# Chapter 9

Neuromuscular mechanisms of exercise therapy

in knee osteoarthritis

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## Abstract

*Objectives.* Although exercise therapy is an effective treatment for reducing pain and activity limitations in knee osteoarthritis (OA), underlying mechanisms are unclear. The aim of this study is to evaluate whether improvement in upper leg muscle strength and knee joint proprioception are longitudinally associated with reductions in pain and activity limitations in patients with knee OA treated with exercise therapy.

*Design.* Secondary analyses from a randomized controlled trial on exercise therapy.

*Setting.* Outpatient rehabilitation center.

*Participants.* One hundred fifty nine participants diagnosed with knee OA.

*Intervention.* Two supervised exercise programs of 12 weeks.

*Main outcome measures.* Changes in pain and in self-reported and observed activity limitations during the 38-week follow-up period.

*Results.* Improved upper leg muscle strength was significantly associated ($P<0.001$) with reductions in pain (B (95% CI)= -2.5 (-3.7, -1.4) and in self-reported (B (95% CI)= -8.8 (-13.4, 4.2) and observed activity limitations (B (95% CI)= -1.7 (-2.4, 1.0)). Improved knee proprioception was not related with better outcome of exercise therapy.

*Conclusions.* This study provides evidence that upper leg muscle strengthening is one of the mechanisms underlying the beneficial effects of exercise therapy in knee OA.

## Introduction

Although numerous studies demonstrated exercise therapy to be an effective intervention in reducing pain and activity limitations in patients with knee osteoarthritis (OA) (1-3), underlying mechanisms of these effects are unclear. Various possible mechanisms have been suggested, including neuromuscular, peri-articular, intra-articular, psychosocial, and general health-related mechanisms (4). As exercise programs for patients with knee OA primarily focus on muscle strengthening (5-8), the neuromuscular mechanism might be the most important one (9). As far as we know, 5 studies in knee OA focused on direct associations between change in muscle strength (10-14) or proprioception (12) following exercise therapy andtreatment outcome. These studies provided conflicting results and 4 of the 5 studies only reported unadjusted correlation coefficients. Therefore, more high-quality studies are needed to understand underlying (neuromuscular) mechanisms of exercise-induced effects (9).

We recently compared 2 exercise programs in a randomized controlled trial in 159 patients with knee OA suffering from instability of the knee joint (15). In this trial, both the experimental and control program focused on muscle strengthening and performance of daily activities, but only in the experimental program, additional knee joint stabilization training was provided. Large effects were found in both exercise groups, with within-group effect sizes of 0.9 for NRS pain and 0.7-0.8 for WOMAC physical function, but without significant differences between groups. In addition, both groups showed similarly large improvements in upper leg muscle strength and knee joint proprioception.

The aim of the study is to evaluate whether improvement in upper leg muscle strength and knee joint proprioception are longitudinally associated with reductions in pain and activity limitations during a 38-week period in patients with knee OA treated with exercise therapy.

## Methods

### *Design*

We previously conducted a single-blinded, randomized, controlled trial (STABILITY-trial) (15) on the effectiveness of 2 exercise programs in 159 knee OA patients with instability of the knee joint. Participants were measured at baseline and at 6-week (mid-treatment), 12-week (directly post-treatment) and 38-week follow-up (FU) (6-months post-treatment), by a single assessor, who was blinded for group assignment.

For the present study, we performed secondary analyses of data from this trial. As both groups demonstrated similar improvements in muscle strength, proprioception and

outcome measures, we have combined data from the 2 groups and adjusted for treatment allocation.

### *Setting and Participants*

The study was conducted in an outpatient rehabilitation center (Reade, center for rehabilitation and rheumatology, Amsterdam, the Netherlands) and approved by the local Medical Ethical Review Board (Reade/Slotervaart Hospital). Participants were recruited from February 2009 to March 2011 through advertisements in local and regional newspapers and from regular referral from rheumatologists or rehabilitation physicians from our rehabilitation center. All participants provided written informed consent.

Inclusion criteria were: (i) diagnosis of knee OA according to the clinical ACR criteria (16), (ii) age between 40 and 75 years, and (iii) presence of self-reported knee instability (i.e., at least 1 episode of buckling, shifting or giving way of knee in past 3 months, as reported by the patient (17)) and/or biomechanically assessed knee instability (i.e., upper leg muscle weakness in combination with proprioceptive inaccuracy and/or high varus-valgus laxity of the knee joint, according to cut-off points based on previous data (15;18;19)).

Exclusion criteria were: (i) other forms of arthritis than OA (e.g., crystal arthropathy, septic arthritis, spondylarthropathy) identified by radiograph and/or blood- and urine samples, (ii) presence of co-morbidity resulting in severe activity limitations, (iii) total knee arthroplasty (TKA) or TKA in near future, (iv) severe knee pain (i.e., numeric rating scale [NRS] >8), (v) insufficient comprehension of Dutch language, (vi) inability to be scheduled for therapy, and vii) unwillingness to give informed consent (15).

### *Experimental and control intervention*

The experimental and control intervention comprised a supervised exercise program of 12 weeks, with 2 sessions of 60 minutes weekly, in groups of approximately 8 participants, and a home-exercise program for 5 days weekly (on non-treatment days only). Each group was supervised by 2 physical therapists, who were specifically trained to supervise only one of both treatments. Training intensity, which gradually increased during the program, and amount of attention from physical therapists were similar in both groups (15). For a detailed description of the exercise protocol, see Knoop et al (15).

In summary, the experimental program consisted of 3 phases: first phase (week 1-4) targeting knee joint stabilization, second phase (week 5-8) targeting muscle strength (i.e., muscle endurance) in addition to knee joint stabilization, and third phase (week 9-12) targeting performance of daily activities, in addition to knee joint stabilization and muscle strength (i.e., maximum muscle power). Knee joint stabilization training consisted of

instructions and feedback from physical therapists on knee position and motion plus specific exercises in which patients were challenged to maintain adequate knee position.

The <u>control</u> program consisted of only 2 phases: first phase (week 1-8) targeting muscle strength (i.e., muscle endurance), and second phase (week 9-12) targeting performance of daily activities in addition to muscle strength (i.e., maximum muscle power). Physical therapists in this group were not allowed to give any instructions or feedback on knee position and motion.

### Outcomes

*Outcome measures. Pain.* Knee pain severity was assessed on a numeric rating scale (NRS 0-10; 0=no pain; 10=worst imaginable pain) by the question 'What was your average knee pain during the last week?' (20).

*Activity limitations.* Self-reported activity limitations were assessed by the Dutch translation of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), subscale physical function, consisting of 17 items, with a total score ranging from 0 (no limitations) to 68 (maximally limited) (21;22). The Get Up and Go (GUG) test, a performance-based test in which a patient is asked to rise up from a chair and walk as fast as possible over a distance of 15 meters (23), was used as a measure for observed activity limitations.

*Determinants. Upper leg muscle strength.* Muscle strength was assessed for both knee flexion (hamstrings strength) and knee extension (quadriceps strength) using an isokinetic dynamometer (EnKnee, Enraf-Nonius, Rotterdam, the Netherlands), with motion velocity of $60^o$/second (18). Each leg was measured 3 times per direction. Mean muscle strength per leg (in Nm) was calculated to obtain a measure of overall upper leg muscle strength (quadriceps and hamstrings strength) and subsequently divided by body weight. This normalized score (in Nm/kg) was used for the analyses.

*Knee joint proprioception.* Proprioceptive accuracy of the knee joint was assessed by a threshold detection test of joint motion ($0.3^o$/second) by measuring the difference between actual onset of passive motion and the subject's detection of motion (in degrees) (18). Visual and auditory stimuli, mechanical vibrations, cutaneous tension and pressure cues were minimized. Each knee was measured 3 times. The mean score was used for analyses.

*Potential confounders.* Sex, age, duration of knee symptoms, use of pain medication and NRS pain severity were obtained by questionnaire. Body mass index (weight/height²) and knee malalignment (i.e., $\geq10^o$ varus or valgus alignment of knee joint in standing position) were assessed by physical examination. Weightbearing, anteroposterior radiographs following Buckland-Wright protocol (24) were graded for OA severity according

to Kellgren/Lawrence grading system (25) by 2 experienced assessors. The intrarater reliability ICC for K/L grade was 0.89. In addition, the number of attended treatment sessions was considered a potential confounder.


*Index knee.* For knee-specific variables, we used data from 1 knee per person (index knee). This index knee was determined in the following order: (i) the knee with a clinical diagnosis of knee OA according to ACR-criteria; (ii) the knee that fulfilled criteria for 'biomechanically assessed knee instability' (described in inclusion-criteria), in case both knees were diagnosed with clinical knee OA; (iii) the knee in which knee instability had been reported by the patient, in case both knees or no knee fulfilled criteria for 'biomechanically assessed knee instability'; (iv) randomly chosen knee, in case of self-reported instability in both knees or no knee.


### Statistical analysis

Data were analyzed using PASW Statistics 18.0 (SPSS Inc., Chicago, IL). Change scores in outcome measures and determinants were calculated by subtracting baseline scores from 6-week FU, 6-week FU from 12-week FU, and 12-week FU from 38-week FU.

Generalized Estimating Equation (GEE) was used to estimate longitudinal associations, in which scores from multiple time point can be analyzed at once, with adjustment for dependency of repeated measures within persons. Independent variables were change scores in upper leg muscle strength and knee joint proprioception. Dependent variables were change scores in outcome measures. Because change scores between 4 subsequent measurements were used for analyses, an independent correlation matrix was chosen (26). Prior to the primary analyses, interactions between group assignment and the independent variables were analyzed to determine whether the 2 exercise groups can be combined, or stratified analyses are necessary. As no interactions were found, analyses could be performed for the total study group. Then, longitudinal associations were estimated. Firstly, the independent variables were analyzed separately, with adjustment only for baseline value of the outcome measure and treatment allocation. Secondly, the other independent variable and any relevant confounder (i.e., a variable that changes the regression coefficient of the independent variable ≥10% (27)) were added to the model. Thirdly, interactions between time and the independent variable were analyzed to see whether associations differed between time periods. Statistical significance was accepted at *P* values of less than 0.05.

## Results

From a total of 159 participants, 5 participants were lost to follow-up. Therefore, 154 participants were analyzed in the present study. From 2 persons who discontinued the treatment due to health conditions (not related to knee OA), only data from the first 6 weeks were used. From 4 other persons who underwent knee surgery post-treatment, only data from the first 12 weeks were used.

Baseline characteristics are shown in Table 1. Participants attended on average 21 out of 24 treatment sessions and performed home exercises for on average 4 days a week. Table 2 shows the course of outcome measures and determinants during 38-week study period. Over the total study period, improvements were found of on average 34%, 30% and 8% for NRS pain, WOMAC physical function and GUG-test, respectively, and 23% and 36% for upper leg muscle strength and knee joint proprioception, respectively, which were all statistically significant compared to baseline.

Table 3 shows the results from longitudinal regression analyses. Improvement in upper leg muscle strength during the 38-week study period was significantly associated with improvement in all 3 outcome measures ($P<0.001$ for all). Change in muscle strength explained 7%, 6%, and 12% of the total variance of change in NRS pain, WOMAC physical function, and GUG-test, respectively. In additional analyses, in which quadriceps and hamstrings muscle strength were analyzed separately, improvement in each muscle group was significantly associated with all 3 outcome measures again. Improvement in knee joint proprioception was not associated with any outcome measure. Similar results for both muscle strength and proprioception were found for other performance-based tests (i.e., stair climbing test and stair descending test; data not shown).

**Table 1**. Baseline characteristics

| | |
|---|---|
| Age (in years), mean ± SD | 61.9 ± 7.1 |
| Sex, n (%) female | 97 (61) |
| Duration of knee symptoms (in years), mean ± SD | 10.6 ± 9.3 |
| Body mass index (kg/m$^2$), mean ± SD | 29.0 ± 4.6 |
| Radiographic severity of knee OA*: | |
|     K/L score 0/1, n (%) | 56 (35) |
|     K/L score 2, n (%) | 44 (28) |
|     K/L score 3, n (%) | 41 (26) |
|     K/L score 4, n (%) | 18 (11) |
| Use of pain medication (including NSAIDs), n (%) | 72 (45) |
| Knee joint malalignment*, n (%) | 42 (26) |

SD=standard deviation; K/L=Kellgren/Lawrence; NSAIDs=non-steroidal anti-inflammatory drug; * data from index knee.

**Table 2**. Course of pain, activity limitations, upper leg muscle strength and knee joint proprioception during 38-week follow-up period

|  | Baseline (mean ± SD) | 6-wk FU (mean ± SD) | 12-wk FU (mean ± SD) | 38-wk FU (mean ± SD) |
|---|---|---|---|---|
| Pain (NRS, 0-10) | 5.0 ± 2.1 | 3.8 ± 2.0* | 3.0 ± 2.0*† | 3.2 ± 2.4* |
| Self-reported activity limitations (WOMAC, physical function, 0-68) | 26.2 ± 12.2 | 21.6 ± 11.0* | 18.0 ± 11.2*† | 18.3 ± 12.9* |
| Observed activity limitations (GUG test, seconds) | 10.7 ± 2.2 | 10.1 ± 2.1* | 9.9 ± 1.8*‡ | 9.9 ± 1.8* |
| Upper leg muscle strength (Nm/kg) | 0.84 ± 0.39 | 0.93 ± 0.37* | 1.00 ± 0.37*† | 1.03 ± 0.38*‡ |
| Knee joint proprioception (degrees) | 3.2 ± 2.4 | 2.5 ± 1.8* | 2.2 ± 1.7*‡ | 2.1 ± 1.4* |

SD=standard deviation; NRS=numeric rating scale; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index; GUG=Get Up and Go; * significantly different (*P*<0.001) from score at baseline; † significantly different (*P*<0.001) from score at previous time-point; ‡ significantly different (*P*<0.05) from score at previous time-point.

**Table 3**. Longitudinal associations between change in outcome measures and change in upper leg muscle strength and knee joint proprioception during 38-week follow-up period

|  | ΔNRS, pain severity (0-10) | | | ΔWOMAC physical function (0-68) | | | ΔGet Up and Go-test (seconds) | | |
|---|---|---|---|---|---|---|---|---|---|
|  | B (95% CI) | β | *P* | B (95% CI) | β | *P* | B (95% CI) | β | *P* |
| ΔMuscle strength (Nm/kg) | | | | | | | | | |
| Upper leg muscle strength | | | | | | | | | |
| model 1 | -2.5 (-3.7, -1.4) | -0.21 | <0.001 | -9.0 (-13.4, -4.5) | -0.18 | <0.001 | -1.7 (-2.4, -1.0) | -0.26 | <0.001 |
| model 2 | -2.5 (-3.7, -1.4) | -0.21 | <0.001 | -8.8 (-13.4, -4.2) | -0.18 | <0.001 | -1.7 (-2.4, -1.0) | -0.25 | <0.001 |
| Quadriceps muscle strength only | | | | | | | | | |
| model 1 | -1.3 (-2.1, -0.6) | -0.16 | <0.001 | -5.0 (-8.3, -1.9) | -0.15 | 0.002 | -0.9 (-1.4, -0.5) | -0.20 | <0.001 |
| model 2 | -1.3 (-2.1, -0.6) | -0.16 | 0.001 | -5.0 (-8.2, -1.8) | -0.15 | 0.002 | -0.8 (-1.2, -0.4) | -0.18 | <0.001 |
| Hamstrings muscle strength only | | | | | | | | | |
| model 1 | -2.8 (-3.9, -1.6) | -0.20 | <0.001 | -9.0 (-14.1, -4.0) | -0.16 | <0.001 | -1.8 (-2.7, -0.9) | -0.25 | <0.001 |
| model 2 | -2.7 (-3.9, -1.6) | -0.20 | <0.001 | -8.8 (-14.0, -3.6) | -0.16 | 0.001 | -1.8 (-2.6, -0.9) | -0.24 | <0.001 |
| ΔKnee joint proprioception (degrees) | | | | | | | | | |
| model 1 | 0.04 (-0.09, 0.18) | 0.03 | 0.51 | 0.30 (-0.26, 0.86) | 0.05 | 0.29 | 0.08 (0.00, 0.15) | 0.10 | 0.06 |
| model 2 | 0.02 (-0.11, 0.15) | 0.02 | 0.74 | 0.25 (-0.32, 0.82) | 0.04 | 0.43 | 0.06 (-0.02, 0.14) | 0.08 | 0.12 |

Δ=change; β=(B*standard deviation of independent variable)/standard deviation of outcome measure; NRS=numeric rating scale; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.
Model 1: adjusted for group assignment and baseline score of outcome measure.
Model 2: additionally adjusted for any relevant confounder and change in knee joint proprioception (in analysis of muscle strength) or change in upper leg muscle strength (in analysis of proprioception).

We found significant interactions between time and improved upper leg muscle strength with respect to reduced pain (*P*=0.03) and self-reported activity limitations (*P*=0.01). These interactions were indicative for stronger associations in the post-treatment period compared to the time-periods during treatment.

## Discussion

In this study, we demonstrated direct, longitudinal associations of improvement in upper leg muscle strength with reductions in pain and activity limitations following exercise therapy. Improvement in knee joint proprioception was not associated with any outcome measure. Although exercise therapy is an effective treatment in knee OA, underlying mechanisms of this effect have not been clarified yet (4). Our study provides evidence that upper leg muscle strengthening is one of the mechanisms underlying the beneficial effects of exercise therapy.

Although the effectiveness of strength training in knee OA is widely recognized, the exact pathway by which muscle strengthening would result in reduced pain and activity limitations is controversial. Upper leg muscle strengthening could theoretically result in lower knee loads with subsequent pain relief (based on the shock-attenuating capacity of muscles (28)), but also in higher knee loads (due to higher compression forces (29)). In a study by Thorstensson et al (30), a reduction in knee loading (i.e., peak knee adduction moment) during one-leg-rise, but not during walking, was reported after an 8-week exercise program. In several other studies, no relation was found between (increased) muscle strength and knee loading (31-34). An alternative, plausible explanation for an effect of muscle strengthening on pain relief and improved physical functioning could be a direct effect on the performance of daily activities. Stronger muscles enable a person to perform physical activities like walking and stair climbing with less effort. Such an improvement in daily functioning through muscle strengthening may also lead to pain relief via changes in psychosocial factors (i.e., reduced depression (35), improved self-efficacy (36), and less avoidance of activities (37)), and in general health (38).

The direct association between improved upper leg muscle strength and outcome of exercise therapy is in line with 3 previous studies (10-12). Furthermore, in a fourth study (14), the association between improvement in quadriceps strength and treatment response was of borderline significance (*P*=0.06), which can be attributed to the short duration (6-8 weeks) and low frequency (1 session weekly) of the intervention, resulting in only minimal improvement in strength. Opposite to the previous studies, we also included hamstrings strength in the strength measure, revealing that not only quadriceps strengthening but also hamstrings strengthening is associated with outcome of exercise therapy. This finding emphasizes that exercises not only need to target the quadriceps muscles, but also the hamstrings muscles. Surprisingly, we found stronger associations between improved upper

leg muscle strength and reduced pain and activity limitations in the post-treatment period compared to time-periods during treatment. This could imply that some effects of exercise occur at a later stage (i.e., post-treatment). Our study group was found to be highly adherent (i.e., 78% of the participants continued exercising after ending the exercise program), which may have played an important role in these stronger associations post-treatment. We showed that larger improvement in muscle strength is related to larger reductions in pain and activity limitations. Therefore, a gradual increase towards maximal intensity of the exercises may need to be pursued. In future studies, exercise programs with higher intensity levels need to be evaluated on effectiveness and safety.

Unexpectedly, we did not find evidence for an important role of proprioception in outcome of exercise therapy. Despite an improvement of 36% in proprioceptive accuracy on average, this improvement was not associated with any outcome measure. This suggests that exercise-induced effects are mainly driven through change in muscle strength. Another explanation could be that our measure of knee joint proprioception may not be a valid test. We used a threshold to detection of passive joint motion test in a non-weight bearing position, of which the relation with proprioceptive accuracy that is necessary for functional activities may be questionable. A study in 38 knee OA patients following an exercise program did find a significant association between change in knee joint proprioception (using an active joint reposition test) and change in pain (12). Remarkably, knee joint proprioception did not change on average in this study. Future studies have to unravel whether improved proprioception plays a role in exercise-induced effects or not.

We found that change in muscle strength explains 6 to 12% of the beneficial effects of exercise therapy. Therefore, other mechanisms play a substantial role as well. There is some evidence that exercise can positively influence cartilage quality (39) and inflammation (40). Furthermore, exercise is likely to have effect on general health-related components as aerobic fitness, comorbidities and general well-being, thereby partly explaining treatment outcome (4). Future research should focus on each of these potential pathways, as more insight in working mechanisms is useful to optimize effectiveness of exercise therapy in knee OA.

Strengths of the present study are a large knee OA cohort (*n*=159), high adherence of the participants, and use of data from multiple time-points, enabling us to determine longitudinal associations during the entire 38-week study period. Some limitations of the study design need to be acknowledged as well. Firstly, we used data from a cohort treated with exercise therapy while underlying mechanisms of exercise-induced effects are ideally determined by analyzing effect modification by group ('exercise' vs. 'no exercise'). However, in absence of a control group, estimating direct associations by longitudinal analysis is the best alternative for our study purpose. Secondly, we specifically included patients with knee OA suffering from instability of the knee joint (i.e., biomechanically assessed and/or self-

reported), therefore our results may only be representative for this subgroup. Thirdly, we assume that improved muscle strength resulted in reduced pain and activity limitations. However, the direction of this association may also be the opposite way (i.e., pain relief leading to improved muscle strength).

In conclusion, this study provides evidence that upper leg muscle strengthening (of both quadriceps and hamstrings muscles) is one of the mechanisms underlying the beneficial effects of exercise therapy in knee OA. Improved knee joint proprioception was not found to be related with outcome of exercise therapy.

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