced recent fractures, corticosteroid injection or physiotherapy treatment. 62 healthy participants between 35 and 70, with no history of LE were recruited such that the control group had a similar proportion of males and females to the overall LE population. Participants were excluded if they experienced concomitant neck or other arm pain that prevented participation in their usual work or recreational activities or necessitated treatment within the past six months. All participants were recruited from the general community through media advertisements. Ethical approval was granted by the institutional review board and informed written consent was obtained from all participants.

Measures

Pressure pain threshold

Pressure pain thresholds (PPT) were measured using a digital algometer (Somedic AB, Farsta, Sweden) with probe size of 1cm^2, applied at a rate of 40 kPa/s until the first sensation of pain was perceived. PPT were measured bilaterally at the lateral epicondyle and C6-C7 facet joints and over the left tibialis anterior muscle. These sites have been previously evaluated in LE, demonstrating substantial intra-rater repeatability (ICC>0.89).[27]

Thermal pain thresholds

Heat (HPT) and cold (CPT) pain thresholds were measured bilaterally over the lateral elbow using the Thermotest system (Somedic AB, Farsta, Sweden).[17] Previous studies have confirmed the reliability of these measures (ICC>0.86).[15] From a baseline temperature of

30°C, the thermode was increased or decreased at a rate of 1°C/s until the first sensation of pain was perceived, or until maximum and minimum cut-out temperatures of 50°C and 5°C were reached.

Pain-free grip

Pain-free grip (PFG) is well established as a highly reliable (ICC>.97) and convenient clinical assessment tool, which correlates more strongly with disability and perceived improvement than maximal grip strength in LE populations.[28-30] It was measured using a digital grip dynamometer with variable handle position (MIE, Medical Research, UK). The participant was positioned in supine with the tested elbow in relaxed extension and forearm in pronation, such that the palm of the hand faced down on the plinth.[26] They were instructed to squeeze the dynamometer handle at a consistent rate and to stop the instant pain was experienced.

Pain, disability and quality of life

The patient rated tennis elbow evaluation (PRTEE) was used to quantify pain and functional disability in LE.[31] The PRTEE has been validated in a MRI-confirmed LE population and demonstrated good reliability and sensitivity to change.[31] Responses were scored on 11-point Likert scales with pain and disability subscales contributing equally to the total score, ranging from 0 (no pain or functional disability) to 100 (worst imaginable pain with a very significant functional disability).[31] Participants were asked to rate the level of pain currently experienced at rest and the worst level of pain experienced during the past week on 100mm visual analogue scales (VAS) with the following endpoints: no pain (0mm) and worst pain imaginable pain (100mm). Their level of function during the past week was also rated on a

100mm VAS with endpoints: no function (0mm) and full function (100mm). Substantial test-retest reliability has been demonstrated for these two VAS measures (ICC 0.89, 0.85).[32]

The EuroQol EQ-5D instrument was used to measure health-related quality of life.[33] Responses to five questions regarding different health dimensions were used to generate an index, ranging from 0 to 1, with 1 representing perfect health, by applying predefined scoring weights.[34]

Psychological factors

The Hospital Anxiety and Depression Scale (HADS) was measured in all participants to quantify the two most common forms of psychological disturbances - anxiety and depression.[35] It comprised questions rated on four point scales, with anxiety and depression subscales contributing equally to the total score, ranging from 0 to 42, with greater scores indicating greater anxiety and depression. The degree of kinesiophobia, also known as fear of movement or injury,[36] was assessed in the LE participants with the shortened Tampa Scale for Kinesiophobia (TSK-11). Each of the 11 items were scored on four point Likert scales giving a total score ranging from 11 to 44, with higher scores indicating greater kinesiophobia.

Procedure

Following completion of relevant questionnaires, testing was performed in the following sequence: PFG, PPT, HPT, CPT. The same examiner (BKC) performed all tests, without knowledge of PRTEE total scores or clustering. Tests were performed in triplicate starting on the unaffected or left side in LE or control participants respectively, with twenty second

intervals. Mean values were used in analyses. In order to determine the reliability of quantitative sensory testing, they were measured twice in the first 46 participants with LE, separated by a one week interval in which their condition was assumed to be stable.

Statistical analysis

Cluster analysis (based on the K-means algorithm) of the PRTEE scores was performed using SPSS 19 (IBM, Somers, New York, USA) to classify LE participants into three subgroups. This procedure, previously used in studies of other musculoskeletal conditions (e.g., whiplash associated disorders[37]) attempts to identify homogenous groups of cases based on selected characteristics. Following the formation of clusters, analysis of variance (ANOVA) was performed for each continuous outcome in order to compare the three LE groups and the control group. To account for any potential influence of hand dominance, the control group was randomly allocated a "matched affected arm" with an equivalent proportion of dominant sided arms as that observed in the LE group.[38, 39] *Sex* (between-subject) and *Side* (within-subject) factors were included in the ANOVA model along with *Group* (between-subject). Where significant side by group interactions were present, follow-up univariate ANOVA was performed separately for affected and unaffected sides. Pairwise comparisons of interest (simple effects) were followed up with Bonferroni post-hoc tests. Significance was nominated a-priori at $P<0.01$. To enable comparison of effect sizes, standardised mean differences (SMD) were calculated by dividing mean differences (MD) relative to the control group (extracted from SPSS) by the pooled standard deviation (SD). SMD scores greater than 0.8 were interpreted as a strong effect.[40] Categorical outcomes were compared between groups using Chi-squared analysis. Intra-class correlation coefficients (ICC) and their 95%

198 confidence intervals (CI) were calculated using an ICC(3,1) model as a measure of test-retest
199 reliability.
200

201 **Results**

202 Analysis was performed using data from 62 healthy controls and 164/165 patients with LE,
203 owing to one missing PRTEE questionnaire. Cluster analysis identified three subgroups
204 within the LE population based on total PRTEE scores (Figure 1). The clusters, referred to
205 herein as mild, moderate and severe LE, showed an expected incremental increase in mean
206 total PRTEE, supported by a similar increase in worst/resting pain and decrease in function as
207 measured using VAS ($P<0.01$). Injury duration was not found to differ between LE
208 subgroups, with the average duration being 25 weeks (range six weeks to four years). Levels
209 of anxiety, depression and kinesiophobia were also not significantly different between LE
210 subgroups. No other demographic differences were found between LE and control groups,
211 including gender, age, body mass index, manual occupation or participation in sports
212 involving gripping.

213 The severe LE cluster contained the smallest number of patients (n=27), of which 59.3%
214 were female. These patients were characterised by substantial worst pain levels (mean ± SD:
215 78.1 ± 16.2) and notable resting pain levels (21.8mm ± 12.5mm). Their health-related quality
216 of life (0.59 ± 0.16) was significantly poorer, and the majority (66.7%) reported sleep
217 disturbances due to their elbow condition. The mild LE cluster (n=53) contained a smaller
218 proportion (28.3%) of females and was characterised by moderate worst pain levels (50.6 ±
219 18.2), minimal pain at rest (6.5 ± 13.8mm), higher quality of life (0.77 ± 0.15) and lower
220 prevalence (32.1%) of sleep disturbance, though the latter was not statistically different to the
221 severe group ($P = 0.011$). The moderate LE cluster comprised the largest number of patients

(n=84), displaying intermediary characteristics for pain, quality of life and other clinical variables (Table 1).

Substantial test-retest reliability (ICC>0.80)[41] was found for all quantitative sensory measures over a one week period (PPT elbow 0.80, PPT neck 0.84, PPT tibia 0.83, HPT 0.86, CPT 0.84). Moderate (ICC 0.79) and substantial (ICC 0.89) reliability was found for PFG testing of the affected and unaffected arms respectively.

Thermal pain threshold

Analysis of pain thresholds to cold stimuli revealed significant main effects for both side (P<0.001) and group (P=0.002) but no interaction effect (P=0.195) (Figure 2). Post hoc analysis revealed only the severe LE group demonstrated significantly reduced thresholds to cold pain compared to controls, evident at both the affected (MD 6.7°C, 99% CI 1.6 to 11.8°C, P<0.001, SMD 1.14) and unaffected elbow (MD 4.4°C, 99% CI 0.3 to 8.5°C, P=0.004, SMD 0.94).

Pain thresholds to heat stimuli demonstrated a significant interaction between side and group (P=0.005). No differences were found for the unaffected elbow between controls and any of the LE groups (P=0.172). In contrast, significant differences were found between groups for the affected elbow (P=0.004) (Figure 2). Post-hoc analysis revealed only the severe LE group demonstrated significantly lower HPT on the affected side in comparison to controls (MD -3.0°C, 99% CI -0.5 to -5.5°C, SMD -1.06).

Pressure pain threshold

A significant interaction between side and group was found for PPT at the elbow (P<0.001). All three LE groups demonstrated significantly lower thresholds in comparison to controls (P<0.01), with differences being greater on the affected (MD -251.5KPa, 99% CI -302.1,-

200.8, SMD -1.92, P<0.001) than unaffected elbow (MD -131.4KPa, 99% CI -184.0,-78.8, SMD -0.97, P<0.001) (Figure 3). In the affected arm, progressively lower thresholds were seen with increasing pain and disability, with the differences between the severe and mild LE subgroups being statistically significant (P=0.005). PPT at the neck was significantly lower than controls, for all LE groups (MD -114.4kPa, 99% CI -163.8,-64.9, SMD -0.90, P<0.001). Similarly, PPT at the remote tibial site was significantly lower than controls for all LE groups (MD -102.6kPa, 99% CI -158.1,-47.1, SMD -0.84, P<0.001). There were no differences between mild, moderate and severe LE groups for PPT at either the neck or tibia

Pain-free grip

A significant three-way interaction between side, group and gender was evident for PFG (P<0.001). The affected arm of all three LE groups was significantly weaker than controls (P<0.001) (Figure 4). Differences were significantly (P<0.001) greater in males (MD -303N, 99% CI -334.3,-271.7, SMD -5.00) than females (MD -177.1N, 99% CI -198.9,-155.4, SMD -4.85), but proportionally (MD/control mean) they were similar (males 75.6% and females 73.4%), which is largely a function of greater normal strength in males.[42] Analysis of the unaffected arm, revealed no differences between controls and any of the LE groups for either gender.

Discussion

LE patients could be clustered into subgroups according to self-rated levels of pain and disability, supported by incremental differences in corresponding pain and function VAS measures. This study is the first to show that the presence of thermal hyperalgesia in comparison to healthy controls is a distinguishing feature in LE patients with severe pain and disability. Specifically, hyperalgesia to both hot and cold were demonstrated at the affected elbow, while cold hyperalgesia was also evident at the unaffected elbow. Previous

investigation of the thermal sensory profile of LE has revealed inconsistent findings, ranging from bilateral deficits in HPT,[16] to no differences in HPT,[17, 43] or reduction of HPT in the area of pain referral.[18] Elevated CPT was found in patients with unilateral LE compared to the unaffected arm[17] and to healthy controls,[15, 16] however only in the most recent study by Ruiz-Ruiz et al were the differences statistically significant. It is highly likely that these studies were either underpowered (the largest number of LE patients examined was 16) or did not comprise sufficient numbers of patients with severe LE. Our findings confirm the suspicions of Smith and colleagues that cold hyperalgesia exists in a subgroup of patients with LE.[19]

The presence of thermal hyperalgesia in severe cases of LE might provide an insight into the possible underlying neurophysiological basis of a condition understood to be musculoskeletal in nature. That cold hyperalgesia was bilaterally present in severe cases of unilateral LE lends support to a central mechanism being involved in these cases.[13-15, 44] Interestingly, there are similarities with CRPS 1 of the upper limb, where cold hyperalgesia has been associated with both peripheral sensitisation of C-fibres and central disinhibition of nociceptive pathways secondary to A-delta fibre degeneration.[22] Others[19] have proposed that cold hyperalgesia in LE may be dependent upon a sympathetic noradrenergic mechanism, based on their findings of selective improvement in CPT following guanethedine but not a control block in LE patients. They postulated that the presence of cold hyperalgesia may be a useful clinical indicator of the likely benefit of a sympathetic block, however this requires further research. It is becoming clear that to reconcile such findings from different studies requires further research.

Apart from the likely central implications of bilateral cold hyperalgesia, the finding of heat hyperalgesia further adds to our understanding of the local neurophysiological mechanisms in

LE. Heat hyperalgesia has been linked with peripheral sensitisation of C-fibres.[45] Peripheral sensitisation commonly occurs when nociceptors are exposed to inflammation or damaged tissue, however other changes in the immediate tissue environment, including the concentration of neurotransmitters, growth factors, hormones and neuropeptides, can act on the nociceptors.[46] Histological evidence suggests LE is characterised by an absence of inflammatory mediators but high local concentrations of the excitatory neurotransmitter glutamate[47] and presence of neuropeptides, Substance P and CGRP, at the origin of extensor carpi radialis brevis.[48] It is tempting to speculate that in LE where there is likely no ongoing tissue inflammation, the observed heat sensitivity might reflect centrally driven neurogenic inflammation, for which Substance P and CGRP have been implicated.

Health-related quality of life in our LE population was comparable to a previous study by Struijs et al.[49] Notably, patients with severe LE demonstrated significantly poorer quality of life than those with lower pain and disability. In addition, sleep disturbance was present in the majority (66.7%) of patients with severe LE, while only 32.1% of those with mild LE, however our study may have been underpowered to detect an effect on sleep. Sleep disturbance is increasingly recognised as a common symptom in chronic pain and may be associated with a number of negative physical and psychological effects, including lowered PPT and depression.[50]

In agreement with previous research,[13, 15, 51] mechanical hyperalgesia was found in the LE population at all evaluated sites and across all levels of pain and disability. A similar pattern of clinical presentation, involving spread of pain sensitivity to areas with no demonstrable pathology, is found in other musculoskeletal conditions and is thought to reflect a commonality of central sensitisation to their pathophysiology.[45] In comparison to controls,

large differences (SMD>0.8) were only evident at the symptomatic elbow in the mild LE group, while moderate and severe LE groups displayed large differences at all evaluated sites. This suggests that the transition from local to widespread hyperalgesia may be associated with increased severity (i.e., greater levels of pain and disability).

Investigation of the role of psychological factors in patients with LE has received limited attention. We found no difference in levels of anxiety and depression between LE groups or controls, which contrasts to the findings of Alizadehkhaiyat et al (2007), which reported significantly higher levels in 16 patients with LE compared to controls.[12] Interestingly, our HADS scores were much lower, even in the most severe LE group, despite displaying comparable levels of pain and disability. Varied inclusion criteria (patients with a minimum three month duration of LE were recruited from an orthopaedic upper limb clinic) may potentially account for study differences. Likewise, we did not detect any difference in fear of movement between different levels of severity of LE. Our data lead us to postulate that levels of anxiety, depression and fear of movement are relatively less important features that distinguish severe from non-severe LE than are thermal hyperalgesia, quality of life and sleep disturbances.

This cross-sectional study of 164 patients with LE and 62 healthy controls provides valuable groundwork toward understanding the relationships of sensory, motor and psychological factors to an individual's pain and disability. However, there are some caveats and limitations that the reader needs to consider. First, the cross-sectional design limits any inferences regarding causal relationships between the various factors, and longitudinal studies are needed to assess their therapeutic and prognostic implications. Second, results may not be generalised to LE patients who have other concomitant musculoskeletal disorders. Third,

potential bias cannot be discounted, as the examiner was not blind to the control group, however the examiner was not aware of PRTEE clustered subgroups. Finally, multiple comparisons were conducted, a danger of which is finding statistically significant differences by chance. To reduce this possibility we set an a-priori p value of 0.01. Of further note, the proportion of females in the severe group was twice that of the mild LE group. Whilst not statistically significant, the potential influence of gender on observed findings cannot be fully ruled out.

In conclusion, this study provides evidence of thermal hyperalgesia in patients with severe LE in comparison to healthy controls. It lends support to LE representing a complex pathophysiology involving peripheral sensitisation, central sensitisation and sympathetic mechanisms. Improved understanding of these physiological mechanisms may provide insight into why patients with higher initial pain demonstrate a poorer long term outcome. Further study is needed to identify optimal treatment strategies for the subgroup of patients with severe symptoms to improve pain, disability and quality of life outcomes.

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Reference list

1. Allander E. Prevalence, incidence, and remission rates of some common rheumatic diseases or syndromes. *Scand J Rheumatol*. 1974;3:145-53.
2. Shiri R, Viikari-Juntura E, Varonen H, et al. Prevalence and determinants of lateral and medial epicondylitis: a population study. *Am J Epidemiol*. 2006;164:1065-74.
3. Smidt N, Lewis M, Van Der Windt D, et al. Lateral epicondylitis in general practice: course and prognostic indicators of outcome. *J Rheumatol*. 2006;33:2053-59.
4. Smidt N, van der Windt DA, Assendelft WJ, et al. Corticosteroid injections, physiotherapy, or a wait-and-see policy for lateral epicondylitis: a randomised controlled trial. *Lancet*. 2002;359:657-62.
5. Bisset L, Beller E, Jull G, et al. Mobilisation with movement and exercise, corticosteroid injection, or wait and see for tennis elbow: randomised trial. *BMJ*. 2006;333:939.
6. Nirschl RP,Pettrone FA. Tennis elbow. The surgical treatment of lateral epicondylitis. *J Bone Joint Surg Am*. 1979;61:832-9.
7. Baker CL, Murphy KP, Gottlob CA, et al. Arthroscopic classification and treatment of lateral epicondylitis: two-year clinical results. *J Shoulder Elbow Surg*. 2000;9:475-82.
8. Lewis M, Hay EM, Paterson SM, et al. Effects of manual work on recovery from lateral epicondylitis. *Scand J Work Environ Health*. 2002;28:109-16.
9. Haahr JP,Andersen JH. Prognostic factors in lateral epicondylitis: a randomized trial with one-year follow-up in 266 new cases treated with minimal occupational intervention or the usual approach in general practice. *Rheumatology (Oxford)*. 2003;42:1216-25.
10. Solheim E,Hegna J,Oyen J. Extensor tendon release in tennis elbow: results and prognostic factors in 80 elbows. *Knee Surg Sports Traumatol Arthrosc*.
11. Coombes BK,Bisset L,Vicenzino B. A new integrative model of lateral epicondylalgia. *Br J Sports Med*. 2009;43:252-8.
12. Alizadehkhaiyat O, Fisher AC, Kemp GJ, et al. Pain, functional disability, and psychologic status in tennis elbow. *Clin J Pain*. 2007;23:482-9.

13. Slater H, Arendt-Nielsen L, Wright A, et al. Sensory and motor effects of experimental muscle pain in patients with lateral epicondylalgia and controls with delayed onset muscle soreness. *Pain*. 2005;114:118-30.

14. Fernandez-de-las-Penas C, de la Llave-Rincon AI, Fernandez-Carnero J, et al. Bilateral widespread mechanical pain sensitivity in carpal tunnel syndrome: evidence of central processing in unilateral neuropathy. *Brain*. 2009;132:1472-9.

15. Fernandez-Carnero J, Fernandez-de-las-Penas C, Sterling M, et al. Exploration of the extent of somato-sensory impairment in patients with unilateral lateral epicondylalgia. *J Pain*. 2009;10:1179-85.

16. Ruiz-Ruiz B, Fernandez-de-las-Penas C, Ortega-Santiago R, et al (2011) Topographical Pressure and Thermal Pain Sensitivity Mapping in Patients with Unilateral Lateral Epicondylalgia. *J Pain*, DOI: 10.1016/j.jpain.2011.04.001.

17. Wright A, Thurnwald P, O'Callahan J, et al. Hyperalgesia in tennis elbow patients. *J Musculoskel Pain*. 1994;2:83097.

18. Leffler AS,Kosek E,Hansson P. The influence of pain intensity on somatosensory perception in patients suffering from subacute/chronic lateral epicondylalgia. *Eur J Pain*. 2000;4:57-71.

19. Smith J, O'Callahan J, Vicenzino B, et al. The influence of regional sympathetic blockade with guanethidine on hyperalgesia in patients with lateral epicondylitis. *J Musculoskel Pain*. 1999;7:55-71.

20. Sterling M, Jull G, Vicenzino B, et al. Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery. *Pain*. 2003;104:509-17.

21. Sterling M, Jull G, Vicenzino B, et al. Physical and psychological factors predict outcome following whiplash injury. *Pain*. 2005;114:141-8.

22. Huge V, Lauchart M, Forderreuther S, et al. Interaction of hyperalgesia and sensory loss in complex regional pain syndrome type I (CRPS I). *PLoS One*. 2008;3:e2742.

23. Leeuw M, Goossens ME, Linton SJ, et al. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. *J Behav Med*. 2007;30:77-94.

24. Bisset LM, Russell T, Bradley S, et al. Bilateral sensorimotor abnormalities in unilateral lateral epicondylalgia. *Arch Phys Med Rehabil*. 2006;87:490-5.
25. Pienimaki T, Tarvainen T, Siira P, et al. Associations between pain, grip strength, and manual tests in the treatment evaluation of chronic tennis elbow. *Clin J Pain*. 2002;18:164-70.
26. Coombes BK, Bisset L, Connelly LB, et al. Optimising corticosteroid injection for lateral epicondylalgia with the addition of physiotherapy: a protocol for a randomised control trial with placebo comparison. *BMC Musculoskelet Disord*. 2009;10:76.
27. Fernández-Carnero J, Fernández-de-las-Peñas C, Sterling M, et al. Exploration of the extent of somato-sensory impairment in patients with unilateral lateral epicondylalgia. *J Pain*. 2009;10:1179-85.
28. Stratford PW,Levy DR. Assessing Valid Change over Time in Patients with Lateral Epicondylitis at the Elbow. *Clin J Sports Med*. 1994;4:88-91.
29. Stratford PW,Norman GR,McIntosh JM. Generalizability of grip strength measurements in patients with tennis elbow. *Phys Ther*. 1989;69:276-81.
30. Smidt N, van der Windt DA, Assendelft WJ, et al. Interobserver reproducibility of the assessment of severity of complaints, grip strength, and pressure pain threshold in patients with lateral epicondylitis. *Arch Phys Med Rehabil*. 2002;83:1145-50.
31. Rompe JD,Overend TJ,MacDermid JC. Validation of the Patient-rated Tennis Elbow Evaluation Questionnaire. *J Hand Ther*. 2007;20:3-10; quiz 11.
32. Stratford PW, Levy DR, Gauldie S, et al. Extensor carpi radialis tendinitis: A validation of selective outcome measuress. *Physiotherapy Canada*. 1987;39:250-255.
33. The EuroQol Group. EuroQol- A new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16:199-208.
34. Connelly LB, Economic Evaluations with Prescored Health Status Instruments, In: Mpofu E and Oakland TD, Editors. *Rehabilitation and Health Assessment*. *Applying ICF Guidelines*. New York: Springer; 2010:163-188.
35. Zigmond AS,Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67:361-70.

447 36. Roelofs J, Sluiter JK, Frings-Dresen MH, et al. Fear of movement and (re)injury in chronic
448 musculoskeletal pain: Evidence for an invariant two-factor model of the Tampa Scale for
449 Kinesiophobia across pain diagnoses and Dutch, Swedish, and Canadian samples. *Pain*.
450 2007;131:181-90.
451 37. Sterling M, Jull G, Vicenzino B, et al. Characterization of acute whiplash-associated
452 disorders. *Spine*. 2004;29:182-8.
453 38. Friedman PJ. Isokinetic peak torque in women with unilateral cumulative trauma disorders
454 and healthy control subjects. *Arch Phys Med Rehabil*. 1998;79:816-9.
455 39. Coombes BK,Bisset L,Vicenzino B (2011) Elbow flexor and extensor muscle weakness in
456 lateral epicondylalgia. *Br J Sports Med*, DOI: 10.1136/bjsm.2011.083949.
457 40. Cohen J, ed. *Statistical power analysis for the behavioral sciences*. 1988, Lawrence Erbaum
458 Associated: Hillsdale.
459 41. Shrout PE. Measurement reliability and agreement in psychiatry. *Stat Methods Med Res*.
460 1998;7:301-17.
461 42. Gunther CM, Burger A, Rickert M, et al. Grip strength in healthy caucasian adults: reference
462 values. *J Hand Surg [Am]*. 2008;33:558-65.
463 43. Wright A,Thurnwald P,Smith J. An evaluation of mechanical and thermal hyperalgesia in
464 patients with lateral epicondylalgia. *Pain Clin*. 1992;5:221-7.
465 44. Vicenzino B,Wright A. Lateral epicondylalgia 1:Epidemiology, pathophysiology, aetiology
466 and natural history. *Physical Therapy Reivew*. 1996;1:23-24.
467 45. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*.
468 2010;152:S2-15.
469 46. Hucho T,Levine JD. Signaling pathways in sensitization: toward a nociceptor cell biology.
470 *Neuron*. 2007;55:365-76.
471 47. Alfredson H, Ljung BO, Thorsen K, et al. In vivo investigation of ECRB tendons with
472 microdialysis technique-no signs of inflammation but high amounts of glutamate in tennis
473 elbow. *Acta Orthop Scand*. 2000;71:475-9.

48. Ljung BO,Forsgren S,Friden J. Substance P and calcitonin gene-related peptide expression at the extensor carpi radialis brevis muscle origin: implications for the etiology of tennis elbow. *J Orthop Res*. 1999;17:554-9.

49. Struijs PA, Korthals-de Bos IB, van Tulder MW, et al. Cost effectiveness of brace, physiotherapy, or both for treatment of tennis elbow. *Br J Sports Med*. 2006;40:637-43; discussion 643.

50. Kundermann B,Lautenbacher S, Effects of Impaired Sleep Quality and Sleep Deprivation on Diurnal Pain Perception, In: Lavigne G, Sessle BJ, and Choiniere M, Editors. *Sleep and Pain*. Seattle: IASP Press; 2007:137-152.

51. Fernandez-Carnero J, Fernandez-de-Las-Penas C, de la Llave-Rincon AI, et al. Widespread mechanical pain hypersensitivity as sign of central sensitization in unilateral epicondylalgia: a blinded, controlled study. *Clin J Pain*. 2009;25:555-61.

Table Captions

Table 1: Demographic and clinical characteristics for the control group and lateral epicondylalgia clusters based on pain and disability scores.

Footnote:

Results are expressed as mean ± standard deviation or count (%). Significant ($P<0.01$) differences between mild-moderate[1], mild-severe[2] and moderate-severe[3] groups. PRTEE Patient Rated Tennis Elbow Evaluation (pain and disability); VAS visual analogue scale (mm); EQ-5D EuroQol (Health-related Quality of Life); TSK-11 Tampa Scale of Kinesiophobia; HADS Hospital Anxiety and Depression Scale.

Table 2: Quantitative sensory and grip force tests for control group and lateral epicondylalgia clusters based on pain and disability scores.

Footnote:

Results are expressed as mean and standard deviations (SD) for affected (AFF) and unaffected (UN) sides as estimated by repeated measures ANOVA adjusting for gender. *Significantly ($P<0.01$) different to control group. Standardised mean differences (SMD) were estimated by dividing mean differences from controls by the pooled SD. Positive SMD represent increased sensitivity in the LE group. †SMD of large effect size (>0.8).. CPT Cold pain threshold (^{0}C); HPT Heat pain threshold (^{0}C); PPT Pressure pain threshold (Kpa); PFG Pain-free grip (N).

Figure Captions

Figure 1. Lateral epicondylalgia (LE) clusters based on Patient Rated Tennis Elbow Evaluation (PRTEE) total scores. The box around the mean scores represents their standard deviations, while the whiskers refer to minimum and maximum scores.

Figure 2: Mean differences in heat pain thresholds (HPT, ^{0}C) and cold pain thresholds (CPT, ^{0}C) and 99% confidence intervals (CI) for lateral epicondylalgia (LE) clusters compared to the control group. Negative values represent increased sensitivity to heat and cold.

Figure 3: Mean differences in pressure pain thresholds (Kpa) and 99% confidence intervals (CI) for lateral epicondylalgia (LE) clusters compared to control group at each site (elbow, neck, tibia).

Figure 4: Mean differences in pain-free grip (N) and 99% confidence intervals (CI) for lateral epicondylalgia (LE) clusters compared to control group.

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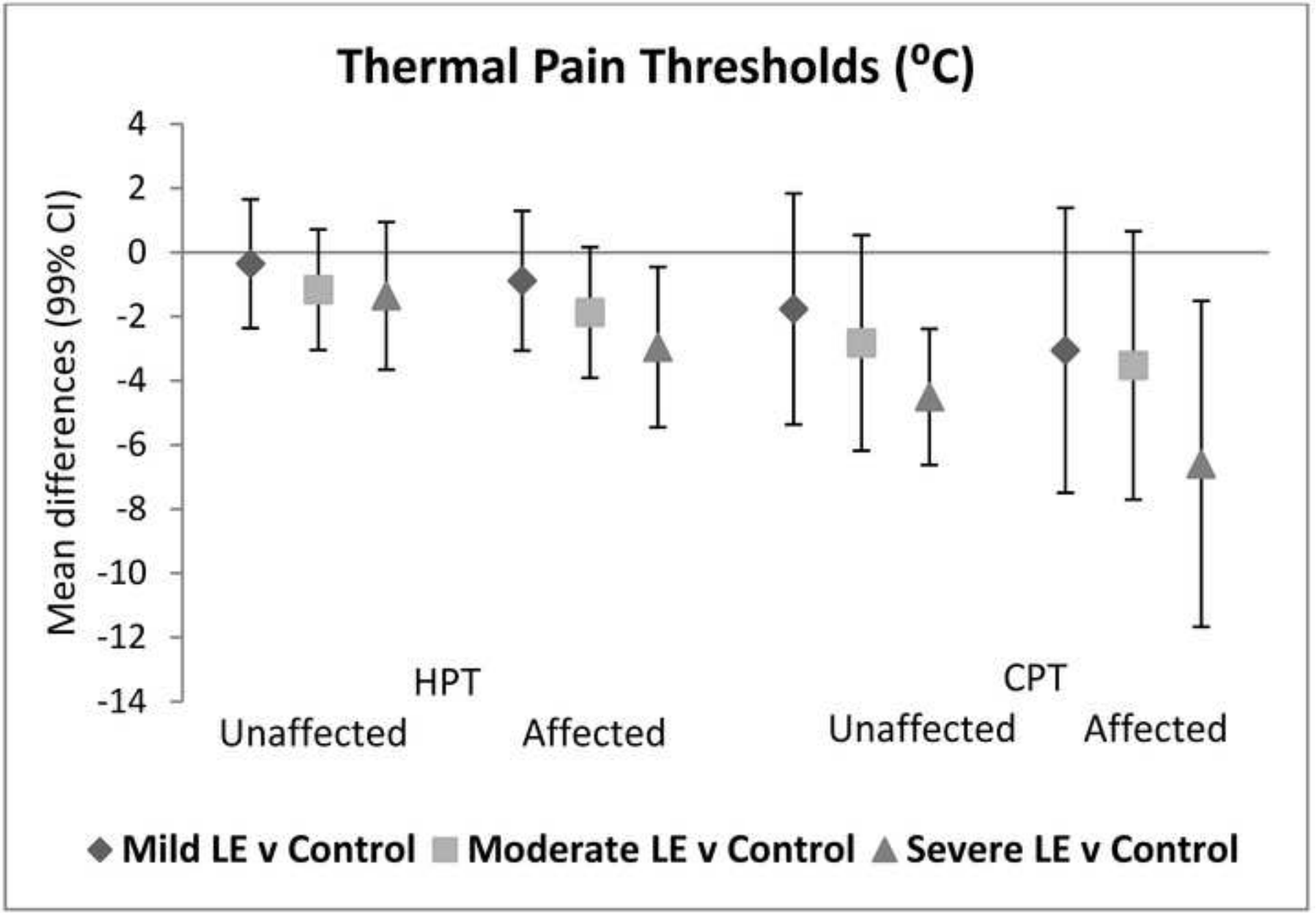

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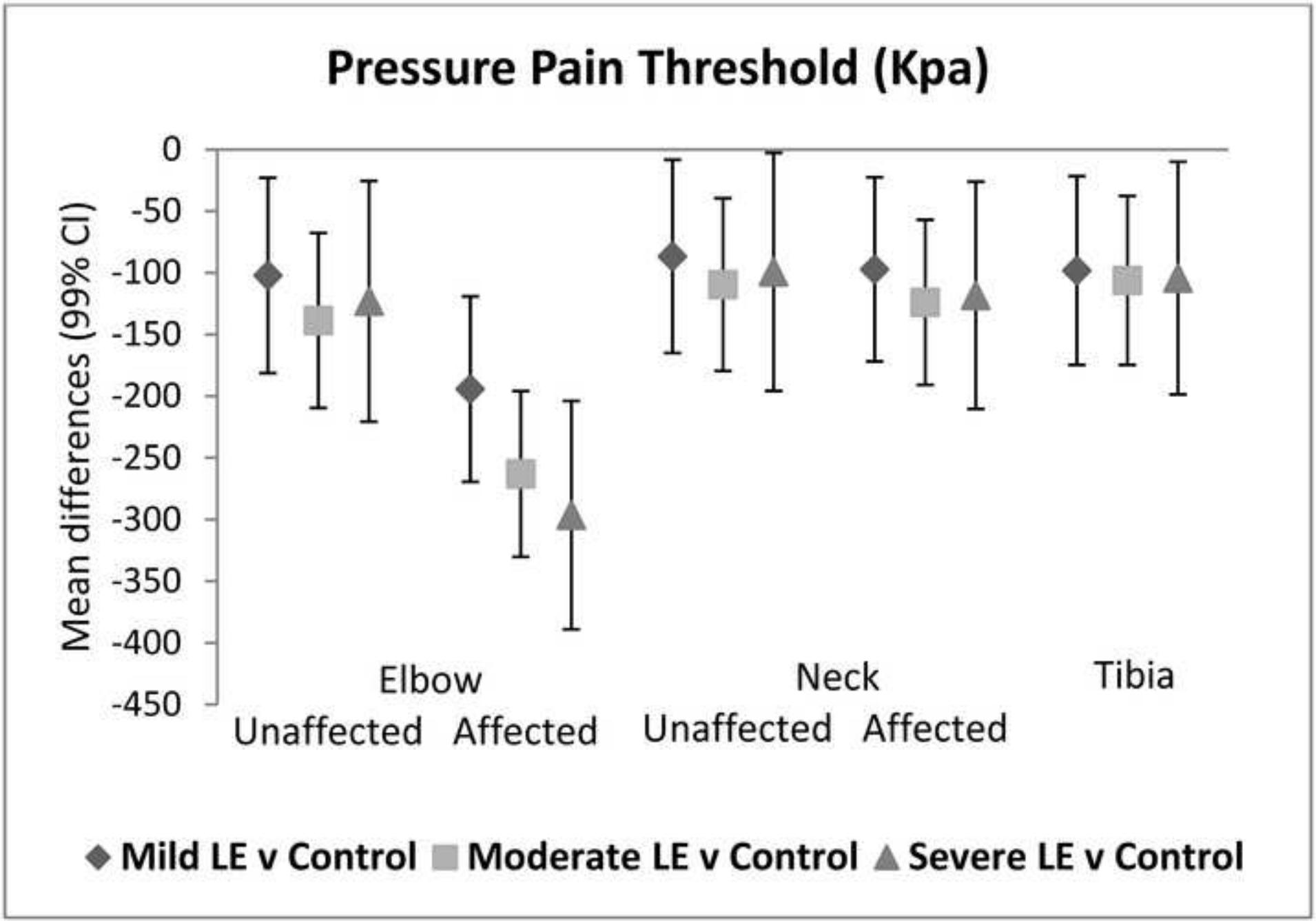

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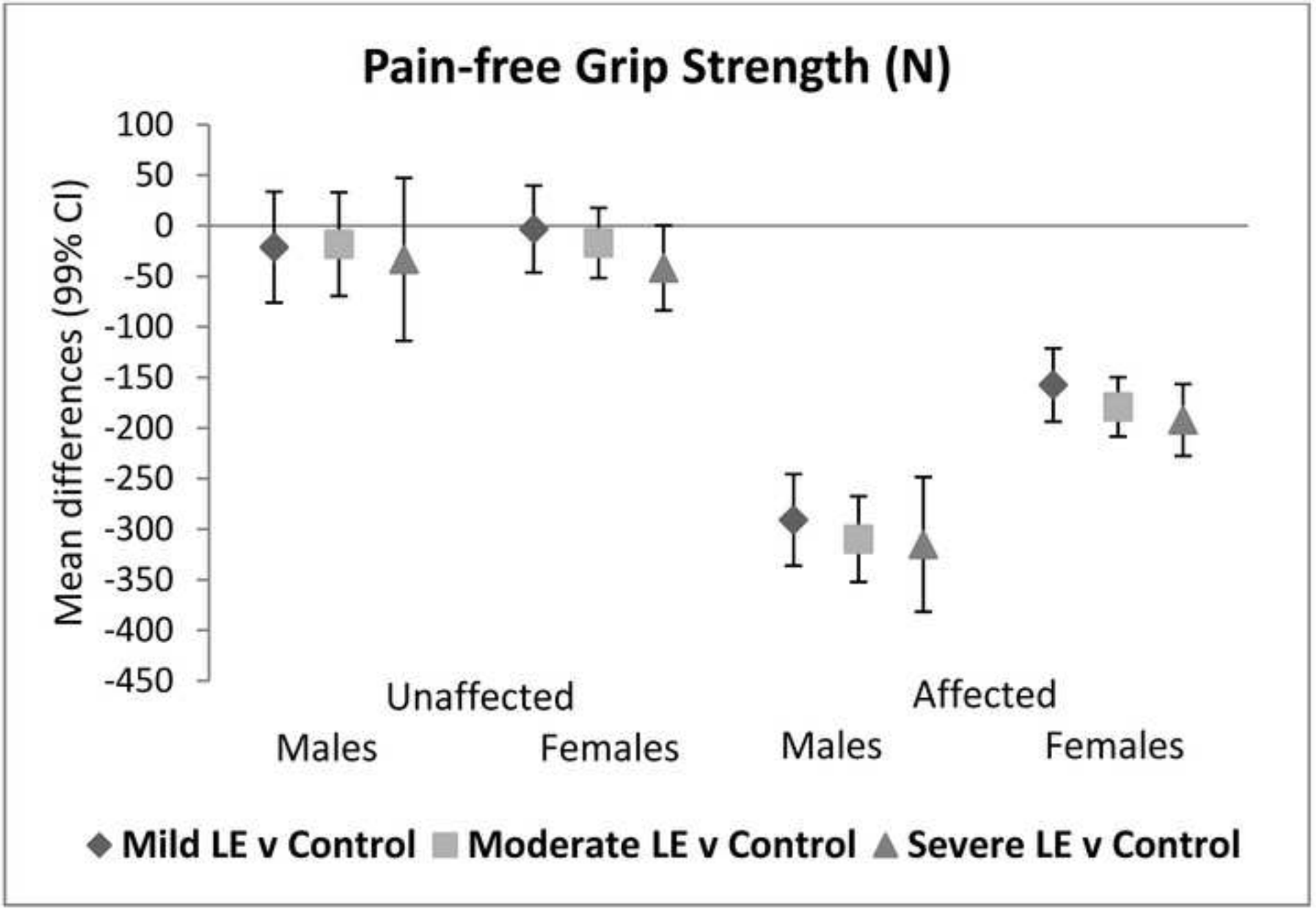

Table 1: Demographic and clinical characteristics for the control group and lateral epicondylalgia clusters based on pain and disability scores.

	Control n=62	Lateral Epicondylalgia				Sig <0.01
		All n=164	Mild n=53	Moderate n=84	Severe n=27	
Age (years)	49.6 ± 8.7	49.6 ± 9.0	50.4 ± 9.5	48.8 ± 9.2	51.4 ± 8.8	
Female	28 (45.2)	63 (38.4)	15 (28.3)	32 (38.1)	16 (59.3)	
Post-menopausal	14 (50)	24 (38.1)	5 (33.3)	10 (31.3)	9 (56.3)	
Body mass index	25.4 ± 4.7	26.5 ± 5.1	26.1 ± 5.1	26.3 ± 4.6	27.1 ± 4.7	
Manual occupation	12 (19.4)	41 (24.8)	11 (20.8)	24 (28.6)	6 (22.2)	
Gripping sport	14 (22.6)	58 (35.2)	18 (34.0)	31 (36.9)	9 (33.3)	
Duration (weeks)	-	24.8 ± 30.8	26.6 ± 32.8	19.7 ± 30.2	32.3 ± 30.1	
PRTEE	-	40.1 ± 14.1	24.0 ± 6.0	42.0 ± 5.2	62.6 ± 5.7	[1,2,3]
Resting pain (VAS)	-	11.0 ± 14.1	6.5 ± 13.8	10.9 ± 12.8	21.8 ± 12.5	[2,3]
Worst pain (VAS)	-	61.9 ± 19.3	50.6 ± 18.2	62.4 ± 16.5	78.1 ± 16.2	[1,2,3]
Function (VAS)	-	68.6 ± 21.8	80.9 ± 21.1	65.8 ± 20.2	58.9 ± 20.3	[1,3]
EQ-5D	-	0.74 ± 0.10	0.77 ± 0.15	0.74 ± 0.09	0.59 ± 0.16	[2,3]
Sleep disturbance	-	75 (45.5)	17 (32.1)	39 (46.4)	18 (66.7)	
TSK-11	-	24.3 ± 5.1	23.4 ± 5.1	24.5 ± 4.6	25.1 ± 4.7	
HADS	6.4 ± 3.9	6.5 ± 3.9	6.1 ± 4.4	6.5 ± 4.6	7.5 ± 4.2	

Results are expressed as mean ± standard deviation or count (%). Significant ($P<0.01$) differences between mild-moderate[1], mild-severe[2] and moderate-severe[3] groups. PRTEE Patient Rated Tennis Elbow Evaluation (pain and disability); VAS visual analogue scale (mm); EQ-5D EuroQol (Health-related Quality of Life); TSK-11 Tampa Scale of Kinesiophobia; HADS Hospital Anxiety and Depression Scale.

Table 2: Quantitative sensory and grip force tests for control group and lateral epicondylalgia clusters based on pain and disability scores.

Variable	Side	Control n=62	Lateral Epicondylalgia All n=164	Mild n=53		Moderate n=84		Severe n=27	
		mean ± SD		mean ± SD	SMD	mean ± SD	SMD	mean ± SD	SMD
CPT	AFF	7.6 ± 6.1	11.8 ± 6.4	10.6 ± 6.6	0.52	11.4 ± 6.4	0.60	13.7 ± 5.7 *	1.12 †
	UN	7.1 ± 4.6	10.2 ± 5.1	8.9 ± 5.1	0.37	10.3 ± 4.6	0.59	11.2 ± 4.7 *	0.95 †
HPT	AFF	44.5 ± 3.1	42.6 ± 3.1	43.3 ± 2.9	0.31	42.5 ± 2.7	0.65	41.8 ± 3.1 *	1.03 †
	UN	44.3 ± 2.5	43.2 ± 2.82	43.6 ± 2.9	0.13	43.0 ± 2.7	0.43	43.2 ± 2.6	0.51
PPT Elbow	AFF	513.3 ± 128.3	261.1 ± 139.6	305 ± 141.2 *	1.52 †	246.6 ± 131.1 *	2.06 †	227.1 ± 129.9 *	2.32 †
	UN	499.5 ± 135.4	367.5 ± 130.6	382 ± 149.2 *	0.76	354.2 ± 138.4 *	1.03 †	394.7 ± 136.7 *	0.91 †
PPT Neck	AFF	403.8 ± 127.6	282.1 ± 134.5	294.2 ± 140.5 *	0.77	271.6 ± 130.1 *	0.98 †	300.3 ± 128.9 *	0.93 †
	UN	396.2 ± 133.1	287.6 ± 130.6	295.1 ± 147.1 *	0.65	277.3 ± 136.6 *	0.83 †	310.9 ± 135.1 *	0.75
PPT Tibia	Left	517.6 ± 130.7	407.4 ± 133.2	401.2 ± 144.1 *	0.76	405.9 ± 133.8 *	0.82 †	438.7 ± 132.0 *	0.80 †
PFG *Males*	AFF	400.6 ± 81.9	97.4 ± 79.4	109.9 ± 71.3 *	3.80 †	90.8 ± 77.0 *	3.90 †	85.6 ± 94.6 *	3.45 †
	UN	387.5 ± 99.2	367.6 ± 90.9	366.5 ± 86.6	0.22	369.4 ± 93.5	0.19	354.4 ± 114.8	0.30
PFG	AFF	241.3 ± 52.8	64.2 ± 62.8	84 ± 66.2 *	2.60 †	62.4 ± 56.8 *	3.29 †	49.3 ± 45.7 *	3.99 †
Females	UN	226.4 ± 62.2	206.5 ± 66.6	223.2 ± 78.6	0.04	209.5 ± 67.8	0.26	184.9 ± 54.6	0.73

Results are expressed as mean and standard deviations (SD) for affected (AFF) and unaffected (UN) sides as estimated by repeated measures ANOVA adjusting for gender. *Significantly ($P<0.01$) different to control group. Standardised mean differences (SMD) were estimated by dividing mean differences from controls by the pooled SD. Positive SMD represent increased sensitivity in the LE group. †SMD of large effect size (>0.8).. CPT Cold pain threshold (^{0}C); HPT Heat pain threshold (^{0}C); PPT Pressure pain threshold (Kpa); PFG Pain-free grip (N).