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Statement of significance: We found no evidence for a clinically relevant ability of QST to predict the transition from acute to chronic low back pain. This indicates that assessment of central hypersensitivity using currently available quantitative sensory tests is unlikely to identify patients at risk and therefore unlikely to inform clinical decision making.

ABSTRACT

Background: It would be desirable to identify patients with acute low back pain who are at high risk for transition to chronic pain early in the course of their disease. This would enable early preventive or therapeutic interventions. Patients with chronic low back pain (CLBP) display signs of central hypersensitivity. This may contribute to the transition to CLBP. We tested the hypothesis that central hypersensitivity as assessed by quantitative sensory tests predicts transition to CLBP.

Methods: We performed a prospective cohort study in 130 patients with acute low back pain recruited in a primary care setting to determine the ability of 14 tests using electrical, pressure and temperature stimulation to predict transition to CLBP after six months. We assessed the association of tests with transition to CLBP in multivariable analyses adjusted for socio-demographic, psychological and clinical characteristics, quantified the performance of tests using receiver operating characteristics (ROC) curves, and calculated likelihood ratios for different cut-off values for most promising tests.

Results: None of the evaluated tests showed a statistically significant or clinically relevant ability to predict the transition to CLBP, with 95% CI of crude and adjusted associations of all tests including one as measure of no association. Corresponding estimates of areas under the ROC curves were below 0.5 and none of the 95% CI crossed the pre-specified boundary of clinical relevance set at 0.70.

Conclusions: We found no evidence to support a clinically relevant ability of current quantitative sensory tests to predict the transition from acute to CLBP.

Keywords: Chronic low back pain, Prognosis, Central hypersensitivity, Quantitative Sensory Tests.

INTRODUCTION

Low back pain is one of the leading causes of years lived with disability (Murray et al., 2015). The life-time prevalence is 70-85% (Andersson, 1999) and the estimated point prevalence is 10-30% (Freemont et al., 1997; Andersson, 1999; Hoy et al., 2012; Hoy et al., 2014). Low back pain is one of the most frequent reasons for doctor visits (Hart et al., 1995; Deyo et al., 2006) and has a high socio-economic burden (Maniadakis and Gray, 2000; Ekman et al., 2005; Dagenais et al., 2008). 10-20% of patients experience recurrent episodes or a chronic course (Andersson, 1999; Hestbaek et al., 2003; Henschke et al., 2008; Chou and Shekelle, 2010; Hasenbring et al., 2012). It would therefore be desirable to identify patients at risk for transition to chronic low back pain (CLBP) early, as this may enable early preventive or therapeutic interventions.

There is evidence for the role of socio-demographic, psychological and clinical characteristics for the transition to CLBP (Dionne et al., 1997; Schiottz-Christensen et al., 1999; Linton, 2000; Picavet et al., 2002; Pincus et al., 2002; Coste et al., 2004; Dunn et al., 2006; Jones et al., 2006; Swinkels-Meewisse et al., 2006; Foster et al., 2008; Chou and Shekelle, 2010; Dunn et al., 2011; Campbell et al., 2013). Significant factors include work-related factors (Dionne et al., 1997; Schiottz-Christensen et al., 1999; Dunn et al., 2006; Jones et al., 2006; Dunn et al., 2011; Campbell et al., 2013); catastrophizing, expectation of poor treatment outcome and fear-avoidance (Dionne et al., 1997; Picavet et al., 2002; Dunn et al., 2006; Jones et al., 2006; Swinkels-Meewisse et al., 2006; Foster et al., 2008; Campbell et al., 2013); depression and anxiety (Dionne et al., 1997; Dunn et al., 2006; Dunn et al., 2011; Campbell et al., 2013); and high pain intensity or disability at baseline (Dionne et al., 1997; Schiottz-Christensen et al., 1999; Dunn et al., 2006; Swinkels-Meewisse et al., 2006; Dunn et al., 2011; Campbell et al., 2013). However, systematic reviews were inconclusive as to the clinical importance of these risk factors (Linton, 2000; Pincus et al., 2002; Hestbaek et al., 2003; Chou and Shekelle, 2010).

Knowledge on the importance of central hypersensitivity led to an increasing application of quantitative sensory test (Birklein and Sommer, 2013) and was proposed to contribute for the transition to CLBP (Giesecke et al., 2004; O'Neill et al., 2007; Blumenstiel et al., 2011; Neziri et al., 2012; Puta et al., 2013). There is overwhelming pre-clinical evidence that acute injuries cause neuroplastic changes that lead to hypersensitivity (Woolf and Salter, 2000), and that hypersensitivity is potentially involved in the transition to chronic pain (Arendt-Nielsen et al., 2018). Noticeably, hypersensitivity has been detected in acute low back pain (ALBP) (Vuilleumier et al., 2017). Furthermore, previous case-control studies found that pain thresholds after painful stimuli at non-painful sites were lower in patients with CLBP as compared to pain-free controls. All but one study included a small number of participants, which made multivariable analysis adjusting for the above mentioned risk factors difficult (Giesecke et al., 2004; O'Neill et al., 2007; Blumenstiel et al., 2011; Puta et al., 2013). The largest case-control study evaluated the discriminative ability of 26 quantitative

sensory tests in distinguishing between patients and pain-free controls (Neziri et al., 2012). Pressure and electrical stimulation modalities ranked first, with areas under the receiver operating curves (ROC) of ≥0.80 (Neziri et al., 2012). Case-control studies are limited by their cross-sectional nature and arbitrary spectrum of cases and controls, and can therefore not determine the ability of different tests to predict transition to CLBP. LeResche et al published the first prospective cohort in 147 primary care patients with ALBP and found none of five tests examined to be associated with transition to CLBP (LeResche et al., 2013). However, the study included highly selected patients, since only about 10% of those initially considered were analyzed. Moreover, a limited number of tests was employed and the study did not evaluate ROCs.

We performed a large prospective cohort study in a representative sample of primary care patients with ALBP, using an extensive protocol of 14 tests evaluating six modalities. The hypothesis was that more pathological test values, pointing to hypersensitivity in early stages of low back pain, predict CLBP after six months. We expected that low thresholds after pressure, electrical and heat stimulation, high thresholds after cold stimulation, short hand withdrawal time of the cold pressor test and impaired conditioned pain modulation were associated with an increased risk of transition to CLBP.

METHODS

Study population

We recruited patients with acute low back pain at a primary care group practice in Bern, Switzerland. We included patients suffering from low back pain with a pain intensity of at least 3 on a numerical rating scale (NRS, 0 = "no pain" and 10 = "worst pain imaginable"), at any day during the week preceding recruitment. We defined acute low back pain as predominant lumbar back pain with or without radiation to the leg, with a maximal duration of six weeks and no more than three pain episodes during the preceding year. Before inclusion into the study, all patients underwent physical examination by their referring general practitioner. At study inclusion, all patients underwent a repeat physical examination by the study staff to identify any sensory or motor deficit of the lower extremity.

We excluded patients with acute lumbosacral radiculopathy defined as pain with dermatome-associated distribution, with or without neurological signs of spinal nerve compression such as dermatome-associated sensory loss, impaired motor function or attenuated reflexes. In case of suspected acute lumbosacral radiculopathy, patients would also receive a magnet resonance image (MRI) in accordance with clinical guidelines (Chou et al., 2007). None of the patients included in the present study had to receive an MRI. Other reasons of exclusion were back pain caused by accident, history of back surgery, rheumatologic inflammatory disease, neurological co-morbidity potentially affecting the neurological function of the lower extremity to be tested, and psychiatric co-morbidity except unipolar depressive disorder. We also excluded patients unable to understand the consequences

of study participation due to language problems and patients who could not be contacted by phone or mail after initial consultation with their general practitioner. Four assessors performed all study-related procedures at the Department of Anesthesiology and Pain Medicine of the University Hospital of Bern, including eligibility screening, baseline and follow-up assessment according to a standardized, prospective protocol. The protocol was approved by the local research ethics committee (study no. 103/08) and conducted in accordance with the Declaration of the World Medical Association (Worlds, 2008). All patients gave written informed consent.

Quantitative Sensory Tests

We performed QST according to a previously applied prospective protocol (Neziri et al., 2012) in a quiet room of our QST laboratory to avoid distraction of the patients. Participants were lying in a bed with a leg rest placed under the knees to obtain a 30° semi-flexion for electrophysiological testing. All patients received identical and clear instruction regarding the testing session and underwent a training session to familiarize themselves with the stimulation procedure before data collection was initiated. This is considered essential before formal testing is started and thus is common practice of testing protocols (Neziri et al., 2012; Backonja et al., 2013). We performed QST at the extremity contralateral to the most painful area of low back pain, the most painful area at the lower back and at a non-painful site of the back. In case of bilateral back pain, the testing extremity was randomly selected according to a computer-generated list. We made two measurements and considered the mean value for data analysis, except for the cold pressor test and the assessment of conditioned pain modulation, for which only one measurement was taken. We randomly assigned the sequence of testing modalities according to a computer-generated list to avoid bias as a result of testing order (Grone et al., 2012). Mechanisms investigated were stimulus-specific pain hypersensitivity (pain detection and pain tolerance threshold to different stimulus modalities), tissue-specific pain hypersensitivity (thresholds to skin and muscle stimulation), localized and widespread pain hypersensitivity (stimulation at the areas of pain and at distant areas), temporal summation (induction of short-lasting central hyper-excitability by repeated stimulation) and endogenous pain inhibition (conditioned pain modulation, CPM). Stimulation sites at the area of pain were expected to reflect sensitivity of neural structures corresponding to the site of a potential primary nociceptive input (regional sensitization), whereas stimulation at areas distant from the site of pain were expected to reflect widespread sensitization of neural structures.

We pre-specified pressure pain tolerance threshold at the second toe as our primary prognostic variable. We assessed pain detection and pain tolerance thresholds using an electronic pressure algometer with a 1 cm^2 surface probe (Somedic, Hörby, Sweden) (Brennum et al., 1989). We performed the pressure tests at the center of the pulp of the 2^{nd} toe contralateral to the side of most pain, the site of most pain at the back and a non-painful site at the back. Pressure was increased from 0 at a rate of 30 kPa/s to a maximum of 1000 kPa. We defined pain detection threshold as the point at

which the pressure sensation turned into pain and pain tolerance threshold as the point at which the subject felt the pain as intolerable. The participants had to press a button when these points were reached and the algometer displayed the corresponding pressure intensity. In case that a participant did not press the button below 1000 kPa, this value was considered as threshold.

We performed electrical stimulation using bipolar surface Ag/AgCl-electrodes placed distal to the lateral malleolus contralateral to the side of most pain, which corresponds to the innervation area of the sural nerve. A computer-controlled constant current stimulator (NCS System, Evidence 3102 evo, Neurosoft, Russia) delivered a train-of-five 1 ms square-wave pulses of an overall duration of 25 ms. This train-of-five is perceived as a single stimulus by the patients. In a single increasing intensity staircase, the current intensity was increased from 1 mA in steps of 1 mA, until the electrical stimulus was perceived as painful (pain detection threshold) and until a nociceptive withdrawal reflex (NWR) of the biceps femoris with an amplitude higher than 20µV for at least 10ms in the 50 to 150ms post-estimation interval was elicited (reflex detection threshold) (Willer, 1977; Willer, 1984; Rhudy and France, 2011). Temporal summation occurs when repetition of a stimulus increases pain perception, likely due to short-lasting spinal cord sensitization. To elicit temporal summation, we repeated the train-of-five stimulus five times with a frequency of 2 Hz at a constant intensity (Arendt-Nielsen et al., 1994). As pre-specified by our protocol, the first 40 patients included in the study were randomly assigned in a 1:1 ratio to either undergo electrical stimulation with assessment of pain and reflex detection threshold, or assessment of EEG activity as response to painful stimulation. Therefore, data on pain detection threshold after single and repeated electrical stimulation were missing in 18 patients and were considered to be missing completely at random. Results of the EEG assessment have been reported in a separate paper (Vuilleumier et al., 2017).

We used a thermode with a surface of 30 x 30 mm to assess pain sensitivity to heat and cold (TSA-II; Medic, Ramat Yishai, Israel). The tests were performed at the lateral aspect of the leg, midway between the knee and the lateral malleolus and the lateral aspect of the arm, midway between the elbow and the wrist. The temperature of the thermode was increased at a rate of 0.5 ºC/sec from 30 ºC to a maximum of 50.5 ºC and to a minimum of 0°C until the stimulus was perceived as painful; at this point, the participants pressed the button and the temperature went back to baseline. Threshold values were truncated in case of participants who did not report pain at the maximum of 50.5°C or the minimum of 0.0°C, respectively.

We assessed the response to a tonic cold painful stimulus with the cold pressor test. The hand was immersed in ice saturated water (1.5± 1°C) for a duration of two minutes. The device consisted of a container separated into an outer and an inner part by a mesh screen. The mesh screen prevented direct contact between the ice (placed in the outer part) and the hand of the subject (placed in the inner part). We recorded the time at which the participants considered pain as intolerable. In case the participant did not perceive the stimulus as intolerable below two minutes, this value of two minutes was considered as tolerance time. We assessed CPM using the cold pressor test as conditioning

noxious stimulus and pressure pain tolerance threshold at the 2nd toe as test stimulus (Chitour et al., 1982; Dubner and Ren, 1999; Danneels et al., 2000; Suzuki et al., 2004; Pud et al., 2009). Thus after two minutes of hand immersion in the ice water we again measured pressure pain detection threshold and considered the difference in pressure pain detection threshold (after – before cold pressor test) as value for CPM. An increase of the threshold while applying the conditioning stimulus indicated efficient endogenous pain inhibitory processes.

Baseline and follow-up assessment

The evaluation of socio-demographic characteristics included age, gender, education (higher vs lower education), civil status (married vs not married), living status (living alone vs not living alone), working conditions (regular work including housewives vs no regular work), current sick leave because of back pain (yes vs no), physical and psychological stress at work (high vs low), and Swiss nationality (yes vs no). Patients with at least high school degree were considered as having higher education. We defined high work related physical or psychological stress as stress of at least 5 on a NRS ranging from 0 "no stress" and 10 "worst stress imaginable". We characterized the degree of depression, anxiety and catastrophizing using the Beck Depression Inventory version 2 (BDI-ll) (Morley et al., 2002), the State-Trait-Anxiety-Inventory (STAI) (Laux et al., 1981) and the Catastrophizing Scale of the Coping Strategies Questionnaire (CSQ) (Keefe et al., 1989), respectively. The clinical assessment included Body-Mass-Index (BMI) with overweight defined as BMI $\geq$ 25kg/m^2, pain localisation (back pain with irradiation to leg vs local low back pain), pain duration, pain intensity, disability, intake of pain medication (yes vs no) and intake of muscle relaxants (yes vs no) at baseline. We used the Roland-Morris-Questionnaire (RMQ) to score disability on a scale from 0 "no disability" to 24 "maximum disability" (Roland and Morris, 1983). We considered non-steroidal anti-inflammatory drugs, acetaminophen, metamizole and opioids as pain medication. We chose these socio-demographic, psychological and clinical variables because of their documented prognostic value for transition to CLBP in previous cohort studies (Dionne et al., 1997; Schiottz-Christensen et al., 1999; Coste et al., 2004; Dunn et al., 2006; Jones et al., 2006; Swinkels-Meewisse et al., 2006; Foster et al., 2008; Dunn et al., 2011; Campbell et al., 2013). We pre-specified to dichotomize education, civil status, living status, working conditions, physical and psychological stress at work and BMI to facilitate a clinically meaningful interpretation. To ensure comparability of regression coefficients for continuous and binary covariates, we expressed the effect for depression, anxiety, catastrophizing, pain intensity and disability as per 2 standard deviation increase (Gelman, 2008).

We performed telephone interviews six months after the baseline assessment to determine the pre-specified primary outcome of transition to CLBP, defined as the presence of low back pain on most days during the four weeks preceding the follow-up interview (Airaksinen et al., 2006; Dionne et al., 2008). We asked all participants the question "Did you suffer from low back pain at most days of the week during the last four weeks?"

Statistical analysis

Assuming a transition to CLBP of 30% at 6 months (Cassidy et al., 2005; Hancock et al., 2007) and a standard deviation of 180 kPa for pressure pain tolerance threshold at the second toe (the pre-specified primary prognostic variable) (Neziri et al., 2011b), a sample size of 140 patients provided more than 80% power to detect a minimally clinically relevant difference in pressure pain tolerance thresholds of 100 kPa between patients with and without transition to CLBP, at a two-sided alpha level of 0.05. A sample size of 140 with 42 patients developing chronic low back pain after 6 months will allow the inclusion of approximately nine variables in a multivariable model (Vittinghoff and McCulloch, 2007).

To determine the predictive ability of different quantitative sensory tests, we estimated odds ratios (ORs) for the transition to CLBP from logistic regression and areas under the receiver operating characteristics curve (ROC) from a non-parametric model based on multiple imputations for tests with missing data (electrical stimulation, temperature stimulation at the arm, cold pressor test, CPM) (Rubin, 1976; Harel and Zhou, 2007; Kenward and Carpenter, 2007; Sterne et al., 2009; Spratt et al., 2010; White et al., 2011). We imputed test data using chained equations with predictive mean matching and linear regression generating 15 multiply imputed datasets. As pre-specified, we dichotomized education, working and living conditions, civil status, BMI and low back pain with radiation to the leg to facilitate a clinically meaningful interpretation. We dichotomized physical and psychological stress at work post-hoc because these variables were neither normally nor log-normally distributed. Quantitative sensory test data with electrical or pressure stimulation were normally or log-normally distributed. Heat and cold pain detection thresholds and hand withdrawal time of the cold pressor test were truncated and neither normally nor log-normally distributed. Therefore, we dichotomized these variables post-hoc using the maximally attainable stimulus as cut-off. To ensure comparability of regression coefficients for continuous and binary covariates, we expressed the effect for all continuous variables per 2 standard deviations change on the normal or logarithmic scale (Gelman, 2008). For continuous socio-demographic, psychological and clinical variables, the effect was expressed per 2 standard deviations increase. For continuous quantitative sensory tests, it was expressed per 2 standard deviations decrease. For all test variables, ORs above one imply that pathological test values (i.e. lower thresholds after pressure, electrical and heat stimulation, higher thresholds after cold stimulation, shorter hand withdrawal time of the cold pressor test and impaired CPM) are associated with an increased risk of transition to CLBP.

In our main analysis, we determined crude ORs from univariable models and adjusted ORs from multivariable analyses adjusting for socio-demographic, psychological and clinical baseline characteristics that were associated with transition to CLBP at a p-value of ≤ 0.20 in univariable analyses, forcing age and gender into the model. We then estimated the area under the ROC curves and pre-specified an area of more than 0.70 as clinically relevant. For the two top ranked tests in both crude and adjusted analyses, we also calculated sensitivities, specificities, positive and negative

likelihood ratios (LR) for different cut-offs, in order to identify potential cut-offs associated with a clinically relevant power to rule in or out transition from acute to CLBP. A test was considered to provide clinically relevant power to rule in or out transition to CLBP if the positive and negative LRs were above 5 or below 0.2, respectively (Jaeschke et al., 1994; Mallett et al., 2012). We performed two sets of sensitivity analyses including the same set of co-variates as in main analyses. First, we stratified uni- and multivariable logistic regression models by assessor. Second, we estimated associations between quantitative sensory tests and pain intensity at 6 months as continuous outcome in uni- and multivariable linear regression. All reported p-values are two-sided; all confidence intervals refer to 95% boundaries. Analyses were performed with Stata (Version 12.1, StataCorp, College Station, TX).

RESULTS

Study flow and completeness of data

We screened 551 patients between 2009 and 2015 who presented with acute low back pain and included 132 patients (Figure 1). Time and resource constraints led us to close the study 10 patients short of the planned number of 140 patients. 82 patients (15%) were ineligible because they suffered from chronic pain as defined above, 65 patients (12%) because they suffered from neurologic or psychiatric co-morbidities, and 57 patients (10%) because their pain intensity at the time of screening was less than NRS 3. Of 279 eligible patients, 15 could not be located (5%) and 132 refused study participation (47%). Patients refusing study participation did not differ in terms of age and gender from those included in the study (data not presented). Telephone follow-up was complete for 130 patients (98%). Thirty-two of them had developed CLBP (25%). Data on pressure stimulation as well as heat and cold pain detection threshold at the leg were complete. Due to logistic reasons, data on heat and cold pain detection threshold at the arm were missing in 9 patients (7%), data on hand withdrawal time of the cold pressor test in 4 patients (3%) and data on CPM in 16 patients (12%). Data on pain detection and reflex threshold after single electrical stimulation and pain detection after repeated electrical stimulation were missing in 18 patients (14%) who were randomly assigned to receive an EEG after electrical stimulation rather than an assessment of pain detection and reflex thresholds. Additionally, we were unable to evoke a NWR in other 42 patients, since painful stimulation became intolerable before a reflex was evoked. Therefore, data of 60 patients were missing on this test (46%). We were already confronted with this issue in previous studies (Curatolo et al., 2015). In view of the large percentage of missing data and the likely violation of assumptions of multiple imputation in patients without evocable reflex, we refrained from analyzing these data.

Characterizing the study population

The study population comprised 71 (55 %) men. Mean age of the total study population was 43.2 years (SD 13.3, range 20 to 78). Mean depression, anxiety and catastrophizing scores were 6.8 (SD 6.5, range 0 to 37), 48.7 (SD 11.2, range 23 to 80) and 1.1 (SD 0.9, range 0 to 4), respectively. Fifty-one (46 %) of all patients were on sick leave because of low back pain. Thirty-six (28 %) of all patients had low back pain radiating to the leg. Mean pain duration was 2.1 weeks (SD 1.4, range 4 days to 6 weeks). Mean baseline values of average, maximum and minimum pain during the last 24h in all patients was 4.0 (SD 1.8), 5.7 (SD 2.1) and 2.1 (SD 1.7), respectively. Patients reported a mean Roland-Morris disability score of 9.7 (SD 5.5). The majority of the patients took pain medication at baseline (N 74, 57%).

Sociodemographic, psychological and clinical predictors for transition to chronic low back pain

Table 1 presents socio-demographic, psychological and clinical baseline characteristics, and their association with transition to CLBP pain after six months. Socio-demographic variables were similarly distributed in both patient groups. There were numerically more males among patients with transition to CLBP (p=0.30) but mean age (p=0.86) was the same in both groups. We found higher scores of depression, anxiety and catastrophizing in patients with transition to CLBP, however only anxiety and catastrophizing showed associations at $p \leq 0.20$. There were more patients with pain radiating to the leg, high pain and high disability among patients with transition to CLBP. Conversely, there were fewer patients with overweight and fewer patients taking pain medication at baseline among patients with transition to CLBP. Anxiety, catastrophizing, pain intensity, disability and intake of pain medication were included into the multivariable model because they showed associations at $p \leq 0.20$. Age and gender were forced into the multivariable analysis irrespective of their p-value. We did not find any significant association for gender (OR 1.50, 95% CI 0.63 to 3.56, p=0.36), age (OR 0.88, 95% CI 0.35 to 2.22, p=0.78), anxiety (OR 1.40, 95% CI 0.49 to 4.06, p=0.53), catastrophizing (OR 1.24, 95% CI 0.42 to 3.60, p=0.70), intake of pain medication (OR 0.39 95% CI 0.15 to 1.02, p=0.06), baseline pain intensity (OR 1.69, 95% CI 0.62 to 4.66, p=0.31) and baseline disability (OR 1.83, 95% CI 0.63 to 5.30, p=0.26) in multivariable analysis.

Quantitative sensory tests as predictors for transition to chronic low back pain and pain intensity after 6 months

Table 2 presents crude and adjusted ORs for the associations of the 14 evaluated tests with transition to CLBP. For the primary prognostic variable, pressure pain tolerance threshold at the second toe, we found no association with transition to CLBP (crude OR 0.99, 95% CI 0.44 to 2.21, adjusted OR 0.76, 95% CI 0.29 to 1.78). In crude analyses, all estimates appeared randomly scattered around the null, with ORs for 10 tests below one and therefore opposite to expectation, and another four above one,

concordant with expectation. None of the association was statistically significant. The strongest associations in the expected direction, even though non-significant, were found for pain detection threshold after single and repeated electrical stimulation, with ORs of 2.00 (95% CI 0.73 to 5.48, p=0.17) and 1.67 (95% CI 0.63 to 4.43, p=0.30), respectively. In adjusted analyses, results were much the same. Except for pressure pain tolerance threshold at a non-painful site of the low back, 95% confidence intervals of all associations included one as measure of no association. Again, we found strongest associations for pain detection threshold after single and repeated electrical stimulation, with ORs of 2.13 (95% CI 0.68 to 6.65, p=0.19) and 1.73 (95% CI 0.54 to 5.51, p=0.35), respectively.

Table 3 presents areas under the ROC curves with corresponding 95% Cis. Figure 2 shows the ROC curves for the two tests with strongest associations, i.e. pain detection threshold after single and repeated electrical stimulation. 95% CIs of all areas under the ROC excluded a clinically relevant estimate of more than 0.70. Table 4 presents sensitivities, specificities and LRs for different cut-offs for the two top ranked tests, i.e. pain detection after single and repeated electrical stimulation. We did not find clinically relevant LRs for any of the cut-offs.

Table S1 and Table S2 (both web appendix) show the results of sensitivity analyses from uni- and multivariable logistic regression models stratified by assessor (Table S1) and uni- and multivariable linear regression models using pain intensity after six months as continuous outcome (Table S2). Again, we found none of the tests to be associated with transition to CLBP or with pain intensity at 6 months.

DISCUSSION

Main findings

In this prospective cohort study in 130 patients, none of 14 tests evaluating six stimulation modalities showed a clinically relevant ability to predict the transition from acute to chronic low back pain. 95% confidence intervals of crude and adjusted associations of all tests with CLBP included one as measure of no association. None of the 95% confidence intervals of the areas under the ROC crossed the pre-specified boundary of clinical relevance set at 0.70. Pain detection after single and repeated electrical stimulation were the two most promising tests, with odds ratios around two in both crude and adjusted analyses and ROC of 0.58 and 0.57, respectively. However, in further analyses we were unable to identify cut-offs that yielded clinically relevant positive or negative likelihood ratios. The negative conclusion of our study remained robust to both sensitivity analyses.

Strengths and limitations

To our knowledge, this large cohort study is the first to prospectively assess the ability of 14 different tests evaluating six modalities to predict transition from acute to CLBP in a primary care setting, using ROC and associated parameters of clinical usefulness of diagnostic tests. A major strength is the near complete follow-up after six months. The definition of transition to CLBP followed established concepts (Airaksinen et al., 2006; Dionne et al., 2008) and the incidence of CLBP of 30% is concordant with previous results (Andersson, 1999; Hestbaek et al., 2003; Henschke et al., 2008; Chou and Shekelle, 2010; LeResche et al., 2013), which suggests generalizability. Still, it may have been useful to include a chronicity grading scale (Gerbershagen et al., 2010). We recruited all study participants in a primary care group practice, the main entry point of care for patients with acute low back pain.

A limitation was the difficulty in recruiting the necessary number of patients in this setting, which is reflected by a six-year recruitment period. The main reason for this was that many people seeking primary care for low back pain suffered from recurrent or chronic low back pain and thus were not screened. Time and resource constraints led us to close the study 10 patients short of the planned number of 140 patients. This resulted in decreased statistical precision. However, none of the 95% confidence intervals of areas under the ROC crossed the pre-specified boundary of clinical relevance set at larger than 0.70, and none of the tests was associated with pain intensity at 6 months. This suggests that the negative conclusion are not merely due to the number of included patients being less of than the planned sample size. While modelling associations between tests and pain intensity as continuous outcome may result in less readily available clinical interpretation, it increases the statistical precision required to detect associations between tests and transition to CLBP.

The calculation of ROC and associated parameters such as sensitivity, specificity and likelihood ratios is a major strength, as these parameters are the main elements to evaluate the clinical usefulness of a diagnostic test. Another limitation was that QST was performed by four different assessors. However, all assessors performed the QST according to a previously applied and standardized protocol (Neziri et al., 2012), and sensitivity analyses stratified by assessor yielded much the same conclusions as the main analyses. Assessors were specialized study nurses and medical doctors working in the laboratory of the Pain Clinic, Bern University Hospital. They were trained by M.C. and A.N., who had performed hundreds of tests in previous studies.

An important strength of our study is the large number of tests that represent different dimensions of nociception and pain experience (Neziri et al., 2011a). However, we did not include other potentially relevant tests such as vibration detection threshold, dynamic mechanical allodynia and pinprick hyperalgesia (Maier et al., 2010). The reasons were two-fold. First, we based the selection on a validated protocol applied in our previous research (Neziri et al., 2011a; Neziri et al., 2012). Second, our protocol took 120 minutes per patient to be completed. We found it difficult to further expand it, also considering that we tested pain patients rather than healthy individuals. Another

strength is that less than 10% of data were missing for covariates and tests, except for pain and reflex thresholds after electrical stimulation.

Context

After initiation of this cohort study, we performed a case-control study and ranked 26 quantitative sensory tests according to their ability to discriminate CLBP patients and pain-free controls (Neziri et al., 2012). The six tests that ranked highest were pressure pain detection threshold at the site of most severe low back pain, pain detection threshold after single electrical stimulation, reflex threshold after single electrical stimulation, pressure pain tolerance threshold at the site of most severe low back pain, pressure pain detection threshold at the supra-scapular region, and temporal summation pain detection threshold. All these tests displayed an excellent discrimination reflected by areas under the ROC of 0.80 or more. In the present study, we report results for all of these tests, except for the third (reflex detection threshold) and the fifth ranked tests (pressure pain detection threshold at the supra-scapular region). We found none of them to display clinically relevant predictive ability and thus could not confirm the findings of our previous case-control study. The difference in results between the current cohort and the previous case-control study is likely to be explained by the study designs per se. Results of the case-control study were based on a cross-sectional, arbitrary contrast between clearly symptomatic cases with long-lasting pain referred to a tertiary-care center and absolutely asymptomatic controls (Lachs et al., 1992; Rutjes et al., 2005; Neziri et al., 2012). Conversely, patients of this cohort study were recruited at the time of developing acute low back pain and prospectively followed up to determine their clinical course. Therefore, a decrease in performance of the tests in the current study in a primary care setting was expected (Neziri et al., 2012). However, the decrease in performance of the top ranked or any other tests was extensive, since none of them showed a clinically relevant ability to predict transition from acute to CLBP.

Our results are in line with the findings of a previously published prospective cohort study of similar design, which assessed the prognostic performance of five quantitative sensory tests in patients with acute low back pain (LeResche et al., 2013) and a recently published systematic review evaluating the prognostic value of QST in low back pain (Marcuzzi et al., 2016). The systematic review found only three studies investigating the prognostic value of QST in acute or CLBP. None of the studies found an association between quantitative sensory tests and low back pain outcomes, which supports our findings (Marcuzzi et al., 2016). The present study also confirms the lacking prognostic performance of two of the five tests examined in the cohort of LeResche et al and adds evidence for the lacking performance of an additional 11 tests. LeResche et al discussed the limited statistical precision as a potential alternative explanation of their negative results. In our study, 95% CIs of the estimated areas under the ROC were all below 0.70, which makes a clinically relevant predictive ability of any test unlikely.

Paradoxically, the majority of the ROCs were below 0.50, suggesting that less central hypersensitivity would be associated with increased risk of transition to CLBP. However, there is no pathophysiological support for this result and all upper limits of 95% confidence intervals were above 0.50, which would be compatible with our hypothesis that more pathological test values are associated with CLBP.

Pain detection thresholds after single and repeated electrical stimulation displayed odds ratios around two in both crude and adjusted analyses. This finding suggests that pain hypersensitivity as detected by electrical stimulation may have a pathophysiological association with the development of CLBP. However, the present study aimed at testing the clinical usefulness of QST in predicting the transition from acute to chronic pain. For this purpose, the values of odds ratios or the level of statistical significance are not of primary importance. Rather, sensitivity, specificity and likelihood ratios have to reach levels that make the tests useful for clinical decision in individual patients. In further analyses of these two electrical pain tests, we did not find clinically relevant positive or negative likelihood ratios that could be used to identify patients at high or low risk of CLBP.

Implications for future research

Our findings do not necessarily imply that central hypersensitivity is not involved in transition to chronic pain, but may reflect the limited ability of current quantitative sensory tests to detect clinically relevant central pain processes. Future research should aim at identifying biomarkers of central hypersensitivity that are better linked to patient-relevant outcomes. Studies should investigate the predictive value of a combination of different tests that are likely to represent different dimensions of nociception. Assessment methods based on the NWR as involuntary response to nociceptive stimulation are able to determine central hypersensitivity more objectively than traditional tests (Banic et al., 2004; Sterling, 2010; Neziri et al., 2012). Therefore, further technical and methodological improvement of this test and the investigation of reasons for the inability to elicit an NWR would be important.

Conclusions

We found no evidence for a clinically relevant ability of QST to predict the transition from acute to CLBP. This indicates that assessment of central hypersensitivity using currently available quantitative sensory tests is unlikely to identify patients at risk and therefore unlikely to inform clinical decision making.

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CONTRIBUTION OF AUTHORS

MC, LAN and PJ conceived the study. MM, FT, AN and MB contributed to data collection. MM, AL and PJ did the data preparation and analysis. All authors participated in interpretation of the data. MM wrote the first draft of the paper with primary assistance by PJ and secondary by MC. All authors contributed to the final draft.

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LEGENDS OF FIGURES

Figure 1: Study flow chart.

Legend:

*defined as pain <6 weeks and/or <3 episodes per year

°NRS: Numerical Rating Scale from 0 (no pain) to 10 (maximum pain)

$other included: 2 doctor denied contact with patient, 8 unclear, 8 language problems, 9 pregnancy

Figure 2: Receiver operating characteristic (ROC) curves showing the area under the curve (solid line) for pain detection threshold after single electrical stimulation (solid line) and pain detection threshold after repeated electrical stimulation (dashed line).

Legend:

Diagonal line represents a hypothetical ROC curve that yielded no discriminative information.

Table 1: Baseline characteristics in patients with and without transition to chronic low back pain after six months. Values are numbers (percentage), means (standard deviation), unadjusted odds ratios (OR) with corresponding 95% confidence intervals (95% CI), and p-values from univariable logistic regression models.

	Transition to chronic low back pain			
	Yes (N=32)	No (N=98)	Crude OR (95% CI)	p-value
Socio-demographic characteristics				
Males	20 (63%)	51 (52%)	1.54 (0.68, 3.48)	0.30
Age (years) [d]	43.5 (13.6)	43.1 (13.3)	1.07 (0.48, 2.43)	0.86
Higher education	17 (53%)	51 (52%)	1.04 (0.47, 2.32)	0.92
Married	12 (38%)	35 (36%)	1.08 (0.47, 2.47)	0.86
Living alone	10 (31%)	30 (31%)	1.03 (0.44, 2.44)	0.95
Regular work [a]	26 (81%)	81 (83%)	0.91 (0.32, 2.55)	0.86
Sick leave because of back pain	12 (38%)	39 (40%)	0.91 (0.40, 2.07)	0.82
High physical stress at work [b]	11 (34%)	35 (36%)	0.94 (0.41, 2.18)	0.89
High psychological stress at work [b]	19 (59%)	56 (57%)	1.10 (0.49, 2.47)	0.82
Psychological characteristics				
Depression (BDI-ll) [e]	8.5 (9.0)	6.2 (5.5)	1.45 (0.64, 3.27)	0.37
Anxiety (STAI Trait) [d]	51.8 (14.0)	47.6 (9.9)	2.13 (0.95, 4.81)	0.07
Catastrophizing (CSQ) [d]	1.3 (0.97)	1.0 (0.81)	2.18 (1.00, 4.74)	0.05
Clinical characteristics				
Overweight (BMI cut-off $\geq$25kg/m^2)	12 (38%)	38 (39%)	0.95 (0.42, 2.16)	0.90
Low back pain with irradiation to leg	11 (34%)	25 (26%)	1.53 (0.65, 3.61)	0.33
Pain duration (weeks) [d]	1.8 (0.9)	2.2 (1.5)	0.53 (0.18, 1.61)	0.27
Pain intensity at baseline [d]	4.4 (2.0)	3.8 (2.8)	1.98 (0.87, 4.51)	0.10
Disability at baseline (RMQ) [d]	11.0 (5.5)	9.3 (5.4)	1.80 (0.82, 3.97)	0.15
Intake of pain medication [c]	15 (47%)	59 (60%)	0.58 (0.26, 1.30)	0.19
Intake of muscle relaxant	7 (22%)	22 (22%)	0.97 (0.37, 2.53)	0.95

[a] includes houseworkers
[b] high stress and high pain defined as at least 5 on a numerical rating scale from 0 (no pain/stress) to 10 (maximum pain/stress)
[c] includes non-steroidal anti-inflammatory drugs, acetaminophen, metamizole, opioids
[d] OR per two standard deviation increase
[e] OR per two log-standard deviation increase
OR>1.0 means increased risk for transition to chronic low back pain

BDI-ll: Beck Depression Inventory Version 2
STAI Trait: State Trait Anxiety Index t-value
CSQ: Catastrophizing Scale of Coping Strategies Questionnaire
RMQ: Roland Morris Questionnaire

Table 2: Results of 14 quantitative sensory tests at baseline in patients with and without transition to chronic low back pain after six months. Values are mean (standard deviation), numbers (percentages), odds ratios (OR) with corresponding 95% confidence intervals (95% CI), and p-values from uni- and multivariable logistic regression models.

	Transition to chronic low back pain					
	Yes (N=32)	No (N=98)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Pressure pain (kPa)						
detection threshold, 2nd toe [b]	273 (148)	267 (93)	0.83 (0.37, 1.86)	0.66	0.68 (0.28, 1.64)	0.39
tolerance threshold, 2nd toe [b]	469 (140)	485 (193)	0.99 (0.44, 2.21)	0.98	0.76 (0.29, 1.98)	0.57
detection threshold, most painful site at back [c]	378 (217)	342 (223)	0.73 (0.33, 1.57)	0.42	0.62 (0.25, 1.56)	0.31
tolerance threshold, most painful site at back [c]	621 (260)	607 (278)	0.90 (0.40, 2.02)	0.80	0.61 (0.22, 1.69)	0.34
detection threshold, non-painful site at back [c]	494 (213)	440 (229)	0.62 (0.28, 1.37)	0.24	0.51 (0.20, 1.30)	0.16
tolerance threshold, non-painful site at back [c]	797 (175)	706 (237)	0.41 (0.17, 1.00)	0.05	0.24 (0.08, 0.72)	0.01
Electrical pain (mA)						
detection threshold, single stimulation [a, c]	7.0 (3.6)	8.0 (3.8)	2.10 (0.67, 6.42)	0.20	2.20 (0.62, 7.86)	0.22
detection threshold, repeated stimulation [a, c]	5.7 (2.7)	6.3 (2.4)	1.95 (0.68, 5.63)	0.22	2.11 (0.60, 7.39)	0.24
Heat pain (°C, cut-off < 50.5)						
detection threshold, leg	26 (81%)	83 (85%)	0.78 (0.28, 2.22)	0.65	0.67 (0.21, 2.13)	0.50
detection threshold, arm [a]	27 (83%)	82 (84%)	0.89 (0.29, 2.71)	0.84	0.77 (0.22, 2.66)	0.68
Cold pain (°C, cut-off >0.0)						
detection threshold, leg	12 (38%)	39 (40%)	0.91 (0.39, 2.07)	0.82	0.69 (0.28, 1.70)	0.43
detection threshold, arm [a]	15 (48%)	59 (60%)	1.64 (0.69, 3.91)	0.26	1.24 (0.48, 3.23)	0.66
Cold pressor test (s, cut-off < 120)						
hand withdrawal time [a]	28 (88%)	79 (81%)	1.60 (0.50, 5.12)	0.43	1.49 (0.45, 5.00)	0.52
Conditioned pain modulation (CPM)						
% of patients without increase in pressure pain tolerance threshold at 2nd toe [a]	9 (27%)	33 (34%)	0.73 (0.28, 1.88)	0.50	0.73 (0.27, 2.00)	0.54

[a] Results after multiple imputation (electrical pain detection threshold:18 missing values; heat and cold pain detection thresholds arm: 9 missing values; cold pressor test: 4 missing values; CPM: 16 missing values)
Adjusted OR included age, gender, anxiety, catastrophizing, pain intensity, disability and intake of pain medication at baseline
[b] OR per two log-standard deviation decrease
[c] OR per two standard deviation decrease
OR>1.0 means pathological values of quantitative sensory tests are associated with increased risk for transition to chronic low back pain (i.e. lower thresholds after pressure, electrical and heat stimulation, higher thresholds after cold stimulation, shorter hand withdrawal time and impaired CPM)

Table 3: Area under the ROC curves (AUC) with corresponding 95% confidence intervals for different quantitative sensory tests.

	Crude AUC (95% CI)
Pressure pain	
detection threshold, 2nd toe	0.46 (0.35, 0.56)
tolerance threshold, 2nd toe	0.51 (0.40, 0.62)
detection threshold, site most pain back	0.43 (0.32, 0.55)
tolerance threshold, site most pain back	0.49 (0.38, 0.60)
detection threshold, site no pain back	0.42 (0.30, 0.53)
tolerance threshold, site no pain back	0.38 (0.28, 0.48)
Electrical pain	
detection threshold, single stimulation [a]	0.58 (0.47, 0.70)
detection threshold, repeated stimulation [a]	0.57 (0.46, 0.69)
Heat pain	
detection threshold, leg	0.43 (0.32, 0.54)
detection threshold, arm [a]	0.37 (0.27, 0.47)
Cold pain	
detection threshold, leg	0.50 (0.40, 0.61)
detection threshold, arm [a]	0.60 (0.48, 0.71)
Cold pressor test	
Hand withdrawal time [a]	0.58 (0.47, 0.69)
Conditioned pain modulation	
difference pressure pain detection threshold, 2nd toe [a]	0.47 (0.35, 0.59)

[a] AUC based on predicted value after multiple imputation

Table 4: Diagnostic accuracy of electrical pain detection threshold after single and repeated electrical stimulation according to different cut-off values. Values presented are point estimates with corresponding 95% confidence intervals.

	No. patients						Likelihood Ratio	
Cut-off value, mA [a]	TP	FN	FP	TN	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive	Negative
Electrical pain detection threshold single stimulation								
5	5	27	10	88	15.6 (5.3, 32.8)	89.8 (82.0, 95.0)	1.53	0.94
6	12	20	26	72	37.5 (21.1, 56.3)	73.4 (63.6, 81.9)	1.41	0.85
7	19	13	49	49	59.4 (40.6, 76.3)	50.0 (39.7, 60.2)	1.19	0.81
8	21	11	57	41	65.6 (46.8, 81.4)	41.8 (32.0, 52.2)	1.13	0.82
9	25	7	68	30	78.1 (60.0, 90.7)	30.6 (21.7, 40.7)	1.13	0.72
10	28	4	76	22	87.5 (71.0, 96.5)	22.4 (14.6, 32.0)	1.13	0.56
Electrical pain detection threshold repeated stimulation								
4	4	28	8	90	12.5 (3.5, 29.0)	91.8 (84.5, 96.4)	1.52	0.95
5	9	23	17	81	28.1 (13.8, 46.8)	82.7 (73.7, 89.6)	1.62	0.87
6	17	15	40	58	53.1 (34.7, 70.9)	59.1 (48.8, 69.0)	1.30	0.79
7	24	8	69	29	75.0 (56.6, 88.5)	29.6 (20.8, 39.7)	1.07	0.84
8	27	5	74	24	84.4 (67.2, 94.7)	24.5 (16.4, 34.2)	1.12	0.64
9	30	2	87	11	93.8 (79.2, 99.2)	11.2 (5.7, 19.2)	1.06	0.55

Values are point estimates with corresponding 95% confidence intervals after predicting missing values based on multiple imputation
[a] cut-off: below cut-off was considered as test positive; equal or above cut-off was considered as test negative
TP: true positive, FN: false negative, FP: false positive, TN: true negative