Pain Mechanisms in Low Back Pain: A Systematic Review

with Meta-analysis of Mechanical Quantitative Sensory

Testing Outcomes in People With Nonspecific Low Back Pain

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BACKGROUND: Mechanical quantitative sensory testing (QST) assesses sensory functioning and detects functional changes in (central) nociceptive processing. It has been hypothesized that these functional changes might be apparent in people with nonspecific low back pain (LBP), although the results are mixed.

OBJECTIVE: The aim of this systematic review was to examine whether sensory function, measured with QST, was altered in people with nonspecific LBP.

METHODS: This systematic review was conducted according to PRISMA guidelines. Six databases were searched for relevant literature. Studies comparing mechanical QST measures involving people with subacute and chronic LBP and healthy controls were included if

(1) pressure pain thresholds (PPTs),

(2) temporal summation, or

(3) conditioned pain modulation were reported.

Risk of bias was assessed using the Newcastle-Ottawa scale. When possible, the results from different studies were pooled.

RESULTS: Twenty-four studies were included. Scores on the Newcastle-Ottawa scale varied between 1 and 6 points. People with nonspecific LBP, compared to healthy controls, had significantly lower PPTs at remote sites and increased temporal summation at the lower back. The PPTs measured at the scapula were significantly lower in patients with nonspecific LBP than in healthy controls (pooled mean difference, 119.2 kPa; 95% confidence interval: 91.8, 146.6 kPa; P<.001).

CONCLUSION: The PPT measurements at remote body parts were significantly lower in people with nonspecific LBP compared with healthy controls. Temporal summation and conditioned pain modulation measurements had mixed outcomes.

LEVEL OF EVIDENCE: Therapy, level 3a.

KEYWORDS: central sensitization; conditioned pain modulation; low back pain; pressure pain threshold; temporal summation

From the FULL TEXT Article:

Introduction

Non-specific low back pain (NSLBP) is one of the most common health problems in the world today that places an enormous burden on individuals, their families and society as a whole. [14] NSLBP is defined as pain felt at the lower back, between the lower rib and gluteal fold for which no specific pathophysiological process can be designated. [1]

Current guidelines for NSLBP suggest biopsychosocial approaches and individually-tailored interventions, consisting of combinations of education, exercise, and hands-on interventions. [8] In cases where monodisciplinary approaches fall short of success, multidisciplinary biopsychosocial rehabilitation is indicated. [1] Although the success of these interventions is well demonstrated, effect-sizes are still generally small and recurrent rates are high. [8, 31] There is a clear need for improvements in the management of NSLBP. One suggestion that is proposed is to better align treatments for low back pain with the underlying biological processes. [15, 28]

It is suggested that changes in the neurophysiological processing of nociceptive information may play an important role in NSLBP. [2, 15] Amplification of peripheral nociceptive information at the height of the dorsal horn, enhanced processing of nociceptive information within several brain nuclei and their interrelated connections that together form a ‘dynamic pain connectome’ are taken as important biological processes that should be considered in NSLBP. [29] This enhanced processing of nociceptive information is currently summarized as ‘central sensitization (CS)’. [15, 42] CS is defined as "an amplification of neural signalling within the central nervous system that elicits pain hypersensitivity". [49]

From a clinical perspective it is valuable to know whether CS is part of the presented NSLBP problem. CS is associated with higher pain intensity, widespread pain, worse prognosis and lower quality of life. [41, 43] It is important to note that CS is a neurophysiological concept and that the underlying processes cannot directly be measured in clinical practice. To study altered sensory processing, as a derivative of signs of CS, quantitative sensory testing (QST) is used. [2, 3]

Roussel et al. performed a narrative review on this topic in which they estimated that CS is the dominant pain mechanism in about 25% of the population with NSLBP. [37] In order to come up with this conclusion, these authors included studies that reported on differences between people with chronic low back pain and healthy controls regarding several QST measures. Higher pain thresholds at remote body parts, enhanced temporal summation and abnormal conditioned pain modulation were interpreted as signs of CS. [4, 10, 18, 23, 27, 33] However, a narrative review does not systematically screen the available literature, may not be comprehensive, does not take methodological quality of included studies into account, and does not pool data statistically to generate firm conclusions.

For these reasons we performed a systematic review and meta-analysis in order to draw conclusions about differences in QST outcomes between people with NSLBP and healthy controls. It was aimed a critically appraise current literature comparing remote PPT’s, local and remote TS and CPM in people with NSLBP and healthy controls to examine whether sensory functioning measured with QST is altered in people with NSLBP.

Methods

Protocol and registration

The review protocol was registered a priori at the International Prospective Register of Systematic Reviews (registration number: CRD42017055599). This systematic review is reported according to the PRISMA guidelines (www.prisma-statement.org).

Eligibility criteria

Studies were included if the following criteria were met:

1) Studies involved adult (age ≥ 18) people with NSLBP (subacute and chronic) and healthy controls;

2) sensory functioning was determined by using pressure pain threshold (PPT), mechanical TS and/or CPM measures; and

3) studies had to be written in Dutch, English or German.

Subacute NSLBP is defined as pain that has been present between six weeks and twelve weeks. [46] Chronic NSLBP is defined as pain that persists for at least twelve weeks. [1] Various QST procedures are described in the literature. The pain threshold is defined as the minimum amount of pressure that elicits a painful sensation. [5] Temporal summation (TS) is the increased pain response after a series of identical stimuli. [23] Conditioned pain modulation (CPM) is the increase in pressure pain thresholds (PPTs) after a painful stimuli on a remote body part. [3] To enable meta-analysis only studies using mechanical procedures were chosen. CS could be a normal physiological phenomenon during the acute low back pain phase, but will resolve in most cases. [16]

Studies involving patients with subacute and/or chronic low back pain were included in the meta-analysis as the difference between these two groups cannot clearly be delineated from a pain physiological perspective, but is merely a difference stemming from epidemiological convention. CS can be apparent in both groups. Studies involving people with sciatica, pelvic problems, pregnancy, whiplash associated disorders, non-specific neck pain, fibromyalgia, low back surgery or any other medical condition besides NSLBP, were excluded.

Information sources and search strategy

Literature was searched up to January 7th, 2019 in Medline, Cochrane, Google Scholar, Web of Science, CINAHL and EMBASE. An information specialist from the medical library of the Erasmus University Medical Centre Rotterdam (the Netherlands) constructed search strategies for the different databases. Main keywords were: central sensitization, pain threshold, hyperalgesia, hypoalgesia, quantitative sensory testing, wind-up, conditioned pain modulation, low back pain, inhibition and facilitation and synonyms. The search string for Medline is displayed in Appendix 1.

Study selection

After removal of duplicates, retrieved articles were screened on titles and abstracts for relevance by two independent investigators (HdB and WP). Full text versions of relevant articles were obtained and assessed for eligibility by the same two investigators. If there was uncertainty whether an article fit the criteria a third investigator (LV) was consulted and made the final decision. Corresponding authors of original studies were contacted in an attempt to obtain extra information if necessary.

Risk of bias in individual studies

Risk of bias was assessed independently by HdB and WP. The Newcastle-Ottawa quality assessment scale (NOS) for non-randomised studies, including case-control studies and cohort studies was used. [48] The NOS has a 'star rating system' in which a study is assessed on three aspects: selection of the study groups, the comparability of the groups and ascertainment of the exposure or outcome of interest. [48] Each aspect contains several items that can be scored with one star (except 'comparability', which can score up to two stars) (see Appendix 2). This process leads to a score between zero and nine stars. [44] Investigators assessed the included studies independently. Inter-rater agreement was calculated (Kappa and 95% Confidence Interval (CI)) using Statistical Package for Social Sciences (version 24; SPSS Inc., Chicago, IL). Disagreements were solved through discussion. If necessary, the third investigator (LV) determined the final score.

Data extraction and data items

The following data were extracted from the included articles: authors and year of publication, number of participants, definition of NSLBP, study design, type of QST measurement(s), location(s) of QST-stimuli and TS protocol, PPT-, TS- and CPM-results and author's conclusion. Data extraction was executed by both investigators independently. In case of missing data, authors were contacted and requested to provide required information.

Data management and meta-analysis

In most articles, results of PPTs, TS and CPM were shown by means, 95% CI, standard deviations and p-values. All data of PPT outcomes from individual articles were recorded or converted to the unit kPa. Studies were grouped based on the applied QST-protocol (remote PPT, TS, CPM and local TS) and further clustered according to the remote body location ('scapula', 'arm', 'hand', 'gluteal', 'lower leg' and ‘lumbar’). If a cluster contained at least two studies reporting means and standard deviations for patients with NSLBP and healthy controls, a meta-analysis was performed for PPT and TS outcomes using a binary random effects meta-analysis model. Meta-analysis were performed using RevMan software (Review manager, version 5.3, Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Meta-analysis for TS were pooled based on the same remote body locations, same TS protocol and outcome unit. Heterogeneity was assessed using I2. For the interpretation of the I2-values the following classification was used: 0% - 40%: no heterogeneity, 30% -60%: moderate, 50%-90%: substantial and 75%-100%: considerable heterogeneity. [13]

If heterogeneity was higher than 60% (predetermined) and a subgroup contained at least three articles, studies were pooled according to their NOS-score, dividing studies scoring below average and studies scoring average or above. [20, 40] If the p-value of 'the overall effect' of the meta- analysis was smaller than 0.05 (predetermined), the effect is considered significant. Studies not included in the meta-analysis were described separately. Funnel plots were created and inspected for publication bias (asymmetrical figure). A meta-analysis was not performed for CPM because of differences in measurement protocols used. Some studies used cold or hot water, while other studies used a thermode as noxious stimuli. In some studies, the participants had to immerse their foot, leg or hand in a bucket of ice water. [4, 22, 25, 32] In another study the participants had to immerse their hand in a bucket of hot water. [12] In one study the noxious stimulus was applied with a thermode on the dorsal part of the hand. [35] The TS measurements were more uniform across studies. Most of the TS protocols referred to the “German Research Network on Neuropathic Pain” (DFNS) and the remaining used TS protocols similar DFNS. [36]

Results

Study selection

The search yielded 6,801 articles. The flowchart of inclusion is shown in Figure 1. After removing duplicates (n= 4,198), the remaining 2,603 articles were screened on title and abstract. Full-texts of 62 articles were read. Finally, 24 articles were included in this review. [3-7, 9, 10, 12, 18, 19, 22, 24-27, 31-35, 38, 39, 45, 50] The corresponding authors of two publications were contacted with the request to provide the required details for meta-analysis. Both authors responded and delivered the required information.

Study characteristics

Study characteristics are shown in Table 1. In all studies, different measurements were taken at the same moment. All studies used PPT as outcome measure, except Meints et al. [24] Eight studies involved TS. [3, 9, 12, 27, 32, 34, 45] and six studies CPM. [4, 12, 22, 25, 32, 35] Seven studies conducted PPT measurements and TS measurements. [3, 9, 12, 22, 27, 32, 34, 45] In half of the studies (n=13), patients and controls were appropriately matched for age and sex. [4, 10, 12, 22, 25-27, 31, 32, 34, 35, 39, 45] In twenty-one studies, PPTs were taken at both the lower back and a remote body site (e.g. forehead, thenar, wrist, hand, M. infraspinatus and M. triceps brachii, M. gluteal maximus or 2nd toe). In one study only the lumbar area was tested using CPM. [35] In another study, only the remote hand was tested using TS. [24]

Risk of bias

Results of risk of bias assessment are shown in Table 2. Measurement of agreement 199 between the two reviewers (Kappa (95%CI)) was 0.69 (0.61, 0.77), which is 'substantial'. [17] Each article could have a maximum score of nine points on the NOS. None of the 24 articles had a score above six points and the average score was four. Only two articles [6, 45] had an adequate case definition. All of the articles, except those of Blumenstiel et al., Farasyn and Meeusen, Farasyn and Lassat, used the "same method of ascertainment for cases and controls". [3, 5, 6] None of the articles reported "non-response rate". The third independent researcher was not required for making final decisions.

Pressure Pain Threshold

The results of the meta-analysis are shown in figures 2a-2e. Funnel plots were symmetrical and no sign of publication bias was noted. The subgroup PPT, measured at the scapula (figure 2a), was significantly lower in patients with NSLBP than in HC (pooled mean difference (MD): 119.2, 95%CI: (91.8, 146.6), P<0.00001. [12, 19, 26, 27, 32, 50] The subgroup PPT, measured at the arm (figure 2b), was significantly lower in patients with NSLBP than in HC (MD: 36.32, 95%CI: 2.27, 70.37), p=0.04. [6, 7, 32, 39, 50] For the subgroup PPT, measured at the hand (figure 2c), heterogeneity was high, I2= 97%. [3, 9, 10, 12, 22, 31, 34, 45]

Subgroup analysis revealed that I2 values dropped to 6% and 0% when taking into account studies with NOS-scores above or below 4 respectively. Pooled PPT values of studies with NOS-score ≥ 4 were significantly lower in the group with NSLBP compared to HC (MD: 5.20, 95%CI: 1.32, 9.07), p=0.009. Pooled PPT values of studies with NOS-score < 4 were significantly higher in the group with NSLBP compared to HC (MD: -28.27, 95%CI: -29.30, -27.24), p<0.00001. [9, 10, 12, 31, 45] The subgroup PPT, measured at the gluteal site (figure 2d), was significantly lower in patients with NSLBP than in HC (MD: 218.63, 95%CI: 49.69, 387.57), p=0.01. [5-7, 19] The subgroup PPT, measured at the lower leg (figure 2e) was significantly lower in patients with NSLBP than in HC (MD: 68.51, 95%CI: 19.15, 117.86), p=0.007. [4, 25, 26, 31]

Three studies with PPT measurements could not be included in the meta-analysis. Two studies used the 'remote site' that did not fit within our subgroups [33, 38] and one study presented their results by reporting the median. [18] All PPT values (lower back and remote site) of the group with NSLBP in this study were significantly lower than in HC. Özdolap et al. measured PPTs at the lower back, twelve sciatic valleix points and the fibromyalgia tender points. All mean PPT values in the group with NSLBP were significantly lower than in HC. [33] Schenk et al. measured PPTs at the lower back and forehead. PPT values measured at the lower back did not differ between people with NSLBP and HC, while PPT values measured at the forehead were lower (P=0.049) compared to HC. [38]

Temporal Summation

The results of the meta-analysis are shown in figures 3a and 3b. Funnel plots were symmetrical and no sign of publication bias was noted. For the subgroup TS, measured at the lower back (figure 3a), heterogeneity was high, I2= 72%. Subgroup analysis revealed that I2 values dropped to 0% (NOS less than 4) and 3% (NOS 4 or more) when considering studies with NOS-scores above or below 4 respectively. Pooled TS values of studies with NOS-score < 4 were significantly higher in the HC group compared to the NSLBP (MD: 1.04, 95%CI: 0.16, 1.93), p=0.02. Pooled TS values of studies with NOS-score ≥ 4 were significantly higher in the group with NSLBP compared to HC (MD: -0.84, 95%CI: -1.24, -0.44), p<0.0001. [3, 9, 22, 34, 45]

The subgroup TS, measured at the hand (figure 3b), revealed no significant difference between the group with NSLBP and the HC (P=0.06). [3, 9, 22, 24, 34, 45] Two studies using TS were not included in the meta-analysis because of a different measurement protocol. [12, 27, 32] Goubert et al. reported that the TS value of people with NSLBP was higher (i.e., more enhanced) compared with HC. [12] Significance was not described. TS values of Owens et al. showed a significantly higher sensitivity within the group with NSLBP compared with the HC. [32]

Conditioned Pain Modulation

In six studies a CPM-protocol was used. Results were not pooled because of differences between the protocols. [4, 12, 22, 25, 32, 35] The study of Rabey et al. found that more HC’s showed a significant inhibitory effect than people with NSLBP. [35] In the study of Corrêa et al. CPM outcomes showed that PPT values at the lower back and the M. tibialis anterior in the group with NSLBP were significantly lower compared to HC. During CPM the group with NSLBP demonstrated a statistically significant decrease in the lumbar PPT while the HC demonstrated a significant increase in the lumbar PPT. [4] Goubert et al. demonstrated no significant differences between patients with NSLBP and HC 12 Mlekusch et al. [25] and Owens et al. [32] showed a normal CPM effect in both groups; PPT values were increased after the conditioned pain stimulus in both the group with NSLBP and the HC. Marcuzzi et al. showed no significant differences between the group with NSLBP and the HC. [22]

Discussion

The aim of the present systematic review and meta-analysis was to critically appraise the current literature on mechanical QST-measurements in patients with NSLBP in order to examine signs of altered sensory functioning in this population. The main results of the meta-analysis found that overall PPT measurements at remote body parts are significantly lower in the group with NSLBP compared with HC. This finding is indicative of CS in people with NSLBP. [11] In the studies with superior methodological quality, TS was enhanced in the lumbar region, but not at remote sites, in people having NSLBP compared to HC. Mixed results were found regarding CPM in patients with NSLBP. Although a clear picture of signs of CS in people with NSLBP was not found, the available literature regarding mechanical somatosensory functioning provides some evidence suggestive of CS in people with NSLBP.

CS is a phenomenon characterized by enhanced nociceptive processing combined with disturbed top-down modulation. QST-measures are taken as a derivative to objectify these neurophysiological processes and to draw conclusions about the way the sensory systems processes different stimuli. In this study, only a small number of studies could be included that used TS and/or CPM. This hampers firm conclusions about changes in this type of QST-measurements and can be an explanation for the inconsistent results that were found, underscoring the importance of conducting a meta-analysis as reported here. Inconsistent findings regarding QST-measurements can also be due to the presence of subgroups within the population with NSLBP. Only two of the included studies reported data on patients with localized or widespread pain separately. Therefore, subgroup analyses were not possible, and the present review was also not designed to reveal or refute subgroups within the population with NSLBP. There is a need for more studies using more extended QST measurements in order to determine the existence of different ‘QST-profiles’ in patients with NSLBP.

As mechanical QST-measurements are most often used in studies of patients with NSLBP, this review is limited to studies using mechanical QST-measurements only. How the somatosensory system in patients with NSLBP responds to i.e. thermal and electrical stimuli in people with CS remains to be examined. Finally, it is currently unknown whether the different results in these static (PPT) and dynamic (TS and CPM) measurements can be explained by methodological issues (e.g. smaller sample sizes and different protocols used) or by underlying physiological differences. Notably, a clear definition of non-specific low back pain was not reported in most studies.

The strength of this review is that this is the first meta-analysis studying and summarizing QST-measurements in people with NSLBP. It should be taken into consideration that a lot of the included studies were rated as low to moderate methodological quality. Based on their narrative analysis of the literature, Roussel et al concluded that signs of CS may be present in patients with low back pain. [37] The results of our meta-analysis confirm that PPTs at remote body parts are significantly lowered and TS at the lower back is enhanced in patients with NSLBP compared to healthy controls. This conclusion would be strengthened if based on studies from higher methodological quality. Since reported standard error of measurements (SEM) of QST-measures vary between measured populations, measured body parts and different protocols used it is difficult to compare scores and evaluate the magnitude of pooled differences properly.

However, the pooled difference found for PPTs measured at the scapula (MD 119.2, (95%CI: 91.8, 146.6)) exceed the range of previously reported SEMs of 18.2-52. [47] The results of this study should be interpreted with caution as we only included cross-sectional studies that compared groups of patients with NSLBP with healthy controls. Additionally, we currently lack clear cut-off scores for QST-measurement that enable health care professionals to make sound judgements in individual cases. However, health care professionals should be aware that altered sensory processing may be present in patients with NSLBP and that this might require a different treatment approach. [30]

Conclusion

This meta-analysis revealed that PPT measurements at remote body parts and TS at the lower back differ between people with NSLBP and HC. Results of studies using CPM measurement showed mixed findings. In conclusion, although a clear picture of CS in people with NSLBP was not found, the available literature regarding mechanical somatosensory functioning provides some evidence suggestive of CS in people with NSLBP. Future work should study whether different QST-profiles can be made for patients with NSLBP to distinguish between subgroups of patients with and without CS. In addition, clear cut-off points for QST-measures are mandatory for health care professionals in order to make sound judgements in individual cases.

Key points

Findings: In people with non-specific low back pain (NSLBP) altered sensory functioning was demonstrated. This was present in the pressure pain threshold (PPT) measurements at remote body parts.

Implications: Health care professionals should be aware that sensory processing might be enhanced in their patients with NSLBP and this might require a different treatment approach.

Caution: The results of this systematic review and meta-analysis are based on cross-sectional studies that compared groups of people having low back pain with healthy controls and therefore no conclusion on an individual level can be made. 0

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Conflict of interest:

I affirm that I have no financial affiliation (including research funding) or involvement with any commercial organization that has a direct financial interest in any matter included in this manuscript. We declare no conflicts of interest (ie, personal associations or involvement as a director, officer, or expert witness).

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