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1 **Pain trajectory and exercise-induced pain flares during 8 weeks of neuromuscular exercise in**
2 **individuals with knee and hip pain**

3

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24 Running title: "Pain trajectory in exercise"

1 **Abstract**

2

3 Objective: Patients considering or engaged in exercise as treatment may expect or experience
4 transient increases in joint pain, causing fear of exercise and influencing compliance. This study
5 investigated the pain trajectory during an 8-week neuromuscular exercise (NEMEX) program
6 together with acute exercise-induced pain flares in persons with knee or hip pain.

7

8 Design: Individuals above 35 years self-reporting persistent knee or hip pain for the past 3 months
9 were offered 8 weeks of supervised NEMEX, performed in groups twice weekly. The program
10 consisted of 11 exercises focusing on joint stability and neuromuscular control. Participants self-
11 reported joint pain on a 0 to 10 numerical rating scale (NRS) at baseline and 8-weeks follow-up.
12 NRS pain ratings were also collected before and immediately after every attended exercise session.

13

14 Results: Joint pain was reduced from baseline (NRS 3.6; 95% CI 3.2 to 4.1) to 8-weeks follow-up
15 (2.6; 95% CI 2.1 to 3.1), ($p < 0.01$). Pain decreased 0.04 NRS (95% CI 0.02 to 0.05, $p < 0.01$) on
16 average per exercise session and pre- to post-exercise pain decreased 0.04 NRS (95% CI 0.03 to
17 0.05, $p < 0.01$) on average per session, approaching no acute exercise induced pain in the last weeks.

18

19 Conclusion: This study found a clear decrease in size of acute exercise induced pain flares with
20 increasing number of exercise sessions. In parallel, pain ratings decreased over the 8 weeks exercise
21 period. Our findings provide helpful information for clinicians, which can be used to educate and
22 balance patient expectation when starting supervised neuromuscular exercise.

23

24 Keywords: neuromuscular exercise, pain measurements, joint pain, osteoarthritis

1 **Introduction**

2

3 Exercise is effective for relieving lower extremity joint pain [1, 2] and recommended as first-line
4 treatment in clinical guidelines for osteoarthritis (OA) treatment [3]. However, patients with lower
5 limb joint pain may experience increased pain during physical activity or exercise and may
6 therefore be hesitant to participate in exercise treatment [4]. Furthermore, joint pain may fluctuate
7 over the course of an exercise intervention period. Knowledge about the trajectory of joint pain
8 during an exercise treatment would be important knowledge for both clinicians and patients; as such
9 information could influence patients' compliance with the exercise therapy. Patients may be more
10 willing to accept transient increases in joint pain during exercise, if knowing what to expect.

11

12 There are no specific recommendations regarding type of exercise for treating musculoskeletal pain
13 such as OA. However, exercise programs that are supervised and have specific aims relief pain
14 more effectively than unsupervised or generic exercise programs [5]. Neuromuscular training, such
15 as the NEuroMuscular EXercise (NEMEX) program, has previously been proven feasible, well
16 tolerated and effective in relieving joint pain and improving function in different populations with
17 knee or hip pain [6-8]. The NEMEX program is an individualised and goal-based program focusing
18 on lower-limb alignment and functional stability during movement [7].

19 The study aimed to investigate the trajectory of joint pain during an 8 week neuromuscular exercise
20 program together with the acute pain flare evoked from each exercise session in middle-aged
21 individuals with knee or hip pain.

22

23 **Methods**

24

1 This study presents ancillary data to a randomized controlled trial (RCT) investigating context
2 effects in exercise (ClinicalTrials.gov identifier NCT02043613). As the current study investigates
3 pain trajectory in relation to exercise, only the exercise groups from the RCT have been included.
4 Ethical approval was obtained by The Regional Scientific Ethical Committee for Southern Denmark
5 (S-20130130). All participants gave their written informed consent.
6 Participants were recruited through newspaper advertisements, social media and through referrals
7 from general practitioners or the orthopaedic department at Odense University Hospital. Eligibility
8 criteria: men and women aged 35 years or older, self-reporting persistent knee or hip pain for the
9 past 3 months, willingness and ability to participate in exercise program twice weekly. . Exclusion
10 criteria: co-morbidities prohibiting exercise, not reading or understanding Danish or already
11 attending structured supervised exercise or other treatment aimed to relieve joint pain. Participants
12 were examined at baseline to assess clinical signs of knee or hip OA, respectively[9] although this
13 was not a specific entry criteria.

14

15 *Neuromuscular exercise*

16

17 All participants were offered 8 weeks of NEMEX. The NEMEX program is based on
18 biomechanical and neuromuscular principles aiming to improve sensorimotor control and achieve
19 functional stability [7]. The exercise program is structured with a 5-10 min warm-up on an
20 ergometer bicycle followed by 11 specific exercises focusing on core stability, postural function and
21 orientation, lower limb muscle strength and functional tasks [7]. All exercises were performed with
22 2-3 sets with 10-15 repetitions. Every exercise had four levels and participants progressed when
23 performing an exercise at its current level with good movement quality and sufficient volume.
24 Sessions were performed in groups, lasting one hour and were supervised by certified instructors.

1 Participant's attendance was registered at each exercise session. Good compliance was defined as
2 attending 75% or more of the exercise sessions.

3

4 *Pain measures and registration*

5

6 Self-reported pain was assessed for the index joint using an 11-point Numerical Rating Scale (NRS)
7 ranging from 0 (no pain) to 10 (worst imaginable pain) [10]. Participants rated their pain for the
8 index joint at the baseline visit and at the 8-week follow-up, when the exercise period was
9 completed. Additionally, participants rated joint pain in an exercise diary before and after every
10 exercise session they attended. Pain was accepted during exercise and was used to monitor and
11 guide progression and regression in exercise levels during the 8-week exercise period. Pain from 0-
12 2 was considered safe, from 3-5 was acceptable and pain above 5 was categorized as high-risk. If
13 participants were reporting pain within the high-risk range, exercise volume or level was reduced to
14 suit the individual at the next exercise session [7].

15

16 *Statistics*

17

18 A Students paired t-test was used to compare difference in joint pain from baseline to 8 weeks
19 follow-up. To check if compliance had any effect on the pain relief from exercise an unpaired
20 Student's t-test was used to compare change in pain from baseline to follow-up between the
21 compliant and non-compliant groups.

22 Pain ratings from the 16 exercise session were used in the pain trajectory analysis. Linear regression
23 analysis was performed to investigate pain trajectory over time, using the group mean pre-exercise
24 pain ratings from each individual exercise session as dependent variable and time as independent

1 variable. Similarly, linear regression was performed to investigate the acute pain flare evoked by the
2 individual exercise session (i.e. group mean difference in pain between before and after each of the
3 16 exercise sessions) (dependent variable) during the exercise period (independent variable). P-
4 values of <0.05 were considered statistically significant.

5

6 **Results**

7

8 In total 82 participants were offered the NEMEX program in the RCT trial; 3 participants never
9 started the exercise program and 1 exercise diary was lost. These 4 participants were excluded from
10 this study. The remaining 78 participants (46 women) had a mean age at baseline of 58.6 years
11 (standard deviation 10.4) and a mean Body Mass Index (BMI) of 28.1 (5.3). Forty-nine participants
12 reported the knee as the primary site of pain. Of these 36 had clinically diagnosed knee OA [9]. The
13 hip was the primary site of pain in 29 participants, of which 10 had clinically diagnosed OA [9].

14 One participant was lost to follow-up.

15 Joint pain was reduced by 1.0 NRS (95% CI 0.5 to 1.6) from 3.6 at baseline (95% CI 3.2 to 4.1) to
16 2.6 NRS (95% CI 2.1 to 3.1) at 8 weeks follow-up ($p<0.01$), (Figure 1). When dividing the group
17 into compliant ($n=52$) and non-compliant ($n=25$), there was no significant difference in pain relief
18 between the groups ($p=0.09$). The compliant group had a pain reduction of 1.3 NRS (95% CI 0.8 to
19 2.0) and the non-compliant had a reduction of 0.4 NRS (95% CI -0.7 to 1.6). No differences were
20 found in age, sex, BMI or pain at baseline between the compliant and non-compliant groups.

21

22 (Insert Figure 1)

23

1 In total 98.5% of all possible pre-exercise pain ratings were available in the dataset. Number of
2 participants contributing with data at the different time-points is reported in Figure 1. A clear
3 relationship was observed between time (i.e. increasing number of exercise sessions) and pre-
4 exercise pain. The pain level decreased over time with 0.04 NRS per exercise session (95% CI 0.02
5 to 0.05, p-value<0.01). Time (i.e. increasing number of exercise sessions) explained 64 % ($r^2=0.64$
6 $p=0.00$) of the change in pain level (Figure 1).

7

8 (Insert Figure 2)

9

10 In total 97.2% of all possible pre- to post-session pain ratings were available. The number of
11 participants contributing with data at the different time-points is reported in Figure 2. The acute
12 pain flare evoked by an exercise session decreased over time by 0.04 NRS per session (95% CI:
13 0.03 to 0.05, p-value<0.01). Time (i.e. increasing number of exercise sessions) explained 84 %
14 ($r^2=0.84$, $p=0.00$) of the variation in size of acute pain flare (Figure 2).

15

16 **Discussion**

17

18 Patients with knee or hip pain reported a pain reduction of 1.0 NRS from the baseline visit to 8
19 weeks follow-up of twice weekly, supervised neuromuscular exercise. The pain trajectory decreased
20 linearly over the 8-week exercise period. Similarly, the acute pain flare from an exercise session
21 gradually decreased over time and approached no flare at all during the last weeks of the 8-week
22 period.

23

1 The 1 point NRS pain reduction from baseline to 8-week follow-up corresponds to an effect size of
2 0.48 (95% CI: 0.16 to 0.80), which is in line with effect sizes reported in recent meta-analyses on
3 exercise as treatment for knee and hip OA [1, 2]. The effect size is also similar to what has been
4 reported previously in a study investigating pain relief from neuromuscular exercise in patients with
5 lower limb OA awaiting total joint replacement[8]. The minimal clinical important improvement
6 has been reported to be 1 NRS-point (corresponding a 15% change) in a population with chronic
7 musculoskeletal pain [11] and in patients with painful knee or hip OA [12]. However, another study
8 including patients with a variety of conditions such as diabetic peripheral neuropathy and post-
9 herpatic neuralgia, OA, chronic low back pain and fibromyalgia, reported a 2-point reduction (30%
10 change) as a clinical important improvement in NRS pain [13]. The 1.0 NRS-point (95% CI 0.5 to
11 1.7) improvement observed from baseline to 8-weeks follow-up in this study corresponded to a 27%
12 improvement in pain and an effect size of 0.48 which we consider a clinical important improvement
13 given the population in this study.

14 To our knowledge, this is the first study to investigate the pain trajectory in participants attending
15 neuromuscular exercise therapy for knee and hip pain. A major strength of this study is the high
16 resolution of pain ratings, including pain ratings not only at baseline and follow-up but also from all
17 16 exercise sessions. Pain ratings from before and after exercise have previously been reported,
18 however only as a median for all exercise sessions during an exercise period, rather than separately
19 for each exercise session. These studies found no differences in pain before and after exercise for
20 patients with severe knee or hip OA awaiting total joint replacement [7, 14].

21
22 Information that regular physical activity and individualized exercise can reduce joint pain and
23 improve physical function has the highest priority, when informing patients with knee or hip OA
24 about their disease [15]. However, patients may feel hesitant to start exercise because of fear of

1 increased joint pain as a result of exercise [4]. The average pain flares within the first 2 weeks was
2 0.79 NRS for the non-compliant group, compared to 0.43 NRS in the compliant group, ($p=0.046$).
3 This difference in initial pain flares may have affected compliance. This study provides detailed
4 information on the magnitude and direction of pain relief, which can be expected from
5 neuromuscular exercise for patients with knee and hip pain. This information is important for
6 clinicians, who can inform patients that small transient pain flares from exercise should be expected
7 starting exercise treatment; however the pain flares diminish over time and should not be expected
8 with exercise after 6-8 weeks. This may motivate patients to start and be compliant with exercise
9 treatment in spite of initial pain flares.

10 It is a limitation to this study that a comparison of pain trajectories for exercising participants and
11 passive controls is not possible, as the waiting-list group in the RCT did not register pain during the
12 8 weeks. However, there was no difference in pain at baseline and follow-up for the RCT's waiting-
13 list group ($p=0.55$). It is also a limitation that all participants did not undertake all 16 exercise
14 sessions. It cannot be eliminated that some participants stopped early because of pain. Similarly, the
15 number of participants included in the regression analyses at the specific exercise sessions
16 decreased with time (see figure 1 and 2). Both factors could create a selection bias potentially
17 overestimating the decrease in acute pain flare with increased number of exercise sessions.

18 However, all participants took part in the follow-up examination where a pain decrease was seen,
19 thereby making this scenario less likely. Also, persisting self-reported pain was an inclusion
20 criterion, but no predefined cut-off for NRS pain was used. Consequently, participants with both
21 very little and very severe joint pain could be included in the study. Mean pain at baseline
22 corresponded to mild to moderate pain.

23

1 In conclusion, this study found a clear decrease in size of acute exercise induced pain flares with
2 increasing number of exercise sessions. In parallel, pain ratings gradually decreased over the 8
3 weeks exercise period. This study provides detailed information about the pain trajectory during
4 exercise treatment. This information is helpful for clinicians as it can help educate and balance
5 patients' expectations when starting supervised neuromuscular exercise as treatment for knee and
6 hip pain.

7

1 **Acknowledgements**

2

3 **Contributions**

4 LFS, ER and JBT were all involved in the design of the study. All authors contributed to drafting
5 the manuscript or revising it. All authors read, commented and approved the manuscripts for
6 publication. LFS is the trial manager and responsible for coordinating and conducting the study.

7 SJB supervised the exercise intervention, performed data collection and data entry. LFS screened,
8 included and performed all baseline and follow-up testing.

9

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14 The funding sources had no role in the design of this study and did not have any role during its
15 execution, analyses, interpretation of the data, or decision to submit results.

16

17 **Competing interests**

18 The authors have no competing interests to declare.

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