Cold hyperalgesia associated with poorer prognosis in lateral epicondylalgia: A one year prognostic study of physical and psychological factors.

BK Coombes (PhD)[1], L Bisset (PhD)[2,3], B Vicenzino (PhD)[1]*

[1] The University of Queensland, School of Health and Rehabilitation Sciences, Division of Physiotherapy, St Lucia QLD Australia 4072

[2] Griffith Health Institute, Griffith University, Gold Coast Campus QLD Australia 4222

[3] Gold Coast Health Service District, Southport QLD Australia 41254 Australian Health Workforce Institute, University of Melbourne, VIC Australia 3010

* Corresponding author; reprint requests to be sent to corresponding author

Address for correspondence:

Bill Vicenzino

Division of Physiotherapy

School of Health and Rehabilitation Sciences

The University of Queensland

Building 84A

St Lucia QLD 4072

Phone: + 617 3365 2781

Fax: + 617 3365 1622

Email: b.vicenzino@uq.edu.au

Funding was received from the National Health and Medical Research Council grant 511238. Coombes was in receipt of a University of Queensland Research Scholarship.

There are no conflicts of interest.

Cold hyperalgesia is associated with poorer prognosis in lateral epicondylalgia: A one year prognostic study of physical and psychological factors.

Abstract

Background Predictors of outcome in lateral epicondylalgia, which is mainly characterised as a mechanical hyperalgesia, are largely limited to socio-demographic and symptomatic factors. Quantitative sensory testing is used to study altered pain processing in various chronic pain conditions and may be of prognostic relevance.

Methods The predictive capacity of early measures of physical and psychological impairment on pain and disability and mechanical hyperalgesia, were examined using data from 41 patients assigned to placebo in a prospective randomised controlled trial of unilateral lateral epicondylalgia. Quantitative sensory testing (pressure, cold pain thresholds), motor function (pain free grip) and psychological factors (Tampa scale of kinesiophobia, Hospital anxiety and depression scale) were measured at baseline. The outcome measures were the Patient Rated Tennis Elbow Evaluation (PRTEE) scale and pressure pain threshold (PPT) measured by digital algometry at the affected elbow. Backwards stepwise linear regression was used to predict PRTEE and PPT scores at two and twelve months.

Results Cold pain threshold was the only consistent predictor for both PRTEE ($p<0.034$) and PPT ($p<0.048$). Initial PRTEE was the strongest single predictor of PRTEE at 2 months, while female sex was the strongest single predictor of PPT ($p<0.002$). At one year, final models explained 9 to 52% of the variability in pain and disability and mechanical hyperalgesia respectively.

Discussion Early assessment of cold pain threshold could be a useful clinical tool to help identify patients at risk of poorer outcomes and might provide direction for future research into mechanism-based treatment approaches for these patients.

Introduction

Lateral epicondylalgia (LE) or tennis elbow is a common musculoskeletal condition with a population of prevalence 1-4%.[1, 2] Considerable variability is found for literature on its prognosis, with typical durations ranging from six months to years, and differing opinions on the likelihood of recurrence.[3] The ability to predict which patients will develop chronic pain is important so that appropriate early management can be targeted to these patients. Investigation of prognostic factors associated with LE has previously focused on socio-demographic and symptomatic factors, many of which have not demonstrated consistency across independent studies[3] or are not readily amenable to secondary and tertiary intervention.[4] The role of other physical and psychological factors on the prognosis of LE has not been addressed.

Over the last couple of decades, quantitative sensory testing (QST) has sometime been used as a potential clinical method for diagnosis and monitoring of pain processing and its alterations in patients with chronic pain.[5] A common technique involves application of noxious stimuli, such as mechanical or thermal, to the patient under standardised conditions and deriving the threshold for the transition to pain (i.e. the pain threshold). As well as the tolerance and the intensity of the noxious stimulation. Cross-sectional evaluation of QST in patients with LE has revealed widespread mechanical hyperalgesia,[6-8] and bilateral cold hyperalgesia in unilateral LE, notably in a subpopulation of severe LE.[8, 9] The presence of generalised hyperalgesia, evident in a large number of other chronic pain conditions, including whiplash,[10] back pain,[11] fibromyalgia[12] and patellofemoral pain syndrome,[13] is cited as a sign of supraspinal central sensitisation.[5] Pre-operative hyperalgesia has been shown to increase the risk of subsequent post-operative chronic pain,[5] while the predictive capacity of cold pain[4, 14] and pressure pain thresholds[15] have been demonstrated following whiplash injury. To date no studies have evaluated the prognostic capacity of QST measures on pain and disability in patients with LE. In addition, serial assessment of mechanical hyperalgesia, a characteristic feature of LE,[8] might be a clinically useful method of monitoring development of chronic pain, hence study of factors associated with its persistence is warranted.

There is also budding interest in psychological factors in chronic musculoskeletal conditions. Fear of movement or injury has been identified as a predictor of disability in acute and chronic low back pain[16] and arm, neck and shoulder pain.[17] Depression commonly co-occurs with chronic pain and may affect a patients' prognosis and hinder recovery.[18] Higher levels of depression and anxiety were associated with pain and disability in a small study of LE,[19] though this was not substantiated in a larger study.[8] Simultaneous measurement of QST and psychological factors may allow exploration of the relative predictive capacity of these possibly interacting factors.[20]

This study aimed to investigate the predictive capacity of early physical and psychological measures on short and long term outcomes of pain and disability and mechanical hyperalgesia at the affected elbow.

Methods

Study design

This was a post-hoc analysis of a previously reported twelve month prospective study of the clinical efficacy of corticosteroid injection and physiotherapy interventions in 165 participants with lateral epicondylalgia.[21, 22] The methodology and results of this trial are presented in detail elsewhere.[21, 22] In summary, consenting patients were randomly assigned to either a placebo intervention (described below) or one of three conservative interventions (corticosteroid injection, physiotherapy or their combination). Due to significant effects of the active treatments on outcomes, only participants randomised to placebo (n=41) were included in the current prognostic analysis. Participants attended the research unit to complete all questionnaires and assessments by a blinded outcome assessor. Ethical approval was granted by The University of Queensland's medical research ethics committee and all participants provided written informed consent.

Participants

Trial participants were recruited via community advertisement from Brisbane, Australia between August 2008 and May 2010 and were screened for eligibility via telephone and physical examination. Inclusion criteria were unilateral lateral elbow pain greater than six weeks duration, over the lateral humeral epicondyle of severity greater than 30 on a 100mm visual analogue scale (VAS), provoked by at least two of: gripping, palpation, resisted wrist or middle finger extension or stretching of forearm extensor muscles with reduced pain-free

grip. Exclusion criteria were injection (preceding six months); course of physiotherapy (preceding three months); concomitant neck or other arm pain necessitating treatment or preventing participation in usual work or recreational activities (preceding six months); symptoms suggesting radicular, neurological or systemic arthritic conditions; pregnancy; breastfeeding; or contraindication to injection.

Placebo assigned participants received a single, blinded injection of a negligible volume (0.5ml) isotonic (0.9%) saline within 10 days of randomisation. Participants received standardised advice and could use an analgesic or anti-inflammatory medication, heat or cold packs, or braces as needed, but were discouraged from seeking treatments other than those assigned during the one year follow up period.

Measures

The two outcome measures (dependent variables) in this study were pain and disability, as measured by the Patient-rated tennis elbow evaluation (PRTEE) and mechanical hyperalgesia, as measured by pressure pain threshold (PPT) over the affected lateral elbow. The independent variables were measures of both physical and psychological impairment recorded at baseline as outlined below. Gender and duration were also included since these have been highlighted as potential predictors of outcome.[23-25]

Pain and disability

The PRTEE is a reliable, reproducible, and sensitive instrument for assessment of pain and disability in LE.[26, 27] It has been found to be at least as sensitive to change as other measurement tools, and is proposed as the standard primary outcome measure in research of LE.[26] Items are scored on a series of 10-point Likert scales, with five items used to assess pain and ten items used to assess function. Pain and disability subscales contribute equally to the overall score, ranging from 0 (no pain or disability) to100 (worst pain or disability).

Quantitative sensory testing

Pressure and cold pain thresholds were measured over the affected lateral elbow, using established protocols.[22, 28] Previous studies have confirmed the reliability of these measures (ICCs > 0.86).[6, 8] PPT was measured using a digital pressure algometer (Somedic AB, Farsta, Sweden), with a probe size $1cm^{2,}$ applied perpendicular to the tissues at the tendinous origin of the wrist extensor muscles, at a rate of 40kPa/s. In order to capture an individual's pain

threshold, participants were instructed to indicate when the sensation changed from a comfortable sensation to the first onset of pain. Cold pain threshold was measured using the Thermotest system (Somedic AB, Farsta, Sweden). From a baseline temperature of 30°C, the thermode was decreased at a rate of 1°C/s until the first sensation of pain was perceived or a minimum cut-off temperature of 5°C was reached. Each QST stimulus was applied three times and the mean value used for all analyses.

Pain free grip

Pain free grip is established as a convenient and reliable (ICC>0.97) assessment tool, which correlates more strongly with disability and perceived improvement than maximal grip strength in LE populations.[29-31] It was measured on the affected arm using a digital grip dynamometer with variable hand position (MIE, Medical Research, UK). The participant was positioned in supine position with the arm in relaxed extension and forearm in pronation, such that the palm of the hand faced down on the plinth. Participants squeezed the dynamometer at a consistent rate and stopped the instant pain was experienced. Three recordings were taken and the mean value used in analyses.

Psychological measures

The hospital anxiety and depression scale (HADS) is a short self-assessment questionnaire that measures anxiety and depression, and has been demonstrated to be an appropriate measure in musculoskeletal pain.[32] It consists of 14 items rated on 4-point scales with a total score ranging from 0-42, greater scores indicating greater anxiety and depression. The Tampa scale of kinesiphobia (TSK) was used to quantify kinesiophobia, defined as an irrational, and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to painful injury or re-injury.[33] The scale is based on the model of fear avoidance, fear of work related activities, fear of movement and fear of re-injury.[33] The 11 item questionnaire, which has been validated in upper extremity disorders, consists of 11 items rated on 4-point Likert scales with a total score ranging from 11-44, greater scores indicating greater kinesiophobia.[34]

Data analysis

Statistical analyses were performed by intention to treat using SPSS (Version 20.0). Baseline data for each potential prognostic variable were presented as means and standard deviations for continuous data, and numbers and percentages for categorical data. Independent t tests and Pearson $\chi 2$ tests were used to evaluate whether continuous and categorical baseline variables differed between participants randomised to placebo, and those randomised to the three active interventions. Descriptive statistics were used to describe the condition at short and long term follow-up.

Potential prognostic variables, including baseline values, were entered into multivariate backward stepwise linear regression analyses for each of the outcomes of PRTEE and PPT at both two and 12 months, in a manner consistent with previous study.[35] Variables with the highest p values were removed one at a time, until all remaining variables were significant at $p<0.10$. Associations within each multivariate model were regarded as significant at $p\leq0.05$. The strength of the predictive ability of identified factors in each multivariate model was evaluated by unstandardised regression coefficients (β) with 95% confidence intervals. Standardised regression coefficients were also reported to determine which of the independent variables had a greater effect on the dependent variable. Overall performance of the final models was evaluated with Nagelskerke's R^2, which estimates the percentage of explained variation of the model.

Results

Of the 41 participants assigned to placebo, one participant did not receive the saline injection, because felt recovered. Baseline demographic and symptomatic characteristics were comparable between participants assigned to placebo (n=41) and the overall randomised controlled trial population (n=165) (Table 1). All placebo-assigned participants were followed up at two months and 40/41 (98%) could be contacted at one year. During the one year follow up, oral analgesic or nonsteroidal anti-inflammatory medication was used by 39% (16/41) of participants, while 15% (6/41) sought additional medical consultations.

Predictors of pain and disability

Mean PRTEE scores improved from 41.6 ± 14.5 at baseline to 23.2 ± 13.5 at two months and 5.2 ± 11.4 at 12 months. The multivariate model for PRTEE at two months revealed that

greater baseline pain and disability (β 0.39, 95% CI 0.15 to 0.62), p=0.002) and greater cold hyperalgesia (β 0.77, 95% CI 0.21 to 1.33, p=0.008) were significantly associated with greater pain and disability (Table 2). The model explained 35% of the total variance, with baseline PRTEE having greater relative effect on the outcome. The 12 month multivariate model found greater cold hyperalgesia (β 0.61, 95% CI 0.05 to 1.17, p=0.034) was the only factor significantly associated with greater pain and disability, explaining 9% of the total variance (Table 2).

Predictors of mechanical hyperalgesia

Mean PPT (kPa) at the affected elbow improved from 273.5 ± 130.5 at baseline to 351.4 ± 140.7 at two months and 462.1 ± 199.7 at 12 months. Multivariate analysis (Table 3) revealed greater hyperalgesia was found at two months in females (β -149.83, 95% CI -222.38 to -77.28, p<0.001) with greater cold hyperalgesia (β -6.19, 95% CI -11.98 to -0.39, p=0.037). The model explained 46% of the total variance, with female sex having a greater relative effect on the outcome. The 12 month multivariate model (Table 3) showed female sex (β -177.98, 95% CI -285.7 to -70.26 , p=0.002) and greater cold hyperalgesia (β -8.45, 95% CI -16.8 to -0.09, p=0.048), as well as baseline PPT (β 0.39, 95% CI 0.01 to 0.77, p=0.046) were independent predictors of greater long term mechanical hyperalgesia. This model explained 50% of the total variance. Of these independent predictors, female sex had the greatest effect on PPT, followed by cold pain threshold, with baseline PPT values having the least prognostic influence.

Discussion

This exploratory study of 41 placebo-assigned participants with unilateral LE is the first to show that the presence of cold hyperalgesia is associated with greater short term and long term pain and disability, as well as hyperalgesia to mechanical stimuli. In combination with baseline PRTEE scores, it explained approximately one third of the variance in pain and disability at two months. In the long term, it was the only significant predictor of pain and disability, although explained only a small proportion (9%) of the variability. Secondly, the results demonstrate that mechanical hyperalgesia persists at the affected elbow in women with cold hyperalgesia, independent of baseline PPT values. At one year, over half the

variability in mechanical hyperalgesia could be explained by baseline cold hyperalgesia and gender.

Cold hyperalgesia is emerging as an important indicator of poorer recovery in other musculoskeletal conditions such as whiplash.[4, 14, 36] Cold pain threshold of >13°C was found to increase the risk of developing chronic moderate to severe pain and disability by 26-fold in individuals with whiplash (odds ratio 95% CI 5.0 to 139.1).[37] We previously reported mean cold pain thresholds over the affected elbow of 13.7°C in LE participants with severe pain and disability (PRTEE>54), which was significantly greater than a healthy control population (mean 7.6°C).[8] The mechanisms underlying cold hyperalgesia following injury are only partially understood, but may include altered processing by second order spinal cord sensory neurons or by changes in ion channel expression at peripheral cold-specific fiber terminals.[38]

Considerable variability is found on review of studies investigating prognostic factors for LE, with methodological weaknesses and low sample sizes likely contributing to this.[3] Consistent with earlier studies of LE,[23] and other musculoskeletal conditions,[39] we found baseline scores to predict short term recovery of pain and disability. However, we did not find an association between duration and pain and disability, as was found by other studies of LE.[23, 40] Unlike two of these studies,[25, 40] we excluded patients with symptoms less than six weeks in duration, hence we cannot draw conclusions on the prognosis of acute LE. In our study population, psychological factors did not significantly influence either pain and disability or mechanical hyperalgesia at the elbow.

Whilst significantly correlated, pain and disability and mechanical hyperalgesia likely represent different aspects of the health condition of LE, the latter proposed to be a composite of physiological and psychological features of the patient and the health problem, mediated by social aspects.[15] In this study, females showed greater mechanical hyperalgesia, which is consistent with findings from pain-free populations,[24] whilst pain and disability was comparable between the sexes. Of note, only a small proportion (9%) of the variability in long term pain and disability was explained by the prognostic factors examined here. Despite a much larger sample size (n=349), Smidt (2006) also found the final set of predictors accounted for a low proportion (11%) of the variability in pain severity at one year.[23] As such

there may be other important predictive factors that were not measured in these studies, or alternatively it might not be possible to predict outcomes after one year for LE. We evaluated the prognostic capacity of QST measured at the affected elbow, while investigation of hyperalgesia at widespread sites or using other measures of central hypersensitivity, such as the nociceptive withdrawal reflex, may have allowed greater insight and speculation of the mechanisms involved in chronic pain development.

Strengths and limitations

The major strengths of this study are its methodological rigor, including high retention of participants and use of valid and reliable psychometric instruments to study pain processing combined with a psychological perspective. However, given the relatively small number of subjects in relation to the statistical requirements of prognostic investigation, this study should be considered exploratory. This study represents a secondary analysis of data from a randomised controlled trial, where predictive models were examined only in placebo-assigned individuals. Whilst avoiding confounding associated with significant effects of corticosteroid injection and physiotherapy, it should be acknowledged that administration of a blinded placebo injection might cause treatment expectations.[41] However, recovery profiles were remarkably similar to previous studies in which 27% [42] and 32%[43] of patients assigned to a wait and see policy reported being completely recovered or much improved after six weeks, compared 29% of patients assigned to placebo at eight weeks in our study. Similar recovery was also seen at one year, with 92.5% of placebo injected patients and 87% of those assigned to a wait and see approach[44] being completely recovered or much improved. Nonetheless, results should be viewed as preliminary until replication in other LE populations is undertaken.

Implications for clinical practice and future research

Although obviously in need of further confirmation, the results provide preliminary suggestions for clinical practice and future research. Assessment of cold pain thresholds may assist early identification of altered pain processing that is associated with higher risk for chronic pain development. The presence of cold hyperalgesia, particularly in LE patients with greater pain and disability, warrants early intervention targeted toward effective control of

nociceptive input, and for example, might distinguish those who may benefit from more centrally acting analgesics. Considerable research is needed before the clinical utility of this measure can be realised. In addition to validation of these findings, further research is needed to determine thresholds for cold hyperalgesia and explore whether the described changes in pain processing recover or persist over time.

Conclusion

Assessment of cold pain thresholds might be a valuable clinical tool to help identify patients with LE at risk of poorer prognosis. This study sheds early insight into the mechanisms underlying the development of chronic pain associated with LE and may provide direction for mechanism-based therapeutic and preventative approaches.

Acknowledgements

None

Author contributions

All authors contributed to the design, data collection, analysis, preparation and review of this manuscript.

Table 1: Baseline characteristics for participants assigned to placebo (saline injection, n=41) or active interventions (corticosteroid injection, physiotherapy or both, n=124).

Only data from the placebo group was analysed in this prognostic evaluation. No baseline differences were found between placebo and intervention groups. Values are mean ± SD or count (%). PRTEE: Patient-rated tennis elbow evaluation, HADS: Hospital anxiety and depression scale, TSK: Tampa scale of kinesiophobia.

Table 2: Prognostic indicators of pain and disability as measured with the Patient Rated Tennis Elbow Evaluation (PRTEE) questionnaire at 2 and 12 months.

Standardised coefficient and unstandardised regression coefficient (ß) and its 95% confidence interval (CI). ß positive refers to more pain and disability per unit potential prognostic indicator and ß negative indicates less pain and disability per unit potential prognostic indicator. Adjusted R^2 represents the proportion of the total variance explained by the final model. CPT: cold pain threshold; PPT: Pressure pain threshold; PFG: pain free grip; TSK: Tampa scale of kinesiophobia; HADS: Hospital anxiety and depression scale.

Table 3: Prognostic indicators of mechanical hyperalgesia as measured by pressure pain threshold (PPT) at the elbow at 2 and 12 months.

Standardised coefficient and unstandardised regression coefficient (ß) and its 95% confidence interval (CI). ß positive refers to less hyperalgesia (higher PPT) per unit potential prognostic indicator and ß negative indicates more hyperalgesia (lower PPT) per unit potential prognostic indicator. Adjusted R^2 represents the proportion of the total variance explained by the final model. PRTEE: Patient rated tennis elbow evaluation; CPT: cold pain threshold; PPT: Pressure pain threshold; PFG: pain free grip; TSK: Tampa scale of kinesiophobia; HADS: Hospital anxiety and depression scale.

Reference List

1. 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.
2. Walker-Bone K, Palmer KT, Reading I, et al. Occupation and epicondylitis: a population-based study. *Rheumatology (Oxford)* 2012;51:305-10.
3. Hudak PL,Cole DC,Haines AT. Understanding prognosis to improve rehabilitation: the example of lateral elbow pain. *Arch Phys Med Rehabil* 1996;77:586-93.
4. Sterling M, Jull G, Vicenzino B, et al. Physical and psychological factors predict outcome following whiplash injury. *Pain* 2005;114:141-8.
5. Wilder-Smith OH. Chronic pain and surgery: a review of new insights from sensory testing. *J Pain Palliat Care Pharmacother* 2011;25:146-59.
6. 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.
7. 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.
8. Coombes BK,Bisset L,Vicenzino B. Thermal Hyperalgesia Distinguishes Those With Severe Pain and Disability in Unilateral Lateral Epicondylalgia. *Clin J Pain* 2012;28:595-601.
9. 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* 12, 1040-8 DOI: 10.1016/j.jpain.2011.04.001.
10. Scott D,Jull G,Sterling M. Widespread sensory hypersensitivity is a feature of chronic whiplash-associated disorder but not chronic idiopathic neck pain. *Clin J Pain* 2005;21:175-81.
11. Giesecke T, Gracely RH, Grant MA, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis Rheum* 2004;50:613-23.
12. Desmeules JA, Cedraschi C, Rapiti E, et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis Rheum* 2003;48:1420-9.
13. Jensen R, Hystad T, Kvale A, et al. Quantitative sensory testing of patients with long lasting Patellofemoral pain syndrome. *Eur J Pain* 2007;11:665-76.
14. 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.
15. Walton DM, Macdermid JC, Nielson W, et al. Pressure pain threshold testing demonstrates predictive ability in people with acute whiplash. *J Orthop Sports Phys Ther* 2011;41:658-65.
16. Crombez G, Vlaeyen JW, Heuts PH, et al. Pain-related fear is more disabling than pain itself: evidence on the role of pain-related fear in chronic back pain disability. *Pain* 1999;80:329-39.
17. Karels CH, Bierma-Zeinstra SM, Burdorf A, et al. Social and psychological factors influenced the course of arm, neck and shoulder complaints. *J Clin Epidemiol* 2007;60:839-48.
18. Manning JS,Jackson WC. Depression, pain, and comorbid medical conditions. *J Clin Psychiatry* 2013;74:e03.
19. Alizadehkhaiyat O, Fisher AC, Kemp GJ, et al. Pain, functional disability, and psychologic status in tennis elbow. *Clin J Pain* 2007;23:482-9.
20. Sterling M. Does knowledge of predictors of recovery and nonrecovery assist outcomes after whiplash injury? *Spine* 2011;36:S257-S262.
21. Coombes BK, Bisset L, Brooks P, et al. Effect of corticosteroid injection, physiotherapy or both on clinical outcomes in patients with unilateral lateral epicondylalgia. A randomized controlled trial. *JAMA* 2013;309:461-9.

22. 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.
23. 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.
24. Neziri AY, Scaramozzino P, Andersen OK, et al. Reference values of mechanical and thermal pain tests in a pain-free population. *Eur J Pain* 2011;15:376-83.
25. Hay EM, Paterson SM, Lewis M, et al. Pragmatic randomised controlled trial of local corticosteroid injection and naproxen for treatment of lateral epicondylitis of elbow in primary care. *BMJ* 1999;319:964-8.
26. Rompe JD,Overend TJ,MacDermid JC. Validation of the Patient-rated Tennis Elbow Evaluation Questionnaire. *J Hand Ther* 2007;20:3-10.
27. Overend TJ, Wuori-Fearn JL, Kramer JF, et al. Reliability of a patient-rated forearm evaluation questionnaire for patients with lateral epicondylitis. *J Hand Ther* 1999;12:31-7.
28. Vicenzino B, Paungmali A, Buratowski S, et al. Specific manipulative therapy treatment for chronic lateral epicondylalgia produces uniquely characteristic hypoalgesia. *Man Ther* 2001;6:205-12.
29. 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.
30. Stratford PW,Norman GR,McIntosh JM. Generalizability of grip strength measurements in patients with tennis elbow. *Phys Ther* 1989;69:276-81.
31. 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.
32. Pallant JF,Bailey CM. Assessment of the structure of the Hospital Anxiety and Depression Scale in musculoskeletal patients. *Health Qual Life Outcomes* 2005;3:82.
33. Vlaeyen JW, Kole-Snijders AM, Boeren RG, et al. Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. *Pain* 1995;62:363-72.
34. Roelofs J, Sluiter JK, Frings-Dresen MH, et al. Fear of movement and (re)injury in chronic musculoskeletal pain: Evidence for an invariant two-factor model of the Tampa Scale for Kinesiophobia across pain diagnoses and Dutch, Swedish, and Canadian samples. *Pain* 2007;131:181-90.
35. Collins NJ, Bierma-Zeinstra SM, Crossley KM, et al. Prognostic factors for patellofemoral pain: a multicentre observational analysis. *Br J Sports Med* 2013;47:227-33.
36. Jull G, Sterling M, Kenardy J, et al. Does the presence of sensory hypersensitivity influence outcomes of physical rehabilitation for chronic whiplash?-A preliminary RCT. *Pain* 2007;129:28-34.
37. Sterling M,Hendrikz J,Kenardy J. Similar factors predict disability and posttraumatic stress disorder trajectories after whiplash injury. *Pain* 2011;152:1272-8.
38. Belmonte C,Brock JA,Viana F. Converting cold into pain. *Exp Brain Res* 2009;196:13-30.
39. Mallen CD, Peat G, Thomas E, et al. Prognostic factors for musculoskeletal pain in primary care: a systematic review. *Br J Gen Pract* 2007;57:655-61.
40. Solveborn SA, Buch F, Mallmin H, et al. Cortisone injection with anesthetic additives for radial epicondylalgia (tennis elbow). *Clin Orthop Relat Res* 1995:99-105.
41. Finniss DG, Kaptchuk TJ, Miller F, et al. Biological, clinical, and ethical advances of placebo effects. *Lancet* 2010;375:686-95.
42. 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.
43. 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.

44. Bisset L, Smidt N, Van der Windt DA, et al. Conservative treatments for tennis elbow do subgroups of patients respond differently? *Rheumatology (Oxford)* 2007;46:1601-5.

Table 1: Baseline characteristics for participants assigned to placebo (saline injection, n=41) or active interventions (corticosteroid injection, physiotherapy or both, n=124).

Only data from the placebo group was analysed in this prognostic evaluation. No baseline differences were found between placebo and intervention groups. Values are mean ± SD or count (%). PRTEE: Patient-rated tennis elbow evaluation, HADS: Hospital anxiety and depression scale, TSK: Tampa scale of kinesiophobia.

	Placebo n=41	Intervention n=124
Age (years)	49.9 ± 7.4	49.8 ± 7.9
Sex (female %)	17 (41.5%)	46 (37.1%)
Duration (weeks)	25.7 ± 28.7	25.0 ± 30.3
PRTEE: Pain and disability (0-100)	41.6 ± 14.5	38.8 ± 13.9
Pressure pain threshold (kPa)	273.5 ± 130.5	270.6 ± 118.0
Cold pain threshold (^{o}C)	10.2 ± 6.2	11.9 ± 6.4
Pain free grip (N)	79.9 ± 47.6	86.5 ± 50.0
TSK: Kinesiophobia (11-44)	23.7 ± 4.8	24.5 ± 5.2
HADS: Anxiety and Depression (0-42)	7.6 ± 4.8	6.2 ± 3.8

Table 2: Prognostic indicators of pain and disability as measured with the Patient Rated Tennis Elbow Evaluation (PRTEE) questionnaire at 2 and 12 months.

Standardised coefficient and unstandardised regression coefficient (ß) and its 95% confidence interval (CI). ß positive refers to more pain and disability per unit potential prognostic indicator and ß negative indicates less pain and disability per unit potential prognostic indicator. Adjusted R^2 represents the proportion of the total variance explained by the final model. CPT: cold pain threshold; PPT: Pressure pain threshold; PFG: pain free grip; TSK: Tampa scale of kinesiophobia; HADS: Hospital anxiety and depression scale.

	8 weeks			52 weeks		
Variables	**Standardised coefficients**	**Unstandardised coefficients (95%CI)**	**p**	**Standardised coefficients**	**Unstandardised coefficients (95%CI)**	**p**
Intercept		-0.66 (-11.54, 10.21)	0.90		-1.28 (-8.00, 5.43)	0.70
Female gender						
Duration, per week						
PRTEE, per point	0.431	0.39 (0.15, 0.62)	**0.002**			
CPT, per ^oC	0.364	0.77 (0.21, 1.33)	**0.008**	0.335	0.61 (0.05, 1.17)	**0.034**
PPT, per KPa						
PFG, per N						
TSK, per point						
HADS, per point						
Adjusted R^2			**0.35**			**0.09**

Table 3: Prognostic indicators of mechanical hyperalgesia as measured by pressure pain threshold (PPT) at the elbow at 2 and 12 months.

Standardised coefficient and unstandardised regression coefficient (ß) and its 95% confidence interval (CI). ß positive refers to less hyperalgesia (higher PPT) per unit potential prognostic indicator and ß negative indicates more hyperalgesia (lower PPT) per unit potential prognostic indicator. Adjusted R^2 represents the proportion of the total variance explained by the final model. PRTEE: Patient rated tennis elbow evaluation; CPT: cold pain threshold; PPT: Pressure pain threshold; PFG: pain free grip; TSK: Tampa scale of kinesiophobia; HADS: Hospital anxiety and depression scale.

	8 weeks			52 weeks		
Variables	**Standardised coefficients**	**Unstandardised coefficients (95%CI)**	**p**	**Standardised coefficients**	**Unstandardised coefficients (95%CI)**	**p**
Intercept		470.80 (407.46, 534.15)	<0.001		583.04 (390.88 775.19)	<0.001
Female gender	-0.538	-149.83 (-222.38, -77.28)	**<0.001**	-0.442	-177.98 (-285.7, -70.26)	**0.002**
Duration, per week						
PRTEE, per point						
CPT, per ^oC	-0.277	-6.19 (-11.98, -0.39)	**0.037**	-0.265	-8.45 (-16.80, -0.09)	**0.048**
PPT, per KPa				0.259	0.39 (0.01, 0.77)	**0.046**
PFG, per N						
TSK, per point						
HADS, per point				-0.210	-8.78 (-18.91, 1.35)	0.087
Adjusted R^2			**0.46**			**0.52**

The Clinical Journal of Pain

Cold hyperalgesia associated with poorer prognosis in lateral epicondylalgia: A one year prognostic study of physical and psychological factors.

--Manuscript Draft--

Manuscript Number:	CJP-D-13-00281R2
Full Title:	Cold hyperalgesia associated with poorer prognosis in lateral epicondylalgia: A one year prognostic study of physical and psychological factors.
Article Type:	Original Article
Keywords:	tennis elbow; lateral epicondylalgia; prognosis; hyperalgesia; Anxiety; depression; kinesiophobia; thermal pain threshold
Corresponding Author:	Bill Vicenzino, Ph.D University of Queensland Brisbane, QLD AUSTRALIA
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Queensland
Corresponding Author's Secondary Institution:	
First Author:	Brooke K Coombes, PhD
First Author Secondary Information:	
Order of Authors:	Brooke K Coombes, PhD
	Leanne Bisset, PhD
	Bill Vicenzino, Ph.D
Order of Authors Secondary Information:	
Manuscript Region of Origin:	AUSTRALIA
Abstract:	Background Predictors of outcome in lateral epicondylalgia, which is mainly characterised as a mechanical hyperalgesia, are largely limited to socio-demographic and symptomatic factors. Quantitative sensory testing is used to study altered pain processing in various chronic pain conditions and may be of prognostic relevance. Methods The predictive capacity of early measures of physical and psychological impairment on pain and disability and mechanical hyperalgesia, were examined using data from 41 patients assigned to placebo in a prospective randomised controlled trial of unilateral lateral epicondylalgia. Quantitative sensory testing (pressure, cold pain thresholds), motor function (pain free grip) and psychological factors (Tampa scale of kinesiophobia, Hospital anxiety and depression scale) were measured at baseline. The outcome measures were the Patient Rated Tennis Elbow Evaluation (PRTEE) scale and pressure pain threshold (PPT) measured by digital algometry at the affected elbow. Backwards stepwise linear regression was used to predict PRTEE and PPT scores at two and twelve months. Results Cold pain threshold was the only consistent predictor for both PRTEE ($p<0.034$) and PPT ($p<0.048$). Initial PRTEE was the strongest single predictor of PRTEE at 2 months, while female sex was the strongest single predictor of PPT ($p<0.002$). At one year, final models explained 9 to 52% of the variability in pain and disability and mechanical hyperalgesia respectively. Discussion Early assessment of cold pain threshold could be a useful clinical tool to help identify patients at risk of poorer outcomes and might provide direction for future research into mechanism-based treatment approaches for these patients.