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Quadriceps or hip exercises for patellofemoral pain? A randomized controlled equivalence trial

Rudi Hansen[1], Christoffer Brushøj[2,] Michael Skovdal Rathleff[3,4], Stig Peter Magnusson[2,5], Marius Henriksen[6]

1. Department of Physical and Occupational Therapy, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark
2. Institute of Sports Medicine Copenhagen, Department of Orthopedic Surgery, Copenhagen University Hospital – Bispebjerg and Frederiksberg, Copenhagen, Denmark
3. Department of Health Science and Technology, Aalborg University, Aalborg, Denmark.
4. Center for General Practice at Aalborg University, Aalborg, Denmark.
5. Center for Healthy Aging, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
6. The Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark

Corresponding author: Rudi Hansen, Department of Physical and Occupational Therapy, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark.
Email: rudi.hansen@regionh.dk
Word count: 3827

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ABSTRACT

Objective: To assess effectiveness equivalence between two commonly prescribed 12-week exercise programs targeting either the quadriceps or the hip muscles in patients with patellofemoral pain (PFP).

Methods: This randomized controlled equivalence trial included patients with a clinical diagnosis of PFP. Participants were randomly assigned to either a 12-week quadriceps-focused (QE) or a hip-focused (HE) exercise program. The primary outcome was the change in Anterior Knee Pain Scale (AKPS) (0-100) from baseline to 12-week follow-up. Prespecified equivalence margins of ±8 points on the AKPS were chosen to demonstrate comparable effectiveness. Key secondary outcomes were the Knee Injury and Osteoarthritis Outcome Score questionnaire (KOOS) pain, physical function, and knee-related quality of life subscales.

Results: 200 participants underwent randomization; 100 assigned to QE and 100 to HE (mean age 27.2 years (SD 6.4); 69% female). The least squares mean changes in AKPS (primary outcome) were 7.6 for QE and 7.0 for HE (difference 0.6 points, 95% CI -2.0 to 3.2; test for equivalence $p<0.0001$), although neither program surpassed the minimal clinically important change threshold. None of the group differences in key secondary outcomes exceeded predefined equivalence margins.

Conclusion: 12-week focused quadriceps and hip focused exercise protocols provided equivalent improvements in symptoms and function for patients with PFP.

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INTRODUCTION

Patellofemoral pain (PFP) is a common knee problem, with point prevalences from 6 to 7 % in adolescents and up to 13% in young adults (1-3). More than one in two with PFP report persistent pain after 5–8 years (4), with an associated frequent use of pain killers, a lower physical activity level, and low quality of life (1, 4-6). Recent systematic reviews and a network meta-analysis recommend exercise therapy (mainly comprising exercises for the hip, the knee, or both the hip and knee) for improving pain and function in people with PFP (7-10). However, these studies also underline the uncertainty about which type of exercises that are most effective for PFP. Despite the latest consensus document on managing PFP recommends including hip exercises, direct comparisons of exercise protocols are few (9), with short intervention and follow-up periods (11), and with sample sizes insufficient to detect clinically relevant differences in outcomes (12, 13). Collectively, this challenges the choice of the most appropriate treatment and may also explain the variation in clinical practice (14). Hence, there is a need for large high-quality studies of comparative effectiveness of quadriceps and hip muscle exercises for PFP. Accordingly, the aim of this study was to assess effectiveness equivalence between a focused “Quadriceps Exercise” (QE) protocol and a focused “Hip Exercise” (HE) protocol on symptoms and function in patients with PFP.

METHODS

Study design

In this single-center randomized, controlled, assessor-blinded, equivalence trial with two parallel intervention groups we compared a QE and HE protocol. Evaluations and assessments took place at the Department of Physical and Occupational Therapy at Bispebjerg-Frederiksberg Hospital, Copenhagen, Denmark at baseline and 12 weeks. Further, the participants were invited to an online collection of patient-reported outcomes 26 weeks after baseline. The trial design is illustrated in the supplements. Ethical approval was obtained from the Health Research Ethics Committee of the Capital region, Denmark (H-16045755). This report follows the CONSORT extension for non-pharmacological treatments guideline and the TIDieR checklist for intervention description (15, 16). The study was registered prospectively at www.ClinicalTrials.gov on March 3, 2017 (NCT03069547).

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Patient and Public Involvement statement

Patients were not engaged in the development stages of the study nor in the conduct or oversight of the study. All participants were offered a lay language resume of results and conclusion of the study by email.

Participants

Between April 10, 2017 and December 3, 2021, participants were recruited from the Institute of Sports Medicine Copenhagen (ISMC), Bispebjerg-Frederiksberg Hospital, Copenhagen, Denmark. Inclusion was halted for 8 weeks from March 12, 2020 due to the COVID-19 pandemic. ISMC is a medical unit for patients with injuries in the musculoskeletal system caused by participation in sports activities. Patients are referred to ISMC from primary care physicians, and from ISMC to specialized rehabilitation at the Department of Physical and Occupational Therapy. All participants underwent a clinical examination by a specialist in sports medicine but were not screened for eligibility using radiographs or other imaging. All participants provided written informed consent before participation.

Inclusion criteria were a clinical diagnosis of PFP in at least one knee confirmed by an experienced sports medicine physician, average knee pain during activities of daily living in the last week of ≥3/10 on a verbal rating scale, insidious onset of symptoms unrelated to trauma, persistent pain for at least four weeks, and anterior knee pain associated with at least three of the following: During or after activity, prolonged sitting, stair ascent or descent, or squatting. The exclusion criteria were other knee conditions, including meniscal or other intra-articular injuries to the knee, history of recurrent patellar subluxation or dislocation, and previous knee surgery. Potential participants were informed about the trial during an interview with a sports medicine physician, and after at least 24 hours of consideration an investigator obtained written informed consent and coordinated trial visits. The most symptomatic knee at baseline was chosen as the study knee.

Randomization and blinding

Before randomization, demographic information and all baseline measures were obtained. Participants were randomly assigned (1:1) in permuted blocks of 4 and 6 (randomly distributed) according to a computer-generated list of random numbers, to one of the two groups (QE or HE). Individual allocations were concealed in sealed opaque envelopes, stored in a locked cupboard without access for investigators or outcome assessor, and delivered sequentially to the study

physiotherapist at randomization. The physiotherapists delivering the interventions and participants were not blinded to treatment allocation. The investigators and the outcome assessor were blinded to allocation, and participants were requested not to disclose allocation during clinical assessments.

Interventions

Both the hip and knee focused exercise programs were inspired by previous research (17) and followed recommended prescribing guidelines (18, 19). The exercise interventions lasted for 12 weeks with three weekly home-based exercise sessions consisting of three sets of 8-12 repetitions. Key parameters of the exercise programs are shown in table 1, and the complete description of the interventions is provided in the supplementary file.

The hip exercise (HE) program consisted of hip external rotation (clam shell), side-lying/standing hip abduction, and prone/standing hip extension. The HE exercises were chosen due to their documented activation of the hip abductors, external rotators, and hip extensors (20-23), wide use in clinical practice, and because they do not strain the patellofemoral joint excessively. *The quadriceps exercise (QE) program* consisted of sitting knee extension, squat, and forward lunge. The exercises has been shown effective in recruiting the quadriceps muscle (22) and appear effective in the treatment of PFP (24, 25).

Both exercise programs were initiated at an individual clinical visit. An experienced physiotherapist introduced the participant to the allocated exercise program (QE or HE) and provided instructions to the individual exercises. Elastic bands, free weights, and body weight were used to provide resistance. The participants were informed to perform 8-12 repetitions in each set. The last repetitions should be difficult to perform while still allowing the participant to maintain high quality of movement (i.e., full range of motion and without any compensatory movements (judged by the physiotherapist)) throughout the entire program. The participants were instructed to increase resistance whenever they could complete 14 repetitions in a set. This was emphasized during the instructional session and during each follow-up visit (19) (progression principles are specified in the supplementary file). To reflect normal clinical practice, the exercise programs included monthly clinical supervision visits. Reduction in the exercise load (ROM, number of sets/repetitions) could be made in case of significant knee pain exacerbations.

All participants – irrespective of group allocation – received the information leaflet "Managing my patellofemoral pain" containing general information on possible causes and management of PFP. The leaflet is available in the supplementary file. Further a comprehensive

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exercise leaflet with guidance on the exercises, progression/regression, and pain management was handed out. All the physiotherapists involved in the study (n=5) were instructed to communicate in the same way, and training sessions were held in the planning stage to ensure standardization of communication and practice.

Adherence to the prescribed exercise protocol was monitored by a self-administered exercise diary, which the participants were encouraged to fill in after each exercise session. The participants were asked to record date, number of repetitions and sets for each exercise, and the resistance (i.e., elastic band color corresponding to a specified resistance or weights in kg). The exercise diary was brought at the monthly clinical visits to optimize compliance and handed in at the 12-weeks assessment. The criteria for satisfactory intervention adherence in both groups was 24 of the 36 scheduled training sessions (66%).

Table 1. Key parameters of the exercise programs

	Number of repetitions/sets	Time under tension	Rest in between sets	Means of progression	Number of exercise interventions per week
QE-1: Sitting leg extension	8-12 reps./3 sets	2-4 sec/repetition	1 min. 30 sec – 2 min.	Adding elastic bands on ankles	3/week
QE-2: Squat	8-12 reps./3 sets	2-4 sec/repetition	1 min. 30 sec – 2 min.	Adding weight in a backpack (e.g. sand, flour, bottles of water) or by holding dumbbells in the hands.	3/week
QE-3: Lunge	8-12 reps./3 sets	2-4 sec/repetition	1 min. 30 sec – 2 min.	As above	3/week
HE-1: Clam-shell	8-12 reps./3 sets	2-4 sec/repetition	1 min. 30 sec – 2 min.	Adding elastic bands just above both knees	3/week
HE-2: Side-lying/standing hip abduction	8-12 reps./3 sets	2-4 sec/repetition	1 min. 30 sec – 2 min.	As above	3/week
HE-3: Standing hip extension	8-12 reps./3 sets	2-4 sec/repetition	1 min. 30 sec – 2 min.	Adding elastic bands from underneath the foot to the knee of the moving limb	3/week

QE: Quadriceps exercise
HE: Hip exercise
Both groups were instructed to warm up by performing 20 repetitions of exercise QE-1 (for QE) or HE-1 (for HE) without external load.
Both groups were instructed to increase resistance whenever the participants were able to perform 2 repetitions more than the desired number (i.e., 14 or more)

Primary outcome

The primary outcome was change from baseline in the Anterior Knee Pain Scale (AKPS) questionnaire at week 12. The AKPS questionnaire is a widely used and well-validated questionnaire for assessing the severity of symptoms and physical limitations in people with PFP (26). The 13 items in the questionnaire are summed up to give a total score ranging from 0 to 100, with high scores indicating less symptoms. The minimal clinically important change is established at 8-10 points (27).

Key secondary and other secondary outcomes

Key secondary outcomes were changes from baseline in the Knee Injury and Osteoarthritis Outcome Score questionnaire (KOOS) pain, physical function, and knee-related quality of life subscales (28). Other secondary outcomes included changes from baseline in the KOOS sports/recreation and symptoms subscales, Pain Self-Efficacy Questionnaire (29), the EuroQoL EQ-5D-3L Questionnaire (30), assessment of pain on a 0–10 numeric rating scale (NRS) during activity (30 s of performing repeated deep knee-bends from a standing position) (31), and global perceived effect on overall health, pain and function measured on a 15-point Likert scale ranging from -7 (much worse) to +7 (much better). Further, isometric muscle strength of hip abductors, hip adductors, hip external rotators, hip internal rotators, hip extensors, hip flexors, knee flexors, and knee extensors were measured with a handheld dynamometer. The testing was performed in a clinical examination room with the participant lying or sitting on an examination table with and without external fixation according to published and validated protocols (32-34). Three consecutive isometric maximal contractions were performed with a 30-s rest period between each trial, and the maximum value was used for analysis. Changes from baseline in the patient reported outcomes (questionnaires) at week 26 were also recorded. The physiotherapists performed an estimation of each participant's prognosis just after the initial instructional session for the purpose of a secondary analysis on outcome prediction (to be reported in a separate paper; study protocol available upon request).

Sample size

The sample size was calculated to allow for test of equivalence of the treatment groups at 90% power and an alpha level of 0.05 using a two one-sided test (one-sided alpha of 0.025) with equivalence margins of ±8 AKPS points, assuming a mean difference of 0 points and a common standard deviation of 15 points (35, 36). From this, 77 patients were required in each treatment group. To account for a dropout rate of approximately 20% the sample size was a priori increased to 100 participants in each group.

Statistical analysis

The primary analysis was performed using the intention-to-treat population; patients were assessed and analyzed as members of their randomized groups, irrespective of adherence to the planned course of treatment. Continuous outcomes were analyzed as change from baseline using repeated

measures linear mixed models with group (2 levels), time (2 levels; week 12 and 26), and the corresponding interaction as fixed effects and participants as random effects (normal distribution assumed). Adjustments were made for baseline values. Assumptions underlying the linear mixed models were assessed by visual inspection of Q-Q plots and residual plots (for normality of residuals and homogeneity of variance, respectively), and plots of quantitative predictors against residuals (for assessment of linearity of covariates). The assumptions were judged as fulfilled. Results are reported as least squares means and differences between least squares means with two-sided 95% confidence intervals (CI). The group difference in the primary outcome was assessed for equivalence by a two one-sided test of equivalence with alpha 0.025 assessing if the 95% CI respects the predefined equivalence margin of ±8 AKPS points corresponding to the established cut-off value for making the distinction between improved or unimproved (27). No explicit adjustments for multiplicity were applied, rather the key secondary outcome measures were analyzed in a prioritized order. Missing values for items in the AKPS and Pain Self-Efficacy Questionnaire were substituted with the arithmetic mean of values from the available items. If more than 25% of items were missing, the outcome was regarded missing for the patient (13, 37). For the KOOS questionnaire, a mean score for each subscale was calculated, as long as at least 50% of the items were answered for each subscale. If more than 50% of the subscale items were omitted, the response was considered invalid. Imputation of missing item values for the EuroQoL EQ-5D-3L Questionnaire, was handled according to the user guide (euroqol.org). Imputation of missing values in AKPS constituted less than 5% of all questionnaire data. Complete missing data were handled implicitly in the intention-to-treat analysis by the linear mixed models (38). Sensitivity analyses were performed for the primary and key secondary outcomes by repeating the primary analyses on the per-protocol population predefined as participants with satisfactory adherence and without major protocol deviations (39). Further, we performed generalized estimating equation analyses of the primary and key secondary outcomes on the ITT population with missing data handled by inverse probability weighting with weights estimated from a logistic regression model for predicting missingness, adjusted for the baseline value. Finally, we performed an analysis of covariance of the primary and key secondary outcomes at week 12 (i.e., without the repeated measures) on the ITT population with missing data replaced using multiple imputation (100 multiply imputed data sets with missing data predicted using baseline data) adjusted for the baseline value. For the sensitivity analysis the underlying assumptions were assessed in the same way as the primary analysis and the assumptions were judged as fulfilled. If the primary analysis and the

sensitivity analyses confirm each other, confidence in the results is increased both regarding equivalence and superiority claims. All analyses were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Equity, diversity, and inclusion statement

The study included individuals with knee pain referred from primary care to specialized rehabilitation. The study population included participants from a broad range of ethnic/racial and socioeconomic backgrounds. The research team included five men and four women. The author team included one junior scholar (man), one senior clinician (man), and three senior academics (all men).

RESULTS

Participants

From April 10, 2017 through December 3, 2021, 288 individuals were screened for eligibility (figure 1); 88 were ineligible for inclusion. Thus, 200 participants underwent randomization; 100 were assigned to QE and 100 to HE. The mean age was 27.2 years (SD 6.4); 69% were females; and the mean BMI was 22.6 (SD 3.0). Baseline characteristics were similar in the two groups (table 2). Participants completed on average 28 (77%) training sessions out of 36 possible sessions. During the course of the intervention, 6 participants (4 QE; 2 HE) had alterations to their allocated exercise programs (mainly reduced ROM in the weight bearing exercises) and 8 (5 QE; 3 HE) had number of sets and repetitions reduced due to knee pain exacerbations.

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Table 2. Demographics and Baseline Characteristics

	Quadriceps exercise group (QE) N=100	**Hip exercise group (HE) N=100**
	Mean (SD)	**Mean (SD)**
Demographics		
Age, years	27.2 (6.3)	27.2 (6.7)
Female sex (n[%])	66 (66%)	72 (72%)
Body mass, kg	68.2 (12.4)	67.6 (13.0)
Height, cm	172.4 (8.5)	173.2 (10.7)
Body Mass Index, BMI (kg/m2)	22.8 (3.01)	22.4 (2.9)
Symptom duration, months	47.3 (49.4)	52.8 (54.1)
Symptoms duration, months (median (IQR))*	36 (48)	30 (60)
AKPS questionnaire score (0-100)	74.2 (11.6)	73.3 (13.0)
KOOS (0-100)		
Pain	70.8 (15.6)	72.2 (14.1)
Physical Function	84.1 (13.2)	83.4 (13.1)
Symptoms	79.6 (14.0)	80.7 (13.3)
QoL	44.4 (15.1)	44.2 (14.7)
Sports & Recreation	56.7 (24.9)	59.3 (24.4)
Dynamic assessment of pain (VRS 0-10)	1.9 (2.2)	1.8 (1.8)
Dynamic assessment of pain (VRS 0-10) (median (IQR))*	1.0 (3.5)	2.0 (3.0)
Isometric muscle strength		
Hip abductors (N)	129.5 (40.9)	129.5 (41.2)
Hip adductors (N)	121.2 (40.6)	122.4 (47.3)
Hip extensors (N)	175.3 (46.8)	181.0 (56.0)
Hip flexors (N)	189.1 (55.8)	194.3 (63.0)
Hip external rotators (N)	101.1 (30.2)	100.7 (37.7)
Hip internal rotators (N)	123.9 (100.9)	109.4 (42.8)
Knee extensors (quadriceps) (N)	299.2 (113.1)	292.0 (121.9)
Knee flexors (hamstrings) (N)	316.6 (117.1)	302.8 (129.5)
Pain Self-efficacy questionnaire (0-60)	47.5 (8.6)	46.8 (9.8)
EuroQoL EQ5D Questionnaire (-0.624 to 1.000)	0.755 (0.175)	0.757 (0.127)

Values are presented as means and standard deviations (SD) unless otherwise stated.
* Both means (SD) and medians (IQR) are presented as data is not normally distributed.
IQR: Inter quartile range
AKPS: Anterior Knee Pain Scale
KOOS: Knee injury and osteoarthritis outcome score.
VRS: Verbal Rating Scale

Primary outcome

The mean changes in AKPS questionnaire score from baseline to week 12 were 7.6 (95%CI 5.8 to 9.5) in the QE group and 7.0 (95%CI 5.2 to 8.9) in the HE group (group difference: 0.6 points, 95% CI −2.0 to 3.2; p=0.636 for test of superiority). The 95% CI of the group difference in change in

AKPS questionnaire from baseline to week 12 was within the predefined equivalence margin of±8 points ($p<0.0001$ for equivalence, table 3). The trajectories of the AKPS questionnaire are shown in figure 2.

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Table 3. Primary and Secondary Outcomes at week 12 in the ITT population. Based on repeated measures linear mixed models, where missing data is assumed to be missing at random.

	QE (N=100)	HE (N=100)	Mean difference (95% CI)	P-value
	Mean (95%CI)	Mean (95%CI)		
Primary outcome:				
Change in AKPS questionnaire score (0 to 100); equivalence test*	7.6 (5.8 to 9.5)	7.0 (5.2 to 8.9)	0.6 (-2.0 to 3.2)	<0.0001
Change in AKPS questionnaire score (0 to 100); superiority test*				0.636
Key Secondary outcome:				
Change in KOOS Pain – score (0-100)	9.3 (6.8 to 11.8)	6.4 (3.8 to 8.9)	2.9 (-0.6 to 6.5)	
Change in KOOS Function – score (0 to 100)	5.8 (3.9 to 7.9)	4.8 (2.8 to 6.8)	1.0 (-1.8 to 3.9)	
Change in KOOS Quality of life – score (0 to 100)	10.7 (7.2 to 14.1)	11.9 (8.4 to 15.3)	-1.2 (-6.1 to 3.7)	
Other Secondary Outcomes:				
Change in KOOS Sports and recreation– score (0 to 100)	13.8 (9.8 to 17.8)	10.6 (6.6 to 14.6)	3.2 (-2.4 to 8.8)	
Change in KOOS Symptoms – score (0 to 100)	4.8 (3.0 to 6.7)	4.7 (2.9 to 6.6)	0.1 (-2.5 to 2.8)	
Change in isometric muscle strength				
Hip abductors (N)	13.8 (8.5 to 19.0)	13.3 (8.0 to 18.6)	0.4 (-7.0 to 7.9)	
Hip adductors (N)	10.9 (5.5 to 16.2)	16.2 (10.8 to 21.6)	-5.4 (-13.0 to 2.3)	
Hip extensors (N)	16.4 (9.3 to 23.4)	13.9 (6.8 to 21.1)	2.4 (-7.6 to 12.5)	
Hip flexors (N)	11.4 (5.6 to 17.2)	11.6 (5.7 to 17.5)	-0.2 (-8.4 to 8.1)	
Hip external rotators (N)	4.7 (-2.4 to 11.8)	4.9 (-2.3 to 12.1)	-0.2 (-10.3 to 9.9)	
Hip internal rotators (N)	9.3 (5.2 to 13.4)	10.6 (6.5 to 14.8)	-1.4 (-7.2 to 4.5)	
Knee extensors (quadriceps) (N)	33.7 (17.6 to 49.7)	32.9 (16.5 to 49.3)	0.7 (-22.2 to 23.7)	
Knee flexors (hamstrings) (N)	37.8 (26.5 to 49.2)	41.8 (30.5 to 53.2)	-4.0 (-20.1 to 12.1)	
Change in Dynamic Assessment of Pain (VRS (0-10))	-0.8 (-1.1 to -0.5)	-0.2 (-0.5 to 0.1)	-0.6 (-1.0 to -0.1)	
Change in EQ5D Questionnaire (index -0.624 to 1.000)	0.07 (0.04 to 0.09)	0.03 (0.01 to 0.06)	0.03 (-0.00 to 0.07)	
Transition Questionnaire of global perceived change in overall health, pain, and function (Likert scale -7 to 7)	2.1 (1.6 to 2.7)	2.1 (1.5 to 2.7)	0.0 (-0.8 to 0.8)	
Treatment adherence				
Treatment adherence (%)	75.0 (23.2)	79.0 (21.3)	-4.0 (-10.2 to 2.2)	
Treatment adherers (adherence ≥66%) - no. (%)	82 (82.0%)	85 (85.0%)		

*Primary outcome was analyzed using both a test for equivalence and a test for superiority.
AKPS: Anterior Knee Pain Scale
KOOS: Knee injury and osteoarthritis outcome score.
VRS: Verbal Rating Scale

Key secondary and other secondary outcomes

For the key secondary outcomes, the estimated treatment differences between groups at week 12 were 2.9 points (95% CI -0.6 to 6.5) for KOOS pain score, 1.0 points (95% CI -1.8 to 3.9) for KOOS function, and -1.2 points (95% CI-6.1 to 3.7) for KOOS quality of life score. The key secondary outcomes all respected the predefined criteria for equivalence (table 3). Finally, the results in the primary and key secondary outcomes appeared unchanged at week 26 (table 5). There were no statistically or clinically significant differences between groups in the other secondary, safety and exploratory outcomes at week 12 (table 3) and week 26 (table 5). The overall pattern of results for all outcomes was unchanged in the sensitivity analyses (online supplemental tables S1-S3).

Safety

Adverse events were typically mild to moderate, mostly related to muscle soreness, and were similar in the two groups (table 4). Severe adverse events that gave interference with the participants' usual activities were exacerbation of knee pain (n=2), headache (n=1), and back pain (n=1).

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Table 4. Adverse events in the intention-to-treat population

	QE (n=100)	HE (n=100)
Exposure time – patient weeks	900	948
AE - no. of patients (%)	15 (15%)	16 (16%)
AE - no. of events (rate – event per patient week)	21 (0.03)	19 (0.02)
AEs leading to discontinuation - no. of patients (%)	1 (1%)	1 (1%)
Maximum reported severity of AEs, no. of patients (%)		
Mild	9 (9%)	8 (8%)
Moderate	4 (4%)	6 (6%)
Severe	2 (2%)	2 (2%)
AEs, relationship to trial treatment, no. of events (rate – event per patient week)		
Not related	2 (0.002)	2 (0.002)
Probably not related	3 (0.003)	6 (0.006)
Probably related	16 (0.02)	11 (0.01)
AEs, classification, no. of events (rate – event per patient week)		
PFP pain exacerbation	8 (0.01)	6 (0.01)
Muscle soreness	12 (0.01)	12 (0.01)
Other	1 (0.001)	1 (0.001)
Deaths - no. of events (rate – event per patient week)	0 (0)	0 (0)
AE; Adverse event. The severity of an adverse event refers to the maximum intensity of the event. An event was considered severe (compared with mild or moderate) if it interfered substantially with the patient's usual activities.		

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Table 5. Primary and Secondary Outcomes at week 26 in the ITT population. Based on repeated measures linear mixed models, where missing data is assumed to be missing at random.

	QE (N=100)	**HE (N=100)**	**Mean difference (95%CI)**	**P-value**
	Mean (95%CI)	**Mean (95%CI)**		
Primary outcome:				
Change in AKPS questionnaire – score (0 to 100); equivalence test*	9.8 (7.9 to 11.7)	9.0 (7.1 to 10.9)	0.8 (-1.9 to 3.4)	<0.0001
Change in AKPS questionnaire – score (0 to 100); superiority test*				0.574
Key Secondary outcome:				
Change in KOOS Pain – score (0-100)	10.5 (7.9 to 13.1)	10.5 (7.9 to 13.1)	-0.0 (-3.7 to 3.6)	
Change in KOOS Function – score (0 to 100)	6.6 (4.5 to 8.7)	7.0 (4.9 to 9.1)	-0.4 (-3.3 to 2.5)	
Change in KOOS Quality of life – score (0 to 100)	15.7 (12.2 to 19.3)	19.2 (15.6 to 22.7)	-3.5 (-8.5 to 1.6)	
Other Secondary Outcomes:				
Change in KOOS Sports and recreation– score (0 to 100)	15.1 (11.1 to 19.2)	14.8 (10.7 to 18.8)	0.4 (-5.4 to 6.1)	
Change in KOOS Symptoms – score (0 to 100)	5.8 (3.9 to 7.7)	6.3 (4.4 to 8.3)	-0.5 (-3.3 to 2.2)	
Change in EQ5D Questionnaire (index -0.624 to 1.000)	0.09 (0.06 to 0.12)	0.07 (0.04 to 0.10)	0.02 (-0.02 to 0.06)	
Transition Questionnaire of global perceived change in overall health, pain, and function (Likert scale -7 to 7)	2.6 (2.0 to 3.1)	2.7 (2.1 to 3.2)	-0.1 (-0.9 to 0.7)	

Group values for QE and HE are presented as least squares means (95% confidence interval).
Mean differences are presented as least squares means and 95% confidence intervals (CI).
*Primary outcome was analyzed using both a test for equivalence and a test for superiority.
AKPS: Anterior Knee Pain Scale
KOOS: Knee injury and osteoarthritis outcome score.

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DISCUSSION

The results of this study provide much needed evidence to inform clinical practice and highlight that an exercise program that focused on either quadriceps or hip muscles provided equivalent improvements in symptoms and function in the short (12 weeks) and medium term (26 weeks). Treatment adherence was similar in the two groups as were adverse events that were few.

Our results support recently published RCTs comparing hip and knee focused exercise protocols. In Hott et al (13), 112 patients were randomized to three groups (a 6-week intervention consisting of patient education combined with isolated hip-focused exercise, traditional knee-focused exercise, or free physical activity); the data indicated no difference in the primary outcome AKPS between groups. This is in line with previous studies, showing no difference in pain and function at 6-8 weeks between a hip and a knee exercise group (40, 41). Three studies have found hip exercises to be more effective than knee-focused exercise (42-44); however, the sample sizes were typically quite modest (15-18 per group), and one study lacked randomization. This study is the first using an equivalence design that allows us to draw reliable conclusions regarding the comparative effectiveness of hip and knee focused exercises for PFP. Hence, our results extend current understanding and effectively demonstrate equivalent effectiveness of hip and knee focused exercise for PFP.

Both exercise programs were associated with improvements in AKPS score (7.6 points for QE and 7.0 points for HE), but the improvements did not surpass the minimal clinically important change. The within-group changes for QE and HE are similar to those previously reported (13), but are somewhat lower than those reported in other RCTs evaluating the effect of hip and knee exercises in adolescents and adults with PFP (35, 40, 41, 45-47). This difference may be explained by the setting of this study. Patients included in this study were referred to specialized rehabilitation most often due to long-standing symptoms, which is reflected in the patient demographics. Previous studies have shown that long symptom duration is associated with worse outcomes (irrespective of treatment) (4, 48, 49) which may explain the somewhat small within group changes. Mean pain duration in this study was higher when compared to most studies that report on this (40, 45, 47). Another plausible explanation for the small within group changes could be differences in attention and supervision during the intervention period compared to other studies. Most of the interventions in comparable studies were supervised, but this is not always feasible in a clinical setting. The patient–physiotherapist relationship and the overall healthcare setting are relevant categories of contextual factors that may modify treatment effects (50). Lastly, the baseline AKPS scores were

relatively high considering the long pain duration, which could potentially introduce a ceiling effect on individual items, which in turn could affect the change scores.

Both groups had 10-11% improvements in hip abduction and knee extension muscle strength after the 12-week training period irrespective of group allocation, which is similar to previous studies (13, 40, 44). Since some aspects of the hip exercises involve weight bearing, several other muscles are recruited when performing the exercise, including the quadriceps. Likewise for the quadriceps focused exercises, a possible parallel training of the hip (and other synergistic) muscles is likely to have occurred. One could argue that this may explain the lack of group difference in the outcomes. However, in a large randomized clinical trial with 218 participants with PFP, increases in muscle strength did not mediate improvements in pain (51). This suggests that improvements in muscle strength might not be the driver of beneficial outcomes, and that other mechanisms are more important.

The somewhat modest improvements seen in our and other recent studies on exercises for PFP raise the question if treatment plans focusing on strengthening and biomechanically informed movement quality alone address the right components contributing to the pain experience. Growing evidence suggests that psychological features may play a role in long-standing PFP (52-54). Future studies should aim at identifying possible patient characteristics that predict successful outcomes.

Clinical Implications

We found that quadriceps exercises and hip exercises are equally effective treatments in the management of patients with PFP. However, the improvements did not reach the established minimally clinical important change threshold, and therefore training the quadriceps or hip muscles separately may not be effective in improving symptoms and function. This is supported by the most recent consensus document that recommends combining quadriceps and hip exercise (9). This may also imply that therapists should use their clinical reasoning and include patient preferences when designing an exercise rehabilitation program for the individual patient. Such shared decision may improve healthcare efficiency and is recommended in the rehabilitation of patients with PFP (9, 55, 56). However, although personalization of exercise interventions to individual patients or subgroup of patients may be a useful strategy that can ultimately lead to improved outcomes for patients (57), such strategy remains to be supported by research evidence – preferably from prospective randomized trials.

Limitations and strengths

There are inherent limitations to this study. First, the exercise programs were home-based with limited supervision, which may introduce a risk that the exercises were not performed correctly. While more regular visits to the clinician would assure adherence and fidelity to the treatments, this would not be in accordance our intention to resemble a clinical setting, where multiple weekly visits are not feasible (14). On the other hand, the resemblance of normal clinical practice increases external validity of our results. Second, the exercise adherence data was based on self-reporting, which introduces an inherent risks of overestimation due to social desirability, recall period, and selective recall (58). Third, this study was a single center trial which may limit the external validity. Fourth, as the main part of the interventions were unsupervised, contamination (deliberate switch of exercise program) may have occurred. Fifth, as part of a prognostic sub-study (to be published separately) the physiotherapists recorded the participants' projected prognosis after the first clinical encounter but not disclosed to the participants. As this was done post randomization it may have introduced some expectation biases with the physiotherapists. However, such prognoses are inherent in clinical interactions between patients and health care providers and thus this does not represent deviations from normal clinical practice. Further, the ITT analysis estimates the effect of assigned but not received treatment and may be biased by non-adherence. Also, missing outcome data can introduce selection bias even when missingness in the two treatment groups are similar. Finally, the primary analysis assumes data missing at random, which may not be true. However, the sensitivity analyses confirm the primary analyses increasing the confidence in the conclusions. The strengths of this trial included the relatively large sample size and the equivalence design, which increase the precision of the estimated group differences, and the reporting of adverse events. Furthermore, this is the first study comparing hip and knee exercises with an intervention period of 12 weeks, with comparable studies ranging from 3 to 8 weeks of intervention (10, 11).

CONCLUSION

In individuals with patellofemoral pain, 12-week quadriceps-focused and hip-focused exercise programs provided equivalent effectiveness for improvements in symptoms and function. More research is required to define personalized or combined exercise programs with greater effectiveness.

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SUMMARY BOX

What is already known on this topic

Current evidence supports exercise therapy in the treatment of patients with patellofemoral pain. However, there is uncertainty about the comparative effectiveness of hip and knee exercises and high-quality evidence is needed to guide clinical practice.

What this study adds

This study demonstrates that quadriceps focused exercises and hip focused exercises provide equivalent benefits for patients with patellofemoral pain, but the improvement did not reach the established minimally clinical important change threshold.

How this study might affect research, practice, or policy

Based on this study, clinicians can include patient preferences and individualization in the choice of either hip or knee focused exercises in the management of patients with patellofemoral pain.

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Contributors

RH: concept/design, data collection, data analysis, manuscript draft, critical revision. MH: concept/design, data analysis, critical revision, guarantor. CB: concept/design, medically responsible, eligibility screening, critical revision. MSR: concept/design, critical revision. SPM: critical revision.

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Competing interests

None declared.

Patient consent for publication

Not relevant

Ethics approval

This study involves human participants and was approved by the Committees on Health Research Ethics, Capital Region (H-16045755 (approved December 15, 2016)). Participants gave informed consent to participate in the study before taking part.

Data availability statement

Data are available upon reasonable request.

FIGURE CAPTION

Figure 1. CONSORT flow diagram

Figure 2. Trajectories of the AKPS questionnaire in the ITT population. High values represent high levels of self-reported function; low values represent low levels of self-reported function. Data points represent least squares means; error bars represent 95% CI.

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