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Impaired Exercise-induced Hypoalgesia in Individuals Reporting an Increase in Low Back Pain During Acute Exercise

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Short Title: Impaired EIH in LBP after painful exercise

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What's already known about this topic?

- The response to exercise is highly variable in individuals with low back pain.
- The reason for such variation in response to exercise may relate to whether exercises are painful or not, and to the status of pro-nociceptive and anti-nociceptive mechanisms.

What does this study add?

- Pain flares in response to exercise seem to impair the beneficial exercise-induced hypoalgesia. Pain flares were associated with baseline pain sensitivity and pain intensity.

Abstract

Objectives: Exercise therapy is recommended for low back pain (LBP) although the immediate effects on pain are highly variable. In 96 individuals with LBP this cross-sectional study explored 1) the magnitude of exercise-induced hypoalgesia (EIH), and 2) measures of pain sensitivity and clinical pain manifestations in individuals reporting a clinical relevant increase in back pain during physical activity compared with individuals reporting low or no increase in back pain during physical activity.

Methods: Cuff algometry was performed at baseline on the leg to assess pressure pain threshold (cPPT), tolerance (cPTT), and temporal summation of pain (cTSP). Manual PPTs were assessed on the back and leg before and after a six minute walk test (6MWT). Back pain was scored on a numerical rating scale (NRS) after each minute of walking. The EIH-effect was estimated as the increase in PPTs after the walk exercise.

Results: Twenty-seven individuals reported an increase of ≥2/10 in pain NRS scores during walking and compared with the individuals with <2/10 NRS scores: cPPT and EIH-effects were lower whereas cTSP, pain intensity and disability were increased ($P<0.03$). Baseline NRS scores, EIH and pain thresholds were associated with the likelihood of an increase of ≥2/10 in back pain intensity during walking ($P<0.05$).

Conclusions: Pain flares in response to physical activity in individuals with LBP seem to be linked with baseline pain sensitivity and pain intensity, and impair the beneficial exercise-induced hypoalgesia. Such information may better inform when individuals with LBP will have a beneficial effect of physical activity.

Keywords: Physical activity, pain sensitivity, pain threshold, pain tolerance, temporal summation of pain, exercise-induced hypoalgesia

1. Introduction

Low back pain (LBP) is one of the leading causes of disability across the world (Vos et al. 2012, Hartvigsen et al. 2018). During the last decade alterations in pro-nociceptive and anti-nociceptive pain mechanisms have been hypothesized to contribute to the magnitude of clinical symptoms in LBP. A recent meta-analysis found facilitated temporal summation of pain (TSP) and impaired conditioned pain modulation (CPM) in subjects with LBP compared to healthy controls where the clinical pain severity was associated with degree of increased TSP and impaired CPM, respectively (McPhee et al. 2020).

Exercise therapy is one of several recommended treatments for LBP (Oliveira et al. 2018). While regular exercise is associated with reduced pain intensity and disability in subjects with LBP (Chou and Huffman 2007, Hayden et al. 2019), systematic reviews generally report small effect size indicating either low average efficacy or high inter-individual variability in the response to physical activity. The variability is supported by observations of pain flares (i.e. an exacerbation or increase in pain) in response to physical activity in some LBP individuals (Sullivan et al. 2009), which may reduce physical activity performance and be an important barrier for adherence to regular physical activity. The reason for such variation in response to physical activity is not clear but may relate to psychological factors such as fear of movement and pain catastrophizing (Alhowimel et al. 2018, Guillaume et al. 2020), and the status of pro-nociceptive and anti-nociceptive mechanisms. For instance, in LBP subjects facilitated pro-nociceptive mechanisms may be associated with an increase in LBP during physical activity. A similar association was reported by Wideman and colleagues where the degree of TSP and the increase in knee pain during walking was correlated in patients with knee osteoarthritis (Wideman et al. 2014).

Similar to after other interventions, pain reduction in LBP are typically observed after 8 to 12 sessions of exercise therapy (Geneen et al. 2017), still an acute reduction of the pain sensitivity can be observed after a single session of exercise, which is commonly known as exercise induced hypoalgesia (EIH) (Vaegter et al. 2014). A single session of exercise has consistently been observed to reduce the pain sensitivity in pain-free individuals (Naugle et al. 2012) with one study observing larger hypoalgesic effects after painful exercises compared with non-painful exercises (Ellingson et al. 2014). In individuals with different pain conditions, the response to a single session of exercise is less consistent and reduced EIH or even hyperalgesia has been observed (Lannersten and Kosek 2010). This is similar to the response observed in experimental research where increased pain sensitivity following induction of short painful stimuli has been observed in some individuals with pain

(Jorgensen et al. 2015). The contrasting EIH response between pain-free individuals and individuals with pain suggests that the presence of clinical pain during exercise may interfere with the mechanisms of EIH. Currently, it is unclear how an increase in clinical pain during exercise affects the magnitude of EIH.

The primary aim of this study was to explore possible differences in EIH and physical activity performance as well as baseline pain sensitivity and clinical pain characteristics between individuals with LBP reporting a clinically relevant increase (≥2/10) in their back pain during walking and individuals reporting no or limited increase in their back pain during walking. In addition, possible associations between change in back pain during walking and baseline measures of pain sensitivity and clinical pain/psychological characteristics were explored. It was hypothesized that the EIH response would be larger in individuals who did not report an increase in back pain during walking compared with individuals who reported an increase in back pain. In addition, it was expected that pain sensitivity, clinical pain, and fear of movement and pain catastrophizing scores would be lower at baseline in individuals who did not report an increase ≥2 in back pain during walking.

2. Methods

2.1 Participants

Individuals referred with LBP (ICD-10: M54.5 Low back pain) to the Rehabilitation Center Hollufgaard, Odense Municipality in Denmark in the period June 2017 to October 2019 were included in this cross-sectional study. This public secondary-care outpatient unit is for individuals referred from hospital for physical rehabilitation. Inclusion criteria were women and men at least 18 years old who were adept in Danish to ensure that they understood the information about the pain testing procedures, pain primarily in the lower back (either with or without pain radiating to the legs), and who were scheduled for participation in an 8-weeks group-based exercise therapy program. Exclusion criteria were pregnancy, neurological, psychological or cardiovascular diseases, and current or previous alcohol or drug addiction. The study was conducted in accordance with the Declaration of Helsinki, approved by the local ethical committee (S-20160202), and all subjects received oral information about the study and provided written informed consent prior to participation.

2.2 Study protocol

Before participation in the exercise therapy program participants completed pain-related questionnaires, and assessments of cuff pressure pain threshold (cPPT), cuff pressure pain tolerance (cPTT), and cuff pressure temporal summation of pain (cTSP) at the right lower leg were performed as well as recordings of manual pressure pain thresholds (PPTs) at the left side of the low back and left lower leg before and after a 6 min walking test (Fig. 1). Manual algometry was used is this study as cuff algometry does not allow for assessment of pain sensitivity on the lower back. Significant correlations between manual PPTs and cuff cPPT have previously been demonstrated (Graven-Nielsen et al. 2015).

Pain sensitivity assessments were undertaken in the same order, and participants were familiarized to the cuff assessments at the opposite (i.e. left) lower leg and to the manual PPT assessment at the opposite (i.e. right) side of the low back and lower leg before the real assessments were made.

2.3 Assessment of pain sensitivity

Computer-controlled cuff algometry (Aalborg University, Denmark) was used to assess cPPT and cPTT on the right lower leg while the participant was seated on a plinth with arms resting on the thighs and no foot support. The silicone tourniquet cuff (13-cm wide; VBM, Sulz, Germany) was wrapped around the calf 8 cm below the tibial tuberosity. The pressure increase was 1 kPa/s and the maximal pressure limit was 100 kPa. During inflation, subjects rated the pain intensity using an electronic visual analogue scale (VAS). The electronic VAS was sampled at 10 Hz. Zero and 10 cm extremes on the VAS were defined as "no pain" and "maximal pain", respectively. Participants were instructed to rate the pain intensity continuously on the electronic VAS from when the pressure was defined as first sensation of pain and to press the pressure release button when the pain was perceived as intolerable (cPTT). The cPPT was defined as the pressure when participants scored 1 cm on the VAS the first time to ensure that a small movement of the VAS marker was not mistakenly interpreted as pain threshold (e.g. VAS = 0.1). Cuff algometry with similar definition of pain threshold has been used in multiple studies on individuals with pain, and several studies have reported adequate reliability (Graven-Nielsen et al. 2015, Imai et al. 2016, Graven-Nielsen et al. 2017).

Ten repeated cuff pressure stimulations lasting 1 s each and 1 s in-between were applied to assess cTSP. Stimulations were delivered by rapid inflation of the cuff with an intensity equivalent to the pressure corresponding to cPTT. In the period between the 10 stimuli a constant non-painful pressure of 5 kPa was kept so that the tourniquet did not move.

Participants rated the pain intensity on the electronic VAS continuously during the sequential stimulation without returning the VAS to zero between stimulations. VAS scores immediately after each stimulus were extracted, and cTSP was calculated as the ratio of the average VAS of the last 3 stimulations to the average VAS of first four stimulations, with values above 1 indicating an increase in pain intensity ratings during the repeated stimulation.

Manual pressure algometry (Somedic Sales AB, Sweden) was used to assess PPTs with the participant lying prone on the plinth with both arms resting along the sides. A stimulation probe of 1 cm^2 was used and the pressure was increased with 30 kPa/s. The first time the participant perceived the pressure as pain, a button was pushed and the pressure intensity defined the PPT. PPTs were assessed locally at the left erector spinae muscle (three centimeters lateral from the 4^{th} lumbar spinous process) and at the left calf (twenty-five centimeters proximal from the upper part of the calcaneal tubercle). The average PPTs across 2 repetitions at each site were used for further analysis as this has shown adequate reliability (Graven-Nielsen et al. 2015, Vaegter et al. 2016).

2.4 Assessment of back pain during physical activity

The 6-minute walk test (6MWT) is a standardized reliable (Rikli and Jones 1998, Unver et al. 2013) walking protocol used for assessing functional aerobic capacity (Du et al. 2009) and in this study it was used to assess physical activity performance (distance) and movement-related back pain. The 6MWT was performed in accordance with the standardized protocol (ATS statement 2002) on a 20 m course between two cones and after 6 min walk the total distance was calculated. Standard instructions were given prior to the walking condition, and participants were encouraged to walk as far as possible within the 6 min without running. At the end of each minute the participants were cheered with standardized phrases; *"Keep up the good work"* or *"You are doing well".*

Participants were asked to rate their pain in the lower back 7 times in relation to the walking task, once immediately before the task (min 0) and once after each minute of walking. Clinical back pain intensity was assessed on a numerical rating scale (NRS) ranging from 'no pain' (0) to 'maximal pain' (10). As several participants rated their back pain intensity as 0/10 just before starting the 6MWT, a movement-related pain index (Walk-Pain-index) was calculated as absolute change with the NRS pain score reported at the 6^{th} min of walking minus the NRS pain score immediately before the walking task.

2.5 Assessment of exercise-induced hypoalgesia

The 6MWT was also used to assess EIH. PPTs at the lower back and lower leg were assessed just before as well as immediately after (i.e. it took approximately 20 sec to move from the course to the plinth) the 6MWT as described above. The EIH-effect was calculated as the PPT after walking minus the PPT before for each assessment site.

2.6 Pain-related questionnaires

Pain-related questionnaires were completed via an electronic questionnaire system (PainData, Clinical Pain Registry) prior to the assessments of pain sensitivity and the 6MWT. Participants were asked to indicate the date for low back pain onset as accurately as possibly, and any use of analgesics (opioids, tricyclic antidepressants, anticonvulsive, NSIADs, paracetamol and muscle relaxants). Participants were not asked to stop taking analgesics on the day of testing.

Clinical pain intensity: Average pain intensity during the past 24 hours was rated on the NRS. Pain intensity ratings on a NRS have shown good test-retest reliability in patients with pain (Ferraz et al. 1990).

Pain distribution: Participants completed pain drawings indicating all areas with current pain and the proportion of patients with radiating leg pain below the knee was calculated.

Pain-related disability: Pain-related disability was assessed with the low-back pain

specific Roland Morris Disability Questionnaire (RMDQ). The Danish 23-items RMDQ (Albert et al. 2003) record whether low-back pain or leg pain affects different functional activities. The RMDQ scores were recalculated to a 0–100 scale using the method of Kent and Lauridsen (Kent and Lauridsen 2011) with a higher score indicating higher disability.

Pain related cognitions: Pain catastrophizing was assessed using the 13 items Pain Catastrophizing Scale (PCS) (Sullivan et al. 1995), and pain-related fear of movement was assessed with the 17-items Tampa Scale of Kinesiophobia (TSK) questionnaire (Kori et al. 1990). Both questionnaires have shown acceptable test-retest reliability and validity in patients with low back pain (Swinkels-Meewisse et al. 2003, Fernandes et al. 2012). The PCS assess the degree to which participants experienced different thoughts or feelings, on a 5-point Likert scale with 0 = not at all and 4 = all the time. The score is 0-52 with a higher score indicating a high level of pain catastrophizing. On the TSK participants indicate the degree to which they agree on each of 17 statements related to avoidance of physical

activities and beliefs about vulnarability of the body, on a 4-point Likert scale with 1 = 'strongly disagree' and 4 = 'strongly agree' with a higher score indicating higher levels of fear of movement/kinesiophobia.

2.7 Statistics

The study was powered to detect a large difference in the EIH response (i.e. effect size of 0.80) between the group reporting an increase of ≥2/10 in pain NRS scores (group 1: Walk-Pain-index ≥2) during walking and the group reporting <2/10 NRS scores (group 2: Walk-Pain-index <2). Using G*power (version 3.1.9.2., Dusseldorf, Germany) it was estimated that 26 participants were required in each group to be able to detect such a difference with a power of 80% and a two-sided significance level of 0.05. It was anticipated that between 1 in 3 and 1 in 4 individuals with LBP would report an increase of ≥2/10 in pain NRS scores, and it was planned to include approximately 100 participants. A pain NRS change of 2 was used as this has recently been demonstrated as a clinically meaningful change in pain in individuals with low back pain (Suzuki et al. 2020).

First, a repeated-measures analysis of variance (RM-ANOVA) with time (0, 1, 2, 3, 4, 5, 6 min) as within-subject factor and groups as between-subject factor was used to describe how NRS scores of low back pain increased in the two Walk-Pain-index groups during performance of the 6MWT.

Second, to explore the local and remote EIH responses in the two groups, PPTs at the lower back and calf before and after walking were compared in a RM-ANOVA with time (before and after walking) and assessment sites (lower back and calf) as within-subject factors and a between-group factor with the two groups. In case of significant differences, Bonferroni-corrected pairwise comparisons correcting for multiple pair-wise comparisons were used. Partial eta squared (partial η^2) was reported to estimate the effect size with the effect size considered small when partial $\eta^2 \leq 0.06$, medium when partial $\eta^2 \leq 0.14$, and large when partial $\eta^2 > 0.14$ (Richardson 2011). Homogeneity of variance in the RM-ANOVAs were evaluated with Levene's Test, and when violated Greenhouse-Geisser correction was applied.

Third, potential differences in pro-nociceptive pain mechanisms, clinical pain characteristics, and physical activity performance between the two Walk-Pain-indices were explored with Chi^2 test for categorical variables, t-tests for normally distributed continuous variables, and Mann Whithey U test for non-normally distributed continuous variables. Effect sizes for continuous clinical pain, pain sensitivity and 6MWT distance measures of the

group differences were calculated based on the Hedges g, due to dissimilar group sizes. Effects sizes were evaluated as small (g =0.20), medium (g=0.50), and large (g =0.80).

Finally, binary logistic regression with forward selection (variables with $p \leq 0.10$ were kept in) was performed to explore whether the 'Walk-Pain-index ≥2' was associated with walking distance, baseline measures of pain sensitivity (PPTs at lower back and lower leg, cPPT, cPTT, and cTSP), EIH (lower back and lower leg), clinical pain manifestations (pain intensity before walking, pain distribution (pain below knee Y/N), pain duration, disability, PCS and TSK) and demographics (age and sex (women/men)). Pain intensity before walking and average pain intensity during the past 24 hours were significantly correlated. Pain intensity before walking which was the most current pain rating with less risk of recall bias was used in the logistic regression to avoid multicollinearity. Multicollinearity was assessed based on variance inflation factor (VIF) scores with values between 5 and 10 indicating high correlation (VIF for all variables < 4.8) (Hair et al. 2010).

For the pain-related questionnaire data, individuals could leave any question or item blank and the missing rate ranged from 8.3% (average pain intensity) to 14.5% (item 2 in TSK). Because the missing rate was relative low, the available data was used and no data was imputed. All statistical analyses were performed in SPSS version 24 (IBM Corporation, Armonk, NY). $P < 0.05$ was considered significant.

3. Results

3.1. Demographics

Ninety-six subjects with low back pain were included in this study (Table 1). For the pain drawings, 8 subjects had blank drawings (8.3%), 38 subjects (39.6%) reported pain below the knee, and 50 subjects (52.1%) did not report pain below the knees (Supplementary Figure 1). In general, there was no significant difference in use of analgesics, however, a higher proportion of participants in the Walk-Pain-index ≥ 2 group used paracetamol compared with participants in the Walk-Pain-index < 2 group (P=0.02). Eleven participants in the Walk-Pain-index < 2 group and 2 participants in the Walk-Pain-index ≥ 2 group, respectively reached the maximal pressure limit of the cuff device.

3.2 Change in back pain during walking

All participants completed the 6MWT. Twenty-seven subjects (28.1%) reported a NRS increase of 2 or more in back pain intensity (pain NRS increase: 2.9±0.9) during the 6MWT, and 69 individuals reported a change of less than 2 in back pain intensity (pain NRS increase:

-0.04±0.8). For pain ratings during walking, significant main effects of time and *Walk-Pain Index* ($F(6,564)=74.71$, $P < 0.001$; $F(1,94)=36.37$, $P < 0.001$), however a significant interaction between *time* and *Walk-Pain Index* (Greenhouse-Geisser corrected, $F(3.59,337.47)=77.10$, $P<0.001$, partial $\eta^2=0.45$) was also found in the RM-ANOVA. Post-hoc test showed that NRS pain ratings were significantly larger in the Walk-Pain-index ≥ 2 group compared with the Walk-Pain-index < 2 group from min 1 to min 6 (Fig. 2; $P<0.05$). In the Walk-Pain-index ≥ 2 group, the NRS scores were significantly higher at each time point compared with the previous time points ($P<0.005$).

3.3 Exercise-induced hypoalgesia

No significant main effects were found for PPTs, however a significant interaction between *time* and *Walk-Pain Index* were found in the RM-ANOVA of the PPTs (Figure 3; $F(1,94)=5.56$, $P=0.02$, partial $\eta^2=0.056$) with post-hoc test showing an increase in PPTs after walking in individuals who reported no or little increase in NRS scores of back pain intensity, and a decrease in PPTs after walking in individuals who reported an increase of 2 or more in NRS scores of the back pain intensity. The effect of *Walk-Pain Index* on PPT was not significantly different between assessment sites, as the *time, assessment site* and *Walk-Pain Index* interaction was not significant ($F(1,94)=0.25$, $P=0.62$). EIH responses are presented separately for women and men in Supplementary Table 1.

3.4 Pain sensitivity, clinical pain characteristics, and physical activity performance

Compared with the individuals with <2/10 pain NRS scores, participants who reported a change of ≥ 2 had lower cPPT, facilitated cTSP, and higher disability as well as average pain intensity scores during the last 24 hours small to large effect sizes (Table 1). No significant differences were observed for manual PPTs, cPTT, TSK, PCS, 6MWT distance or pain intensity before walking although this variable approached significance.

3.5. Factors associated with change in back pain during walking

Of the 16 included variables only four were statistically significant in the final model explaining 37.8% (Nagelkerke R^2) of the variance in Walk-Pain Index: back pain NRS scores before walking, cPPT and PPT at the lower leg, and the EIH response at the lower back (Table 2). Increased back pain NRS scores before walking was associated with an increased likelihood of Walk-Pain Index ≥2, but increasing cPPT, and EIH was associated with a reduction in the likelihood of Walk-Pain Index ≥2. Surprisingly, higher PPT at the lower leg

was associated with an increased likelihood of Walk-Pain Index ≥2, although the effect estimate was quite small.

4. Discussion

The first aim of this study was to explore if local and remote EIH responses were different between LBP individuals who reported an increase in back pain intensity during walking and individuals who reported no or limited increase in back pain intensity. This showed that the EIH responses were impaired in the low back and in the lower leg in participants who reported an increase in back pain during walking. This result may be useful in clinical practice in relation to whether exercises should increase pain or not. Future studies are encouraged to investigate, if an increase in clinical pain during exercise interferes with the hypoalgesic effects of long-term exercise treatments. The second aim was to explore whether pain sensitivity and clinical pain characteristics at baseline were different between individuals with and without an increase in back pain intensity during walking. Lower cuff pain threshold (cPPT), facilitated temporal summation of pain, and increased clinical pain intensity during the last 24 hours and disability were observed in participants with a NRS increase ≥2. Surprisingly, fear of movement and pain catastrophizing scores were not different between groups. In addition, pain thresholds, EIH and back pain intensity before walking were associated with the likelihood of an increase of ≥2 in back pain NRS scores during walking. These results may better inform when individuals with LBP will have a beneficial effect of physical activity.

4.1. Change in pain in response to physical activity

In the current study, the intensity of back pain increased during walking on a group level, however more than 70% of the participants did not report a clinically relevant increase in pain during walking. These participants demonstrated local and remote EIH suggesting that walking may serve as a beneficial non-pain provoking physical activity in most individuals with LBP. This is in line with Hviid et al. (Hviid et al. 2019), who recently showed that walking induced hypoalgesia compared with a control condition in pain-free individuals. Higher cuff pain thresholds and lower clinical pain during the last 24 hours were associated with pain during walking suggesting that both pain sensitivity and clinical pain manifestations influence the sensitivity to physical activity. Interestingly, back pain NRS assessed just before walking, which was somewhat lower than the average clinical pain intensity during the last 24 hours, did not as robustly differentiate participants who reported

an increase ≥2 NRS from participants who reported an increase of <2 NRS during walking, indicating that the association between EIH and clinical pain intensity is not consistent and may be influenced by how and when clinical pain intensity is assessed.

The association between pain flares during exercise and impaired EIH has often been observed in individuals with widespread pain conditions (Vierck et al. 2001, da Cunha Ribeiro et al. 2018), however almost 30% of the participants with LBP in the current study reported an increase in NRS score ≥2/10 during walking, and in contrast to participants with no or little increase in pain during walking these subjects also showed increased pain sensitivity after walking. These findings are similar to previous studies that have observed increases both in clinical pain and pain sensitivity in response to exercise in individuals with spinal pain. E.g. Kuithan and colleagues (Kuithan et al. 2019) observed increases in clinical pain and impaired EIH after repeated back exercises in 21 subjects with chronic LBP, and in a recent study on 26 patients with chronic neck and shoulder pain reduced PPTs and increases in clinical pain during light aerobic arm exercises and lasting for up to 2 days were reported (Grimby-Ekman et al. 2020).

The association between higher pain during walking and less EIH is somewhat opposite to the findings from a previous study in pain-free individuals where larger hypoalgesic effects were observed after painful exercises compared with non-painful exercises (Ellingson et al. 2014). The "pain inhibits pain" phenomenon has been suggested as a potential mechanism responsible for the widespread hypoalgesic response after exercise as several studies have found correlations between CPM and EIH (Ellingson et al. 2014, Vaegter et al. 2014, Gajsar et al. 2018). One possible explanation for these contrasting effects of pain during exercise is the alterations in anti-nociceptive pain mechanisms (e.g. impaired CPM) in individuals with LBP (McPhee et al. 2020), suggesting that when CPM is impaired, exercise results in smaller acute hypoalgesic effects. Another possible explanation is the alterations in the net balance between pain inhibition and pain facilitation in some individuals with pain. Coombes and colleagues showed that isometric exercise above but not below the individual's pain threshold increased pain responses to exercise in people with lateral epicondylalgia (Coombes et al. 2016) indicating more input to facilitated central pain mechanisms resulting in a reduced net balance of pain inhibition after exercise. In line with this, participants reporting increase in back pain in the current study also demonstrated facilitated temporal summation and higher pain sensitivity. Further, the increased pain in response to physical exercise in participants with facilitated temporal summation is in line with a previous observation in individuals with pain. Vaegter and colleagues observed

reduced EIH and increased temporal summation after exercise in patients with primarily chronic LBP who had high pain sensitivity compared with patients with lower pain sensitivity (Vaegter et al. 2016). Of note, compared with previous studies investigating pain during physical activity in clinical populations (Wideman et al. 2014, Kuithan et al. 2019), the increase in clinical pain on a group level was only modest in this study, which was likely due to the fact that the physical activity was related to the legs and not directly to the back. Future studies in individuals with LBP should investigate associations between pain sensitivity and pain during physical activity in more back-related tasks. In addition, additional research investigating the possible scenario that high pain sensitivity is associated with the experience of more pain during exercise, which in turn results in less EIH/increased pain sensitivity afterwards as indicated by the present findings, is warranted, as this may subsequently facilitate inactivity.

4.2. Implications

In individuals with LBP, the response to exercise is less consistent compared with pain-free individuals, and reduced hypoalgesia or even hyperalgesia are commonly observed. In contrast to pain-free individuals where exercises appear to have larger hypoalgesic effects than non-painful exercises, [36], considerations of non-painful exercises may be useful in rehabilitation of individuals with painful conditions. In line with the results of the current study, Burrows and colleagues observed increases in pressure pain threshold after upper body but not lower body resistance exercise in individuals with knee osteoarthritis [17]. These findings suggest that the acute EIH response is impaired when exercises are painful or performed in painful areas, and that short-lasting hypoalgesia can be induced by exercises that do not increase clinical pain or by exercising non-painful muscles. However, an acute increase in pain after a single bout of exercise should not necessarily lead to avoidance of subsequent bouts of exercises as exercise may lead to many relevant physiological and mental benefits other than changes in pain.

4.3. Limitations

This cross-sectional study also has a number of weaknesses that could influence the interpretation of the results. First, as this was a study in a clinical setting no pain-free control group was included. Second, the changes in PPTs after walking were not compared with a non-exercise control condition and effects of habituation to the PPT assessments, as well as

regression to the mean, are not accounted for, however walking induces EIH compared with a control condition in pain-free individuals (Hviid et al. 2019). Third, the use of a 2-point absolute change in back pain NRS as a clinical relevant change in pain may be too simplistic as a meaningful change may vary depending on baseline score. However, as several participants reported a NRS score of zero at baseline, percentage or ratio was not a sensible approach. Fourth, most of the pain sensitivity measures were assessed at the legs and not the lower back due which is a limitation of the cuff algometry, and assessors were aware of the response to the walking task. Fifth, data was not collected on subjects' levels of habitual physical activity (Coriolano et al. 2015, Umeda et al. 2015) or expectations (Vaegter et al. 2020), which might influence pain responses to acute exercise. Sixth, as this study was exploratory, without randomization and manipulation, it does not allow for the study of mechanisms, and hypotheses based the current findings should be tested in future studies.

4.4. Conclusion

Individuals with LBP reporting pain flares in response to a 6 min walking task had impaired EIH after walking as well as facilitated temporal summation, and increased pain sensitivity, clinical pain and disability. These results may help to inform when individuals with LBP will have a beneficial effect of physical activity.

Author contributions

Henrik Bjarke Vaegter: Responsible for protocol design, data analysis, and preparation of manuscript.

Kristian Kjær Petersen: Responsible for setting up equipment for data collection.

Line Vandborg Sjodsholm, Pia Schou, and Michael Berg Andersen: Responsible for data collection.

Thomas Graven-Nielsen: Responsible for protocol design.

All authors discussed the results and commented on the manuscript.

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Figure legends:

Fig. 1: Illustration of the experimental procedure. Baseline pressure pain thresholds (cPPT), pain tolerance (cPTT) and temporal summation of pain (cTSP) was assessed with cuff algometry. Back pain intensity was reported using numerical rating scales (NRS) and manual pressure pain thresholds (PPT) at the back and calf assessed before and after walking was used to evaluate exercise-induced hypoalgesia.

Fig. 2: Mean (±95% CI, n = 96) Numerical Rating Scale (NRS) ratings of the low back pain intensity before and during the 6-minute walk test. Significantly different between Walk-Pain Index ≥ 2 and Walk-Pain Index < 2 (*, $P < 0.05$).

Fig. 3: Mean (+SEM, n = 96) change in pressure pain thresholds reflecting the exercise-induced-hypoalgesia effect (EIH-effect) at the lower back and calf after the 6-minute walk test in participants reporting an increase in Numerical Rating Scale (NRS) ratings of clinical back pain ≥ 2 during walking compared with participants reporting no or little increase in clinical pain. Significantly different between groups (*, $P < 0.05$).

Supplementary Fig. 1: Pain drawings from 88 participants (in 8 participants, pain drawings were blank).

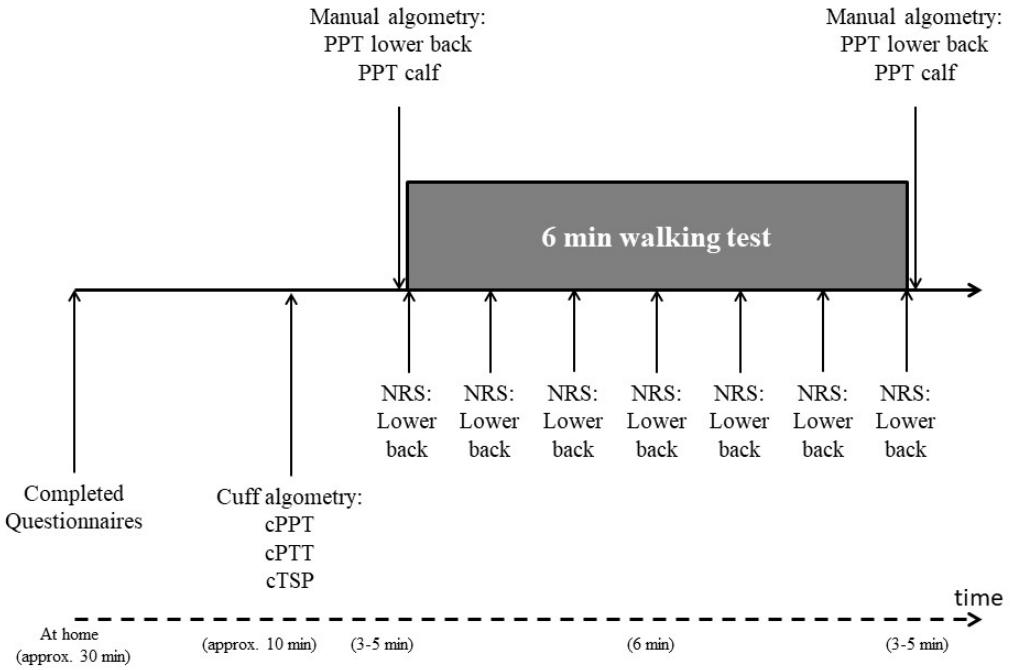
Table 1: Demographics, clinical pain manifestations and pain sensitivity before walking, walking distance, and the Walk-Pain Index for the total sample (n = 96), and for the two Walk-Pain index groups. Data presented as mean+-SD for normally distributed continuous variable, median (range) for non-normally distributed continuous variables, and count (%) for dichotomous variables. P-value based on t-test, Mann Whitney U test or Chi^2, and effect sizes for pain sensitivity measures and 6MWT distance reported as Hedges G. 'BMI*: Body Mass Index. 'NRS': Numerical Rating Scale. 'RMDQ': Roland Morris Disability Questionnaire. 'TSK': Tampa Scale of Kinesiophobia. 'PCS': Pain Catastrophizing Scale. 'PPT': Pressure Pain Threshold. 'cPPT': Cuff Pressure Pain Threshold. 'cPTT': Cuff Pressure pain Tolerance. 'cTSP': Cuff Pressure Temporal Summation of Pain.

Variable	**Total (n=96)**	**Walk-Pain Index ≥ 2 (n=27, 28.1%)**	**Walk-Pain Index < 2 (n=69, 71.9%)**	**P-value for group comparison**	**Effect size**
Female, n (%)	36 (37.5)	11 (40.7)	25 (36.2)	0.68	
Age (years)	47.0 (20 - 73)	47.0 (23 – 73)	47.0 (20 – 73)	0.91	0.04
BMI (kg/m^2)	26.5 (16.2 – 44.8)	27.2 (20.8 – 38.78)	26.3 (16.2 – 44.8)	0.36	0.26
Pain duration (days)	255 (91 – 6207)	256 (121 – 4019)	253 (91 – 6207)	0.32	0.11
Pain intensity (avg last 24 hours; NRS: 0-10)	4.0 (0 – 10)	6.0 (1 – 10)	3.0 (0 – 8)	<0.001	0.95
Radiating pain below the knee (%)	38 (39.6%)	11 (40.7%)	27 (39.1%)	0.17	
Any analgesic use, n (%)	55 (57.3%)	19 (70.4%)	36 (52.2%)	0.11	
Opioid use, n (%)	24 (25.0%)	7 (25.9%)	17 (24.6%)	0.90	
Tricyclic antidepressant use, n (%)	4 (4.2%)	1 (3.7%)	3 (4.3%)	0.89	
Anticonvulsant use, n (%)	6 (6.3%)	2 (7.4%)	4 (5.8%)	0.77	
NSAID use, n (%)	10 (10.4%)	5 (18.5%)	5 (7.2%)	0.10	
Paracetamol use, n (%)	46 (47.9%)	18 (66.7%)	28 (40.6%)	0.02	
Muscle relaxant use, n (%)	6 (6.3%)	1 (3.7%)	5 (7.2%)	0.52	
Disability (RMDQ: 0-100)	54.7 ± 22.1	63.0 ± 18.1	51.2 ± 22.8	0.01	0.54
Kinesiophobia (TSK17: 17-68, higher is worse)	37.4 ± 7.0	39.2 ± 8.3	36.6 ± 6.3	0.12	0.37
Pain Catastrophization (PCS: 0-52, higher is worse)	16.4 ± 10.9	18.8 ± 12.2	15.4 ± 10.3	0.17	0.31
PPT low back (kPa)	579 (149 – 1665)	450 (203 – 1368)	586 (149 – 1665)	0.56	0.10
PPT lower leg (kPa)	590 (181 – 1506)	581 (183 – 1416)	603 (181 – 1506)	0.90	0.08
cPPT (kPa)	27.2 (7.1 – 74.6)	24.5 (7.1 – 38.4)	29.2 (7.5 – 74.6)	0.03	0.58
cPTT (kPa)	52.9 (13.3 – 100)	46.9 (13.3 – 99.5)	55.0 (26.9 – 100)	0.09	0.44

cTSP (ratio)	1.3 (0.08 – 23.0)	1.6 (1.0 – 23.0)	1.2 (0.08 – 15.7)	0.007	0.35
6MWT distance (m)	499.4 ± 87.8	473.7 ± 77.2	509.4 ± 90.2	0.07	0.41
Pain intensity (before walking; NRS: 0-10)	1 (0-7)	2 (0-7)	1 (0-5)	0.051	0.52
Walk-Pain-Index	0.8 ± 1.6	2.9 ± 0.9	-0.04 ± 0.8	<0.001	3.3

Table 2: Final binary logistic regression model including factors associated with the Walk-Pain Index ≥2. 'NRS': Numerical Rating Scale. 'PPT': Pressure Pain Threshold. 'kPa': Kilo Pascal. 'cPPT': Cuff Pressure Pain Threshold. 'EIH': Exercise-Induced Hypoalgesia.

	B	**SE**	**Wald**	**df**	**P**	**Odds Ratio**	**95% CI for Odds Ratio**	
							Lower	Upper
Back pain intensity before walking (NRS: 0-10)	0.44	0.19	5.58	1	0.02	1.55	1.08	2.22
PPT lower leg (kPa)	0.003	0.001	7.89	1	0.005	1.003	1.001	1.006
cPPT (kPa)	-0.12	0.039	9.28	1	0.002	0.89	0.82	0.96
EIH response lower back (kPa)	-0.004	0.002	3.75	1	0.05	0.99	0.99	1.00
Constant	-0.42	0.94	0.20	1	0.65	0.66		



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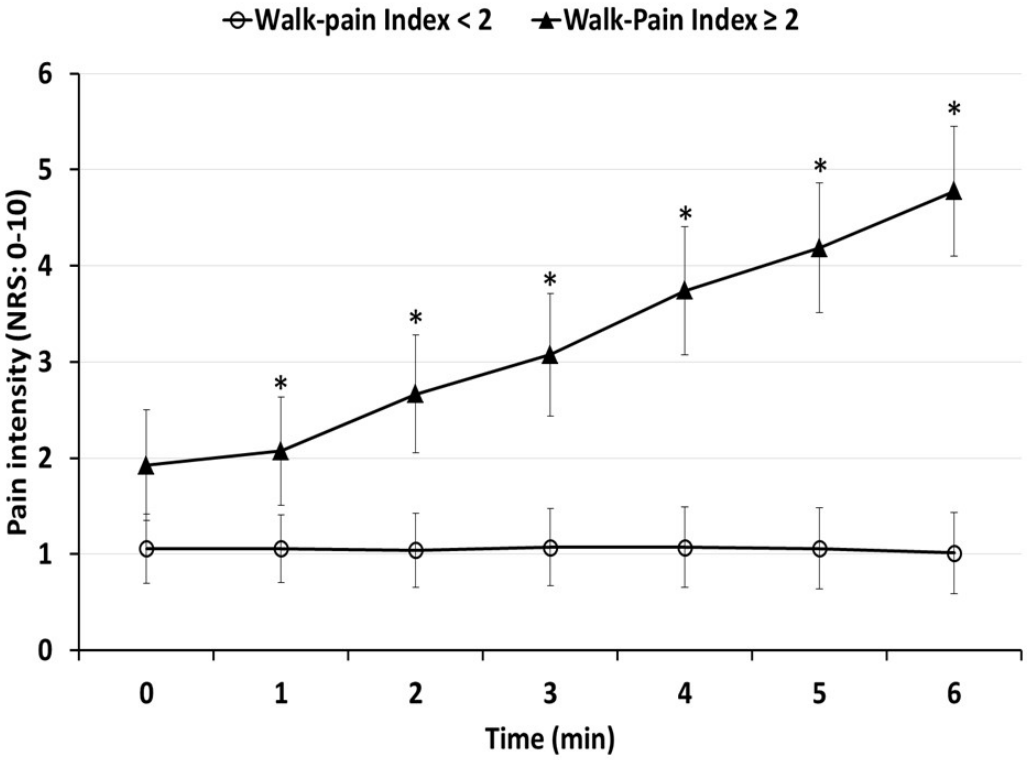

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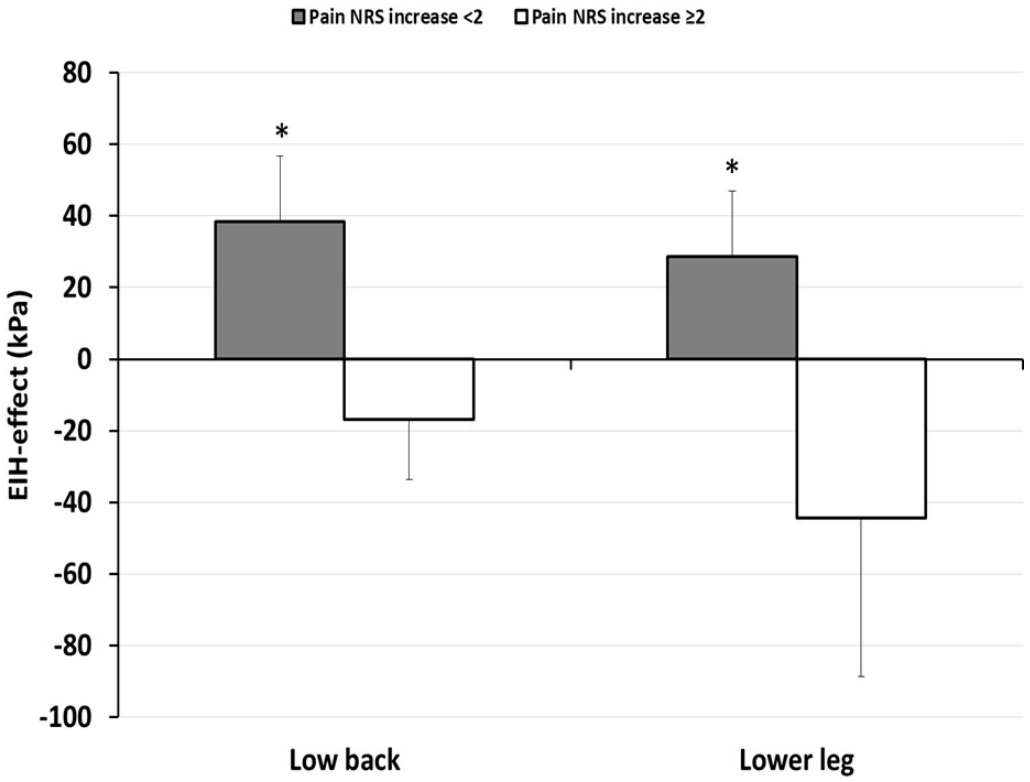

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