Immediate Efficacy of Neuromuscular Exercise in Patients with Severe Osteoarthritis of the Hip or Knee: A Secondary Analysis from a Randomized Controlled Trial

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ABSTRACT. ***Objective.*** Knowledge about the effects of exercise in severe and endstage osteoarthritis (OA) is limited. The aim was to evaluate the efficacy of a neuromuscular exercise program in patients with clinically severe hip or knee OA.

Methods. This was a randomized controlled assessor-blinded trial. Patients received an educational package (care-as-usual) only, or care-as-usual plus an 8-week neuromuscular exercise intervention (NEMEX-TJR). NEMEX-TJR was supervised by a physiotherapist, twice weekly for 1 h. The primary outcome was Activities of Daily Living (ADL) subscale from the Hip disability and Osteoarthritis Outcome Score (HOOS) and the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire. The secondary outcomes were the HOOS/KOOS subscales Pain, Symptoms, Sport and Recreation, and Joint-related Quality of Life. Exploratory outcomes were functional performance measures and lower limb muscle power.

Results. Included were 165 patients, 56% female, average age 67 years (SD ± 8), and a body mass index of 30 (SD ± 5), who were scheduled for primary hip or knee replacement. The postintervention difference between mean changes in ADL was 7.2 points (95% CI 3.5 to 10.9, p = 0.0002) in favor of NEMEX-TJR compared with control. Second, there were statistically significant differences between groups in favor of NEMEX-TJR on all self-reported outcomes and most functional performance tests (walk, chair stands, and 1-leg knee bends). Stratified analyses according to joint revealed moderate effect size for ADL for hip patients (0.63, 95% CI 0.26 to 1.00). Corresponding effect size for knee patients was small (0.23 95% CI –0.14 to 0.60).

Conclusion. Feasibility of neuromuscular exercise was confirmed in patients about to have total joint replacement. Self-reported activities of daily living and objective performance were improved and pain reduced immediately following 8 weeks of neuromuscular exercise. While the effects were moderate in hip OA, they were only small in knee OA. ClinicalTrials.gov Identifier: NCT01003756.
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Key Indexing Terms:
OSTEOARTHRITIS REHABILITATION EXERCISE

Exercise improves function and relieves pain for mild to moderate osteoarthritis (OA)[1,2,3]. For clinically severe OA, however, current evidence of the effects of exercise is based on small studies and interventions of poor therapeutic validity[4,5]. Empirical evidence suggests that exercise can reduce pain in patients with severe knee and/or hip OA and

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improve self-reported physical function in patients with severe hip OA[4].

Neuromuscular Exercise in Total Joint Replacement (NEMEX-TJR) is a physiotherapist-supervised, individualized, and goal-based exercise program addressing functional instability and impaired muscle function. It has been demonstrated to be feasible in elderly people with severe knee and hip OA in terms of self-reported pain, decreased or unchanged pain during training, and progression in level of training[6], but the effect has not been tested in a randomized controlled design. In the primary analysis from this trial, we reported that preoperative neuromuscular exercise in addition to total joint replacement (TJR) improves activities of daily living and reduces pain at 6 weeks postoperatively, but that changes are no longer evident at 3 months[7]. The observed short-term postoperative differences may originate from the effects experienced by the intervention group prior to surgery (i.e., the immediate effects from exercise intervention). With a rigorous design, a well-described intervention and a large sample size, we believe our report will contribute to the understanding of the effects of exercise for patients eligible for TJR.

The aim was to confirm the feasibility and evaluate the immediate effects (prior to surgery) of an 8-week neuromuscular exercise program in patients eligible for TJR. To our knowledge, this is the first exercise study in patients with severe OA with a sufficient sample size to not only allow detection of clinically relevant differences between groups, but also to allow comparison of patients with knee OA and patients with hip OA.

MATERIALS AND METHODS

Study design. A randomized assessor-blinded controlled trial was approved by The Regional Scientific Ethical Committees for Southern Denmark (identifier: S-20090099) and registered with ClinicalTrials.gov (identifier: NCT01003756). The results from the primary endpoint at 3 months after surgery have been reported[7]. This manuscript reports on the efficacy of education and the exercise program compared to education alone immediately after the intervention.

Participants. Eligible patients were at least 18 years of age and scheduled for primary unilateral total hip or knee replacement at the Svendborg Hospital, Odense University Hospital, Denmark, because of symptomatic OA. Exclusion criteria were current or previous fractures in or adjacent to the joint, inflammatory arthritis and comorbidity diseases, e.g., severe heart disease and neurological deficits, making exercise and testing impossible. Patients were not included if scheduled for bilateral TJR in the same procedure or for geographic reasons, e.g., living on adjacent islands with logistics making frequent attendance unrealistic. Patient interest and eligibility were screened by the principal author by telephone and patient records. Written information was given to the participants in the clinic by the scheduling surgeon, who was not otherwise involved in our study. Informed written consent was obtained on the day of baseline testing. The patient's transportation was reimbursed when attending exercise and testing sessions.

Randomization. Allocation was conducted by the principal author after baseline assessment using sequentially numbered, opaque, sealed envelopes. The allocation sequence was stratified by sex and municipality, and blocked in groups of 4 to allow for similar recruitment rates into both groups. The sequence and envelopes were produced by a person not otherwise affiliated with the trial. The allocation was performed either with the patient present or over the telephone.

Interventions. Participants in the intervention group received a basic educational package (EP; described below in detail for the control group) in addition to attending a neuromuscular exercise program (EX) for about 8 weeks (EX + EP). The neuromuscular training method is based on biomechanical principles and focuses on the quality of the performance in each exercise with an appropriate positioning of the joints in relation to each other, i.e., alignment of the hip, knee, and foot during weight-bearing. The NEMEX-TJR was delivered twice a week for 1 h. The exercise program was adopted in full from the original paper[6] and the supervising physiotherapist in this trial participated in a training session together with the originators of the NEMEX-TJR program in Lund, Sweden. The detailed exercise program is available as an additional file to the original publication[6]. We stated *a priori* that attendance at 12 exercise sessions (out of a possible 16 to 18, depending on what weekday the patient joined the training) was considered good compliance. Individualization is possible through progression of the level of difficulty of each exercise based on the quality of the performance evaluated by the supervising physiotherapist. There were no differences in the exercises performed by hip and knee patients, respectively.

The control group received only the EP, which consisted of written information on the operating procedure, expected postoperative progress, and a leaflet on various exercises normally given when scheduled for total hip or knee replacement. No limitations were imposed on either group with regard to changing exercise habits or seeking out other treatment during the study period.

Patient assessment. The intervention was evaluated by patient self-assessment, a range of functional performance measures and maximal muscle function in the form of dynamic muscle power (velocity of the movement × the force exerted) of the muscles around the hip and knee. The primary outcome was the Activity of Daily Living (ADL) subscale of the Hip disability and Osteoarthritis Outcome Score (HOOS) and the Knee Injury and Osteoarthritis Outcome Score (KOOS), respectively[8,9,10]. Secondary outcomes were scores for the HOOS/KOOS Pain, Symptoms, Sport and Recreation, and Joint-related Quality of Life subscales. The HOOS and KOOS are scored from 0 to 100, with higher scores indicating fewer problems. Questionnaires were sent out by mail and patients were instructed to fill them out at home and return them on the day of their clinical assessment.

To assess functional performance and muscle power, 3 performance measures (20-m walk, 5 timed repeated chair stands, and maximal number of knee bends/30 s) and 4 unilateral leg muscle power variables [single-joint knee extension (seated), hip extension and hip abduction (upright; MuscleLab Power, Ergotest Technology), plus multijoint leg extension press (seated; Nottingham Power Rig)] were used. All measures showed good to excellent reliability for the current patient group[11]. Four assessors conducted the physical testing and all underwent the same laboratory training. However, interrater reliability was not formally assessed. Allocation concealment was attempted by instructing the patients not to reveal this to the assessor. The postintervention assessors had no access to baseline data.

Statistical analysis. Seventy-four patients were needed to detect a clinically relevant change of 10 points on the HOOS/KOOS ADL subscale (SD ± 15, power = 0.80 and $\alpha = 0.05$)[8,12]. To allow for separate analysis of patients with knee OA and hip OA, 74 patients with knee OA and 74 patients with hip OA were needed. To allow for around 10% loss to followup, we decided to include 160 patients in total.

Data were analyzed according to the intention-to-treat principle with the baseline observation carried forward in cases where data were missing. Data were checked for completeness and normality and descriptive statistics were calculated for patient characteristics. To evaluate the efficacy of the intervention, all outcome change values were analyzed using analysis

of covariance with change-value in the listed outcome measure as the response variable and baseline value, joint operated (hip or knee), and group (EP + EX or EP) as covariates/group structure; the interaction term of Group × Joint was included.

The number needed to treat (NNT) was calculated using the formula 1/(EER - CER), where EER was the event rate (proportion of responders, i.e., patients improving at least 15%) in the exercise group and CER in the control group[13]. A patient was characterized as a responder when improving at least 15% from baseline according to the ADL or Pain subscales[14]. Standardized mean differences were calculated for the subscales ADL and Pain with the difference in group mean change scores in the numerator and the pooled SD in the denominator.

All p values and 95% CI are reported as 2-sided; p values < 0.05 were considered statistically significant. The data analyst (RC) was kept blinded to the allocated interventions and joints when performing the analyses. Analyses were performed using the SAS statistical package (version 9.2; SAS institute Inc.).

RESULTS

Patients. Recruitment took place from January 4, 2010, to March 21, 2011. In total, 628 patients were screened and 499 patients were found to be eligible. The Danish Health Care System guarantees that one will be operated on within 1 month of being scheduled for TJR. Entering this study meant that all patients accepted an additional waiting time of up to 5 weeks, in comparison with the treatment guarantee. One hundred five patients were unwilling to wait longer for surgery and 108 patients were unwilling to participate because of logistical constraints such as traveling distance or lack of transportation. Of the eligible patients, 165 (81 with knee OA) were included and underwent randomization (Figure 1). The 334 patients unwilling to participate were on average 4 years older (95% CI 2.3 to 5.6), 58% had hip OA, and 60% were women. After randomization, the additional waiting time applied only to patients randomized to the exercise intervention.

The 165 patients randomized to the 2 groups were on average 67 ± 8 years old; 84 (51%) had hip OA and 92 (56%) were women (Table 1). The median time from baseline to postintervention assessment was 8.6 weeks [interquartile range (IQR) 8.0 to 9.4 weeks] in the EX + EP group and 5.1 weeks (IQR 3.6 to 6.9 weeks) in the EP group. The EX + EP group attended a mean of 13 ± 5 exercise sessions and all patients, in both groups, received the folder containing educational material. Of the 84 patients in the intervention group, 62 attended the prespecified goal of 12 or more exercise sessions, indicating good compliance.

Primary and secondary outcomes. Following intervention, there was a statistically significant difference between the groups in favor of the EX + EP for all self-reported variables (Table 2). For the primary outcome, HOOS/KOOS ADL subscale, the difference in mean change between groups was 7.2 points (95% CI 3.5 to 10.9, p = 0.0002) in favor of the intervention compared with control. For the secondary outcomes of Pain, Symptoms, Sport and Recreation Function, and Joint-related Quality of Life, the mean differences were 5.3 (95% CI 2.1–8.4, p = 0.0012), 3.8 (95% CI 0.3–7.3, p = 0.0358), 4.5 (95% CI 0.4–8.7, p = 0.0329), and 5.6 (95% CI 1.9–9.3, p = 0.0034) points, respectively (Figure 2). For the purpose of sensitivity, the per-protocol analyses showed the same pattern of group contrasts. Further, adjusting for body mass index (BMI), age, and sex did not change the results (supplementary material available from the author upon request). Following stratified analyses, we found that patients with hip OA reported greater improvement in physical function and reduction in pain than did the patients with knee OA, shown by significant effect of the interaction term joint × group (p = 0.0497 and p = 0.0544 for the ADL and Pain subscales, respectively). The difference between groups in HOOS/KOOS ADL scores showed improvement in favor of the EX + EP group of 10.9 for the hip patients (95% CI 5.8 to 15.9) and 3.5 for the knee patients (95% CI 1.8 to 8.8; Table 2). On the basis of 15% improvement in ADL, the number needed to treat was 7 (4 and 23 for patients with hip and knee OA, respectively; Table 3). For ADL and Pain, we found moderate effect sizes in patients with hip OA (0.63, 95% CI 0.26–1.00 and 0.57, 95% CI 0.20–0.94) and low effect sizes in patients with knee OA (0.23, 95% CI –0.14 to 0.60 and 0.15, 95% CI –0.21 to 0.52; Table 2).

Exploratory outcomes. There was a significant difference between the groups in favor of the EX + EP group in chair stands (1.9, 95% CI 0.9 to 3.0 s), 20-m walk, self-chosen pace (0.9, 95% CI 0.0 to 1.8 s), and maximal number of knee bends on the index leg (leg to undergo surgery; 3.3, 95% CI 1.0–3.9; Table 4). There was no difference between groups for the 20-m walk at maximal pace and maximal number of knee bends on the contralateral leg. In the leg muscle power variables, we found statistically significant differences in single-joint hip abduction on the index leg [3.9, 95% CI 0.1 to 7.8 Watts (average peak power)] and in multijoint leg extension on the contralateral side (10.1, 95% CI 0.8 to 19.3 Watts) in favor of the EX + EP group (Table 4).

Adverse events. We did not prespecify recording of adverse events. One patient with hip OA discontinued the exercise intervention after experiencing an increase in pain (Figure 1).

DISCUSSION

This randomized, assessor-blinded controlled trial evaluated the effects of an 8-week supervised neuromuscular exercise program in combination with an educational package compared with the educational package alone (usual-care) delivered to patients with severe hip or knee OA. The results showed improvements of about 20% in self-reported physical function and functional outcomes in favor of the neuromuscular exercise intervention. After the intervention, this group experienced significant improvement in self-reported ADL, and pain and functional performance related to rising, sitting, and walking compared with the control group. The results are in line with previous smaller studies and confirm exercise to be beneficial in patients with

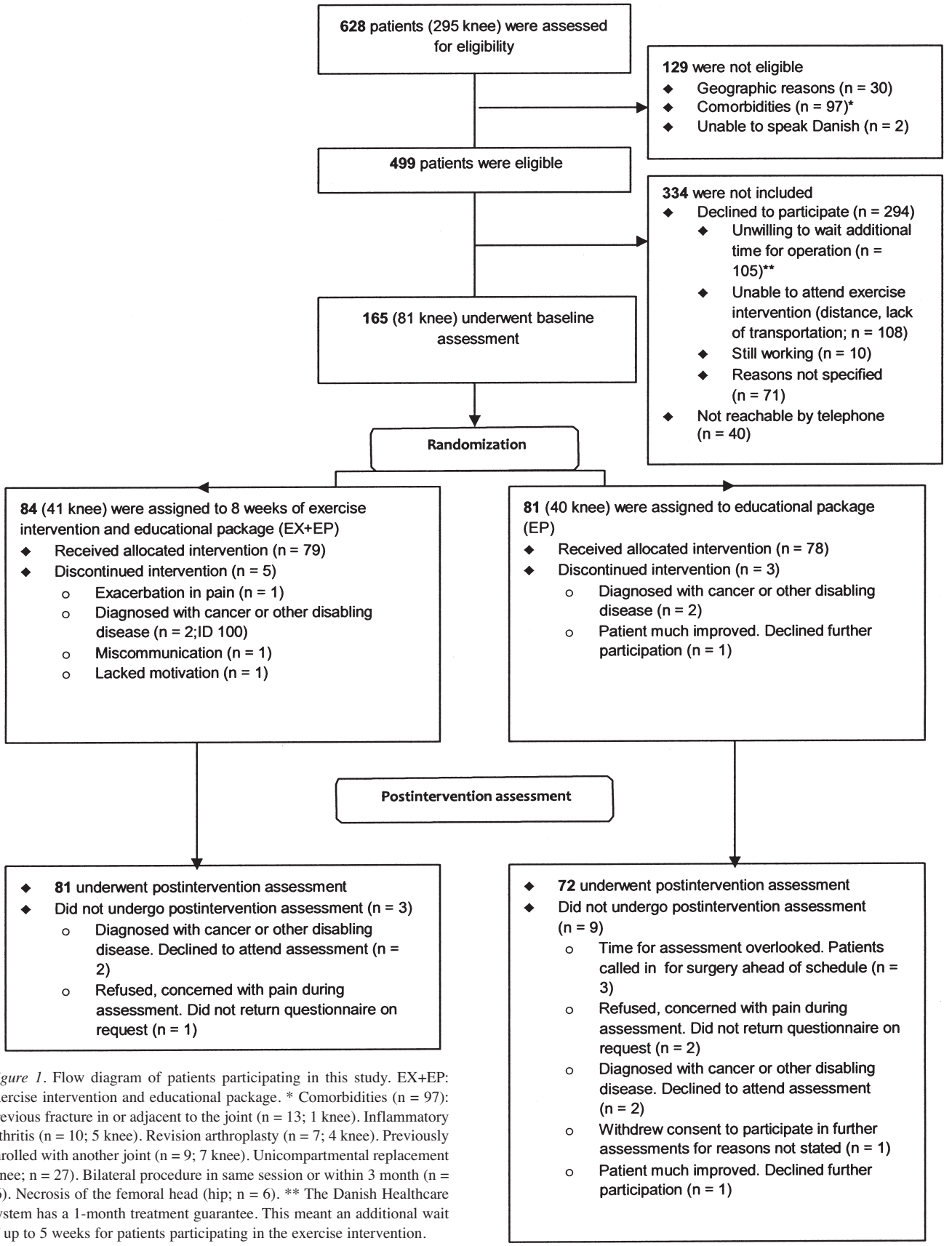

Figure 1. Flow diagram of patients participating in this study. EX+EP: exercise intervention and educational package. * Comorbidities (n = 97): Previous fracture in or adjacent to the joint (n = 13; 1 knee). Inflammatory arthritis (n = 10; 5 knee). Revision arthroplasty (n = 7; 4 knee). Previously enrolled with another joint (n = 9; 7 knee). Unicompartmental replacement (knee; n = 27). Bilateral procedure in same session or within 3 month (n = 16). Necrosis of the femoral head (hip; n = 6). ** The Danish Healthcare System has a 1-month treatment guarantee. This meant an additional wait of up to 5 weeks for patients participating in the exercise intervention.

Table 1. Baseline characteristics of study participants*.

Characteristics	All Patients, n = 84	EX + EP Knee OA, n = 41	Hip OA, n = 43	All Patients, n = 81	EP Knee OA, n = 40	Hip OA, n = 41
Female sex, no.	47	25	22	45	24	21
Age, yrs	67.9 ± 8.6	67.1 ± 8.8	68.7 ± 8.4	66.9 ± 8.3	65.1 ± 9.0	68.6 ± 7.1
BMI, kg/m^2	29.6 ± 4.5	30.8 ± 4.9	28.5 ± 3.9	31.1 ± 6.1	33.4 ± 5.8	28.8 ± 5.5
Patient-reported						
KOOS/HOOS ADL	50.6 ± 15.3	53.3 ± 15.2	48.0 ± 15.0	45.6 ± 16.9	43.9 ± 13.8	47.3 ± 19.4
KOOS/HOOS Pain	46.8 ± 14.3	47.8 ± 14.9	45.8 ± 13.9	42.7 ± 14.4	39.7 ± 12.6	45.6 ± 15.6
KOOS/HOOS Symptoms	49.4 ± 14.3	57.8 ± 20.9	41.4 ± 14.6	44.6 ± 18.6	49.3 ± 19.0	40.0 ± 17.4
KOOS/HOOS Sport and Recreation	24.6 ± 17.2	20.0 ± 18.4	29.0 ± 14.8	19.8 ± 18.1	10.7 ± 15.0	28.5 ± 16.7
KOOS/HOOS Quality of Life	31.2 ± 12.1	30.9 ± 13.1	31.5 ± 11.2	28.9 ± 15.9	27.1 ± 16.8	30.6 ± 15.1
Functional performance						
Chair stands, s	13.3 ± 5.4	13.5 ± 5.9	13.1 ± 5.1	13.9 ± 4.4	14.4 ± 4.3	13.4 ± 4.5
20-m walk, self-chosen pace, s	18.6 ± 5.5	18.8 ± 5.9	18.4 ± 5.2	19.9 ± 6.0	20.3 ± 6.1	19.5 ± 6.0
20-m walk, maximal pace, s	15.0 ± 4.8	14.8 ± 4.4	15.2 ± 5.3	16.3 ± 5.4	17.0 ± 6.1	15.6 ± 4.7
Knee bends, no.§, Index	15.5 (6;23.5)	11 (1;18)	19 (10;28)	14 (2;23)	2.5 (0;10)	20 (15;26)
Knee bends, no.§, Contra	20 (12.5;26.5)	16 (8;24)	22 (16;28)	19 (12;26)	15 (10;20)	24 (16;28)
Muscle power						
Single-joint knee extension, W§ Index	38.5 (18.2;68)	34.5 (12;51.3)	41.2 (21.3;74.4)	32.6 (17.5;62)	35.5 (16.5;57.2)	32.2 (18.1;71)
Contra	53.2 (30;84.6)	46.7 (23.6;72.5)	56.8 (38.3;94.6)	48.3 (30.6;90.4)	43.4 (27.8;87.6)	58.3 (33.6;90.7)
Single-joint hip extension, W§ Index	30 (15.5;49.4)	33.9 (17.2;55.9)	22.2 (15.3;38)	32.3 (19.6;52.3)	36.1 (25.2;61.9)	30.3 (16.2;45.3)
Contra	33.7 (18;56.4)	37.5 (14.7;54.9)	31.1 (18.4;57.3)	33.8 (18;51.4)	34 (19.8;64.8)	32.9 (15.9;48.7)
Single joint hip abduction, W§ Index	18.8 (12;27.9)	24.2 (13.2;39.9)	14.2 (7.8;22.2)	18.9 (12.4;33.4)	26.3 (17.7;46.7)	15 (10.1;21)
Contra	23.8 (14.2;34.1)	22.3 (13.1;35.1)	23.8 (16;30.7)	22.1 (13;38.3)	27.1 (17.3;41.8)	20 (11;28.5)
Multijoint leg extension, W§ Index	72 (46;102)	67 (46;87)	74.5 (48;108)	70 (46;119)	69 (43;114)	73 (51.5;130)
Contra	86 (69;121)	82 (67;117)	92.5 (73;124)	95 (62;149)	88.5 (62;133.5)	107 (65;150)

EX + EP: 8 weeks exercise intervention plus educational package; EP: educational package alone. * Continuous variables are expressed as the mean ± SD; noncontinuous variables are expressed as the number of patients. § Data showed a non-gaussian distribution, thus they are presented as median and interquartile range. OA: osteoarthritis; KOOS: Injury and Osteoarthritis Outcome Score; HOOS: Hip Disability and Osteoarthritis Outcome Score (scores range from 0 to 100 with higher scores indicating fewer problems); Index: leg to undergo surgery; Contra: contralateral leg; ADL: Activities of Daily Living.

severe OA[4,15]. Further, separate analysis of patients with hip and knee OA confirm a more favorable result for the patients with hip OA[4,15]. This is the first exercise study in patients with severe OA with a sufficient sample size to not only allow detection of clinically relevant differences between groups, but also to allow comparison of patients with knee and hip OA.

Explanation of the results. The exercise interventions applied in OA research are heterogeneous, which makes comparison across studies challenging. The neuromuscular exercise intervention used in this study is well described, focuses on the quality of the performance in each exercise, and is individualized, and it progressed through therapist supervision[6]. It is encouraging to observe a significant effect on patient perception of their ADL alongside improvement in functional performance. Only 1 patient discontinued the exercise intervention owing to exacerbation of pain. Whether the exacerbation in pain was induced by the exercise or a flare in disease is unknown. Seventy-eight percent of the patients receiving the exercise treatment had good compliance. Overall, we can confirm the NEMEX-TJR program is safe and feasible in patients with clinically severe hip or knee OA.

OA is often thought of as a general chronic condition with variation only in the joints affected. The differences between patients with hip and knee OA observed in our study confirm that patients with severe hip and knee OA respond differently to different treatments for OA. While our finding of greater improvement in patients with hip OA is in line with prior smaller exercise studies[4,15] and surgical studies[16], the results are contradictory to the greater effect in patients with knee OA seen after treatment with naproxen[17]. We have found no consistency in our exploratory outcomes to explain the greater improvement seen in the patients with hip OA. To our knowledge, there are no previous sufficiently powered studies on exercise in OA that enable direct comparison on the same intervention in patients with hip and knee OA. Whatever the exact course of rehabilitation in OA, our study adds to the body of evidence suggesting that different measures may need to be taken to individualize and optimize the treatment for patients with hip and knee OA[3].

The overall number needed to treat was 7 patients in our study (4.5 and 23 for hip and knee OA, respectively). For the patients with hip OA, we found a moderate effect size of about 0.6 for ADL and Pain, making the treatment effect of neuromuscular exercise similar to that of exercise as

Table 2. Mean change in patient-reported outcomes between baseline and following 8 weeks intervention*.

Outcome	Change EX + EP, n = 84	Change EP, n = 81	Difference Between Mean Changes	95% CI of Difference Between Mean Changes	P	SMD‡ Estimate (95% CI)
Primary outcome, Intention to treat analysis						
KOOS/HOOS ADL						
All patients	5.0 ± 1.3	–2.2 ± 1.3	–7.2	–10.9;–3.5	0.0002	0.45 (0.19, 0.70)
Knee OA	2.6 ± 1.9	–0.9 ± 1.9	–3.5	–8.8;1.8	0.1915	0.23 (–0.14, 0.60)
Hip OA	7.3 ± 1.8	–3.6 ± 1.8	–10.9	–15.9;–5.8	< 0.0001	0.63 (0.26, 1.00)
Primary outcome, per protocol analysis†						
KOOS/HOOS ADL	n = 78	n = 67				
All patients	5.3 ± 1.4	–2.7 ± 1.4	–8.0	–12.0;–4.0	0.0001	—
Knee OA	2.7 ± 2.0	–1.1 ± 2.0	–3.8	–9.4;1.8	0.1832	—
Hip OA	7.8 ± 1.9	–4.3 ± 2.1	–12.1	–17.7;–6.5	< 0.0001	—
Secondary outcomes, Intention-to-treat analysis						
KOOS/HOOS Pain						
All patients	4.2 ± 1.1	–1.1 ± 1.1	–5.3	–8.4;–2.1	0.0012	0.37 (0.11, 0.62)
Knee OA	3.0 ± 1.6	0.8 ± 1.6	–2.2	–6.7;2.4	0.3479	0.15 (–0.21, 0.52)
Hip OA	5.4 ± 1.6	–3.0 ± 1.6	–8.4	–12.8;–4.0	0.0002	0.57 (0.20, 0.94)
KOOS/HOOS Symptoms						
All patients	3.4 ± 1.2	–0.4 ± 1.3	–3.8	–7.3;–0.3	0.0358	—
Knee OA	4.9 ± 1.9	0.5 ± 1.8	-4.4	-9.4;0.7	0.0907	—
Hip OA	1.9 ± 1.8	–1.3 ± 1.8	–3.2	–8.1;1.7	0.1978	—
KOOS/HOOS Sport & recreation						
All patients	2.9 ± 1.4	–1.6 ± 1.5	–4.5	–8.7;–0.4	0.0329	—
Knee OA	–1.7 ± 2.1	–2.8 ± 2.3	–1.1	–7.1;5.0	0.7268	—
Hip OA	7.6 ± 2.1	–0.5 ± 2.1	–8.0	–13.8;–2.2	0.0068	—
KOOS/HOOS Quality of Life						
All patients	3.2 ± 1.3	–2.4 ± 1.3	–5.6	–9.3;–1.9	0.0034	—
Knee OA	3.8 ± 1.9	–2.5 ± 1.9	–6.3	–11.6;–1.0	0.0202	—
Hip OA	2.7 ± 1.8	–2.2 ± 1.9	–4.9	–10.1;0.3	0.0643	—

*Values are mean ± SEM. † A full per-protocol analysis was carried out for all outcome measures. ‡ SMD: Standardized mean difference. Calculated with the difference in between-group mean change scores in the numerator and the baseline-pooled SD in the denominator. Intention-to-treat analysis. EX + EP: 8 weeks exercise intervention plus educational package; EP: educational package alone. Statistical analysis by analysis of covariance, adjusted for the effect of baseline value, OA location, group, and the location-group interaction term. OA: osteoarthritis; ADL: Activities of Daily Living; KOOS: Injury and Osteoarthritis Outcome Score; HOOS: Hip disability and Osteoarthritis Outcome Score (scores range from 0 to 100 with higher scores indicating fewer problems).

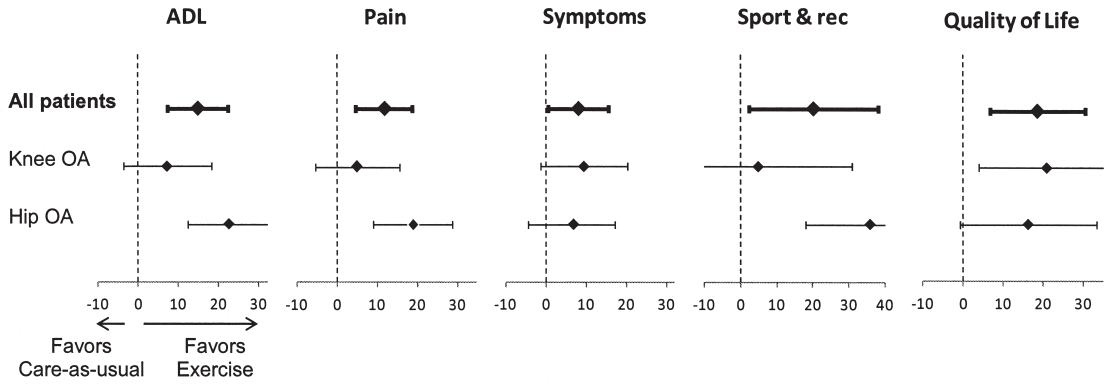

Figure 2. HOOS/KOOS difference between means given in percent of the overall baseline mean. OA: osteoarthritis; HOOS/KOOS: Hip disability and Osteoarthritis Outcome Score and the Knee Injury and Osteoarthritis Outcome Score; ADL: Activities of Daily Living.

Table 3. Number needed to treat and standardized mean difference for ADL and Pain subscales.

Measure	EX + EP		EP		NNT†
	N	n (%)	N	n (%)	Estimate (95% CI)§
ADL improvement					
All patients	84	28 (33)	81	15 (19)	7 (4, 72)
Knee OA	41	10 (24)	40	8 (20)	23 (5, –7)
Hip OA	43	18 (42)	41	7 (17)	4 (2, 19)
Pain improvement					
All patients	84	29 (35)	81	16 (20)	7 (4, 86)
Knee OA	41	13 (32)	40	10 (25)	15 (4, –8)
Hip OA	43	16 (37)	41	6 (15)	4 (2, 27)

† NNT: number needed to treat. Calculated as 1/(EER-CER), where CER is the event rate in the control group and EER is the event rate in the exercise group, with the event being at least a 15% improvement. § CI are calculated by reciprocal transformation of risk difference CI. EX + EP: 8 weeks exercise intervention plus educational package; EP: educational package alone; OA: osteoarthritis; ADL: Activities of Daily Living.

treatment for mild to moderate knee OA[2] and twice as effective as weight loss for obese patients with knee OA[3,18,19] and nonsteroidal antiinflammatory drugs in patients with moderate to severe pain from knee OA[3,20].

We are aware of the challenges in defining minimal important change[21,22,23]. We chose to characterize patients as responders when improving 15% or more on the ADL and Pain subscales. This cutoff was chosen to allow direct comparison with a recently published exercise trial in patients with chronic knee pain[14]. The number needed to treat in the respective studies was 4 for patients with chronic knee pain recruited within primary care and 7 (23 for knee OA) in our study, which involved patients with severe OA recruited from secondary care. For knee OA, the BMI and age of our cohort were similar to those reported by Hurley, *et al*[14], but our cohort had more pain and worse physical function at baseline, which reflects a more severe disease stage. It should be noted that the interventions used here and by Hurley, *et al* differed both with respect to the level of information given and the exercise program used.

The strength of our study is that it comprised a rigorous trial with a well-documented intervention evaluated with outcome measures valid within the context of OA. We included patients with hip and knee OA based on a sample size that allowed subgroup analysis.

Our study also has limitations. The design of the study, a randomized controlled trial comparing neuromuscular exercise with a minimal intervention (care as usual), was chosen to serve our 2 purposes: (1) to evaluate the efficacy of neuromuscular exercise in patients with clinically severe OA (as opposed to those with mild or moderate OA), and (2) to allow postoperative evaluation of the additional effect of preoperative neuromuscular exercise to surgery. Because many studies evaluating the postoperative results of preoperative exercise have applied programs with a low therapeutic effect[5], we found it of great value to report the immediate preoperative effects from the exercise program separately. It would have been optimal with a placebo exercise intervention for the control group. However, we are unaware of one that is believable or valid. The current study, like all studies comparing exercise therapy to interventions without an exercise component, is limited by the inability to conceal the treatment allocation from the patient. We included patients with OA scheduled for TJR to serve as a model for clinically severe OA. The clinical severity of the disease was confirmed not only through eligibility for surgery but also by a mean HOOS/KOOS Pain score of about 45 (Table 1). A limitation of our study is that radiographs obtained were for clinical use only and not scored using a common OA grading system such as the Kellgren and Lawrence system[24]. Thus, it is not known whether these patients actually had severe structural OA.

This trial was conducted in 1 location by 2 therapists, so one could argue that the improvements seen were therapist-dependent or location-dependent. We included 165 (33%) of 499 eligible patients. The high number of patients not included was mainly due to geographic reasons and/or their decision not to have additional waiting time before undergoing surgery. Owing to the treatment guarantee in Denmark, we considered it unethical to leave the control group waiting an additional 4 to 5 weeks because no additional intervention was applied in this time period for this group. Hence, they were added to the usual waiting list. We considered of no clinical importance the resulting 3.5 weeks' difference in median waiting time between groups[25,26].

The observed differences in self-reported outcomes may be due to attention bias, because no measures were taken to comply with this. However, we included functional performance measures because it has been emphasized that patient-reported outcomes may not give the full picture of the patient's physical state[27,28]. The observed parallel improvements in most of the functional performance measures support the improvements in the primary and

Table 4. Mean change in functional performance measures and muscle power variables*.

Outcome	Change		Difference Between Means	95% CI of Difference Between Means	p
	EX + EP	EP			
Functional performance					
Chair stands, s†					
All patients	–2.9 ± 0.4	–0.9 ± 0.4	1.9	0.9;3.0	0.0003
Knee OA	–3.0 ± 0.5	–1.1 ± 0.5	1.9	0.5;3.3	0.0093
Hip OA	–2.7 ± 0.5	–0.8 ± 0.5	1.9	0.5;3.4	0.0106
20-m self-chosen pace, s†					
All patients	–1.2 ± 0.3	–0.3 ± 0.3	0.9	0.0;1.8	0.0491
Knee OA	–1.3 ± 0.4	–0.9 ± 0.5	0.4	–0.8;1.7	0.5100
Hip OA	–1.1 ± 0.4	0.2 ± 0.5	1.4	0.1;2.7	0.0339
20 m maximal pace, s†					
All patients	–0.7 ± 0.3	0.1 ± 0.3	0.9	–0.1;1.8	0.0645
Knee OA	–0.5 ± 0.5	–0.4 ± 0.5	0.1	–1.2;1.4	0.8648
Hip OA	–1.0 ± 0.5	0.7 ± 0.5	1.6	0.3;3.0	0.0154
Knee bends, no. Index†					
All patients	3.3 ± 0.8	–0.3 ± 0.8	–3.6	–5.8;–1.4	0.0018
Knee OA	2.2 ± 1.1	–2.0 ± 1.3	–4.1	–7.3;–1.0	0.0115
Hip OA	4.3 ± 1.1	1.3 ± 1.2	–3.0	–6.2;0.1	0.0577
Knee bends, no. Contra†					
All patients	2.0 ± 0.8	0.5 ± 0.9	–1.5	–3.9;1.0	0.2349
Knee OA	0.7 ± 1.2	–0.1 ± 1.3	–0.8	–4.3;2.7	0.6514
Hip OA	3.2 ± 1.2	1.1 ± 1.3	–2.1	–5.6;1.3	0.2185
Leg muscle power					
Single-joint knee extension, W Index†					
All patients	7.1 ± 3.3	4.5 ± 3.5	–2.6	–12.2;7.1	0.5970
Knee OA	9.3 ± 4.9	–2.2 ± 5.1	–11.6	–25.6;2.5	0.1052
Hip OA	4.8 ± 4.6	11.2 ± 4.9	6.4	–6.9;19.7	0.3424
Single-joint knee extension, W Contra†					
All patients	2.8 ± 2.8	–0.7 ± 2.9	–3.4	–11.4;4.5	0.3935
Knee OA	–2.2 ± 4.0	–0.2 ± 4.1	2.0	–9.2;13.3	0.7249
Hip OA	7.8 ± 3.9	–1.1 ± 4.1	–8.9	–20.2;2.4	0.1206
Single-joint hip extension, W Index†					
All patients	2.6 ± 3.1	–4.4 ± 3.2	–7.0	–15.9;1.9	0.1200
Knee OA	7.4 ± 4.2	1.3 ± 4.6	–6.1	–18.4;6.3	0.3315
Hip OA	–2.1 ± 4.5	–10.1 ± 4.6	–7.9	–20.7;4.8	0.2196
Single-joint hip extension, W Contra†					
All patients	10.6 ± 4.6	4.6 ± 4.8	–6.0	–19.2;7.3	0.3724
Knee OA	5.7 ± 6.5	11.5 ± 6.9	5.8	–12.9;24.5	0.5420
Hip OA	15.5 ± 6.6	–2.3 ± 6.8	–17.8	–36.5;0.9	0.0626
Single-joint hip abduction, W Index†					
All patients	5.4 ± 1.3	1.5 ± 1.4	–3.9	–7.8;–0.1	0.0448
Knee OA	5.0 ± 1.7	1.2 ± 1.9	–3.9	–9.0;1.2	0.1351
Hip OA	5.8 ± 2.0	1.9 ± 2.0	–3.9	–9.4;1.7	0.1701
Single joint hip abduction, W Contra†					
All patients	4.3 ± 2.4	4.4 ± 2.5	0.1	–6.9;7.1	0.9814
Knee OA	4.8 ± 3.4	6.0 ± 3.6	1.2	–8.6;11.1	0.8061
Hip OA	3.9 ± 3.5	2.8 ± 3.6	–1.1	–11.0;8.9	0.8342
Multijoint leg extension, W Index†					
All patients	6.5 ± 3.1	0.7 ± 3.2	–5.9	–14.6;2.9	0.1874
Knee OA	7.7 ± 4.3	2.7 ± 4.5	–5.0	–17.3;7.2	0.4167
Hip OA	5.4 ± 4.3	–1.3 ± 4.6	–6.7	–19.1;5.8	0.2913
Multijoint leg extension, W Contra†					
All patients	12.1 ± 3.2	2.0 ± 3.4	–10.1	–19.3; –0.8	0.0328
Knee OA	5.6 ± 4.6	–1.9 ± 4.7	–7.5	–20.5;5.4	0.2533
Hip OA	18.5 ± 4.6	5.8 ± 4.8	–12.7	–25.8;0.5	0.0592

*Values are mean ± SEM. † Statistical analysis by analysis of covariance, adjusted for the effect of OA location and body mass index. EX + EP: 8 weeks exercise intervention plus educational package; EP: educational package alone; Index: leg to undergo surgery: Contra: contralateral leg; OA: osteoarthritis.

secondary outcomes being generated by the neuromuscular exercise.

Lastly, by chance, the patients with knee OA differed from the control group in baseline characteristics because they had a larger BMI and were slightly younger. To evaluate the effects of this, we performed a posthoc-adjusted per protocol analysis on the primary and secondary outcomes. These adjusted analyses showed no difference from the primary unadjusted analyses (supplementary material available from the author upon request). Further, adding the interaction term adherence (defined as participating in at least 12 supervised sessions) revealed no interaction of adherence on the difference in effect seen between hip and knee patients or between the 2 intervention groups (data not shown).

Participation in neuromuscular exercise for 8 weeks according to the NEMEX-TJR program improves ADL, objective functional performance, and quality of life and reduces pain in patients with OA prior to total joint replacement. While it was only necessary to treat 4 patients with hip OA for 1 to report a clinically meaningful improvement of activities of daily living, 23 patients with knee OA needed to be treated for one to improve in a clinically meaningful way. Our study confirms previous findings from nonrandomized studies that neuromuscular exercise is feasible and safe for patients with severe OA. Neuromuscular exercise offers clinically relevant improvements of up to 20% in physical function and pain and constitutes a viable treatment option before surgery in patients eligible for total joint replacement.

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