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Progressive resistance training before and after total knee arthroplasty

Associations between muscle strength and functional performance

and efficacy of preoperative progressive resistance training

PhD thesis

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Preface

The scientific work presented in this thesis was carried out as a PhD project from November 2011 to October 2014 at the Orthopedic Research Center, Department of Physical and Occupational Therapy, Aarhus University Hospital, and Department of Public Health, Section for Sports Science, Aarhus University.

The following pages contain an introduction describing the current knowledge regarding physical exercise before total knee arthroplasty (TKA), a description of the applied methods, a presentation of the findings, and a discussion followed by conclusions and perspectives. The review (Paper I) also deals with and discusses progressive resistance training (PRT) before and after total hip arthroplasty (THA), but in this introduction the focus is on TKA. Finally, the results are presented in four papers (I–IV).

List of papers

I Skoffer B, Dalgas U, Mechlenburg I. Progressive resistance training before and after total hip and knee arthroplasty: A systematic review. Clin Rehabil. 2015 Jan;29(1):14-29.

II Skoffer B, Dalgas U, Mechlenburg I, Søballe K, Maribo T. Functional capacity is associated with both extensor and flexor strength in patients scheduled for Total Knee Arthroplasty: a cross-sectional study. Journal of Rehabilitation Medicine 2014. Accepted for publication

III Skoffer B, Maribo T, Mechlenburg I, Hansen PM, Søballe K, Dalgas U. Efficacy of preoperative progressive resistance training on postoperative functional performance and muscle strength in patients undergoing total knee arthroplasty. A randomized controlled study. *Submitted*

IV Skoffer B, Dalgas U, Maribo T, Søballe K, Mechlenburg I. No exacerbation of knee joint pain and effusion following preoperative progressive resistance training in patients scheduled for total knee arthroplasty. *Submitted*

Contents

Abbreviations

ANOVA	Repeated measures analyses of variance
KOOS	Knee injury and osteoarthritis outcome score
OA	Osteoarthritis
PEDro	Physiotherapy evidence database
PRT	Progressive resistance training
RCT	Randomized controlled trials
RM	Repetition maximum
ROM	Range of motion
SD	Standard deviation
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
TUG	Timed-up-and-go
6 MWT	6 minute walk test
10 mWT	10-m walk test
30sCST	30-s chair stand test

1. Summary

Efficacy of preoperative progressive resistance training on postoperative functional performance and muscle strength in patients undergoing total knee arthroplasty

Reduced knee extensor muscle strength is a common clinical finding in subjects with knee osteoarthritis (OA), and the strength deficit appears to play a key role in the development and progression of the disease. An additional surgery-induced loss of knee extensor muscle strength of 60–80% has been demonstrated at discharge following total knee arthroplasty (TKA), and the loss of muscle strength is closely associated with a decline in functional performance. Even several years after TKA, patients do not reach the level of functional performance seen in healthy adults.

The main purposes of this PhD thesis were A) In a systematic review to investigate the effect of progressive resistance training (PRT) on muscle strength and functional performance before and/or after total hip arthroplasty (THA) and TKA (Paper I). B) To test in patients scheduled for TKA whether muscle strength would be 1) strongly associated with both measured functional performance and patient-reported measures; 2) more closely associated with functional performance when measured during concentric rather than during isometric contractions and; 3) more strongly related to the 30-s chair stand test (30sCST) than to the timed-up-and-go (TUG) and walking measures (Paper II). C) To investigate the efficacy of 4 weeks of preoperative and 4-week post-operative PRT compared to 4 weeks of post-operative PRT only on functional performance, muscle strength, and patient-reported outcomes in patients undergoing TKA (Paper III); and D) to examine whether PRT initiated 5 weeks prior to TKA exacerbate pain and knee swelling (Paper IV).

Literature from a systematic search in nine databases was reviewed (Paper I). Fifty-nine patients were included, and associations between muscle strength and measured functional performance and patient-reported measures were calculated (Paper II). The 59 included patients were randomized to 4 weeks of pre-operative PRT (intervention group) or to a group who “lived as usual” (control group). Both groups performed 4 weeks of PRT after TKA. At 6 and 1 weeks before TKA, and at 1, 6, and 12 weeks after TKA, performance-based measures, muscle strength, and patient-reported measures were evaluated (Paper III). Thirty patients performed preoperative PRT, three sessions per week for 4 weeks. At each training session, training load, knee pain, and knee swelling were recorded (Paper IV).

Four randomized controlled trial (RCT) studies on PRT and THA and three RCT studies on TKA were identified and rated according to the PEDro scale. Weak evidence of a beneficial effect of PRT before and/or after THA on muscle strength and functional performance was found. There was no effect of PRT on muscle strength and functional performance before TKA. The results of postoperative PRT were too heterogeneous to allow conclusions (Paper I). Both knee extensor and knee flexor strength were associated with performance-based measures. Generally, concentric knee flexor muscle strength was more strongly associated with functional performance than isometric knee flexor strength. Concentric and isometric knee extensor strength were of equal importance. The 30sCST was better than the TUG and the walking tests at determining muscle strength (Paper II). A significant group difference in favor of the intervention group was found for the 30sCST, TUG, knee extensor muscle strength, and knee flexor muscle strength when evaluated at the predefined primary test point 6 weeks after TKA. No differences were found between groups with regard to patient-reported outcomes (Paper III). The majority of patients experienced only minor knee pain during the PRT, despite a substantial increase in training load over time. Likewise, knee swelling was modest (Paper IV).

2. Summary in Danish

Effekten af præoperativ progressiv styrketræning vurderet på funktionsniveau og muskelstyrke postoperativt hos patienter med total knæalloplastik

Reduceret knæextensor muskelstyrke er et almindeligt klinisk fund hos patienter med artrose i knæet og dette styrkedeficit ser ud til at spille en central rolle i udviklingen og progression af sygdommen. Et yderligere kirurgiinduceret tab af knæextensor muskelstyrke på 60-80% er blevet påvist ved udskrivelsen efter total knæalloplastik (TKA), og tabet af muskelstyrke er tæt forbundet med et fald i funktionsniveauet. Selv flere år efter TKA, synes patienterne ikke at nå samme funktionsniveau som hos raske voksne.

De vigtigste formål med denne afhandling var A) i et systematisk review at undersøge effekten af progressiv styrketræning (PST) på muskelstyrke og funktionsniveau før og/eller efter total hoftealloplastik (THA) og TKA (Paper I). B) at undersøge hos patienter, opskrevet til TKA, om muskelstyrke var 1) associeret med både målt funktionsniveau og patientrapporterede outcomes; 2) tættere associeret med funktionsniveau, når der blev målt med koncentriske kontraktioner end ved måling af isometriske kontraktioner og; 3) stærkere associeret med 30-s chair stand test (30sCST) end timed-up-and-go (TUG) og gangtest (Paper II). C) At undersøge effekten af 4 ugers præoperativ og 4 ugers postoperativ PST sammenlignet med 4 ugers postoperativ PST alene på funktionsniveau, muskelstyrke og patientrapporterede outcomes hos patienter, der har gennemgået TKA (Paper III); og D) at undersøge, om præoperativ PST med start fem uger før TKA ville forværre knæsmerter og hævelse (Paper IV).

Litteratur fra systematisk søgning i ni databaser blev gennemgået (Paper I). Blandt 59 inkluderede patienter blev associationer mellem muskelstyrke og målt funktionsniveau og patientrapporteret funktionsniveau beregnet (Paper II). De 59 inkluderede patienter blev randomiseret til 4 ugers præoperativ progressiv styrketræning (interventionsgruppen) eller til en gruppe, der "levede som de plejede" (kontrolgruppe). Begge grupper gennemførte 4 ugers PST efter TKA. Ved test 6 uger og 1 uge før TKA og 1, 6 og 12 uger efter TKA blev funktionstest, muskelstyrke, patientrapporteret outcome evalueret (Paper III). Tredive patienter gennemførte præoperativ PST 3 sessioner ugentligt i 4 uger. Ved hver træningssession blev knæhævelse, knæsmerter og træningsbelastning registreret (Paper IV).

Fire randomiserede, kontrollerede undersøgelser om PST og THA og 3 randomiserede undersøgelser om TKA blev identificeret og vurderet i henhold til PEDro skalaen. Der fandtes svag evidens for effekt af PST før og/eller efter THA på muskelstyrke og funktionsniveau. Ingen effekt af PST på muskelstyrke og funktionsniveau før TKA. Resultaterne af postoperativ PST var for heterogene til, at konklusioner kunne drages (Paper I). Både knæets extensor og flexor styrke var associeret med funktionsmål. Generelt blev den koncentriske knæflexor muskelstyrke stærkere associeret med funktionsniveau end den isometriske knæflexions styrke. Koncentrisk og isometrisk knæextensor styrke havde samme betydning. 30sCST var bedre end TUG og gangtestene til evaluering af muskelstyrke (Paper II). En betydelig gruppeforskel til fordel for interventionsgruppen blev fundet for 30sCST, TUG, knæextensor muskelstyrke og knæflexionsstyrke, evalueret ved det foruddefinerede primære testtidspunkt 6 uger efter TKA. Der blev ikke fundet nogen forskelle mellem grupperne på patient rapporterede resultater (Paper III). Størstedelen af patienterne oplevede kun mindre smerter i knæet under PST, på trods af en betydelig stigning i træningsbelastning over tid. Ligeledes var knæhævelsen beskeden (Paper IV).

3. Thesis at a glance

Paper	Purpose	Patients	Methods	Results	Conclusion
I	In a systematic review to investigate the effect of progressive resistance training on muscle strength and functional capacity before and/or after total hip or knee arthroplasty.	Four randomized controlled trials of total hip arthroplasties that included 136 patients and three randomized controlled trials of total knee arthroplasty that included 284 patients.	A systematic literature search in nine databases was performed. The methodological quality was evaluated using the PEDro scale.	Beneficial effect of PRT before and/or after THA. No effect of PRT before TKA. Results of postoperative PRT were heterogeneous.	PRT is safe and feasible before and/or after THA. PRT is safe, but the methodological quality of TKA studies permits no conclusion on the effectiveness of PRT before and/or after TKA.
II	To test whether knee extensor and knee flexor strength in patients scheduled for TKA would be 1) associated with both measured functional performance and patient-reported measures and; 2) more strongly related to the 30sCST than to the TUG test and walking measures.	59 patients with end-stage knee OA scheduled for TKA at two hospitals.	Patients were tested 6 weeks before surgery. The assessment included tests of muscle strength and functional performance, and patients completed questionnaire items on pain, functional performance, and quality of life.	Knee extensor and knee flexor strength were associated with functional performance outcomes. The 30sCST was better than the TUG and the walking tests at determining muscle strength.	Future rehabilitation programs may include both the knee extensor muscles and the knee flexor muscles to improve functional performance. The 30sCST may be a proxy measure of the knee extensors and the knee flexors.
III	To investigate the efficacy of 4 weeks of pre-operative and 4-week post-operative PRT compared to 4 weeks of post-operative PRT only on functional performance, muscle strength, and patient-reported outcomes in patients undergoing TKA.	59 patients with end-stage knee OA scheduled for TKA were randomly assigned to preoperative PRT or to the control group.	At 6 and 1 weeks before TKA, and at 1, 6, and 12 weeks after TKA performance-based measures, muscle strength, and patient-reported measures were evaluated.	A significant group difference in favor of the intervention group was found for the 30sCST, the TUG**,** muscle strength when evaluated 6 weeks after TKA. No differences were found between groups on patient-reported outcomes.	Pre-operative PRT is an efficacious intervention, improving post-operative recovery of functional performance and muscle strength, but not patient-reported outcomes.
IV	To investigate whether PRT initiated 5 weeks prior to TKA exacerbates pain and knee swelling.	30 patients performed preoperative PRT 3 sessions per week for 4 weeks.	At each training session, training load, knee pain, and knee swelling were recorded.1RM was tested at the first and last training session.	Patients experienced only minor knee pain after PRT, despite a substantial increase in training load over time. Likewise, knee swelling was modest.	PRT of the affected leg initiated shortly before TKA does not appear to exacerbate pain and knee swelling.

PEDro, Physiotherapy Evidence Database; PRT, progressive resistance training; THA, total hip arthroplasty; TKA, total knee arthroplasty; 30sCST, 30-s chair stand test; TUG, timed-up-and-go; RM, repetition maximum.

4. Introduction

4.0 Osteoarthritis

Osteoarthritis (OA) is a worldwide disease afflicting both load bearing and non-weight bearing joints (2). The disease is a prevalent health problem, often causing pain, decreased muscle strength, reduced functional capacity, and ultimately a lowered quality of life (2-4). OA can be defined pathologically, radiographically, or clinically (5); however, radiographs with use of the Kellgren and Lawrence grading system (6) are often used as the gold standard for defining the presence and severity of OA.

OA is the result of a complex interplay between mechanical, genetic, cellular, and biochemical factors (5,7). Age is one of the strongest predictors of OA (5,8); however, the exact mechanism behind the increased incidence and prevalence of OA with age is poorly understood. The female gender is associated with a higher prevalence and severity of OA than the male gender (2,3,9). Furthermore, considerable evidence indicates that obesity is one of the most important risk factors for knee OA (10,11).

According to the National Health Profile 2013, almost 900,000 Danes suffer from some degree of OA (12), and the annual costs for the Danish society are approximately 11.5 billion DKK (direct and indirect costs), including 5.4 billion DDK for treatment (13).

4.1 Knee osteoarthritis

Knee OA is characterized by progressive loss of articular cartilage, sclerosis of the subchondral bone, formation of osteophytes, and the presence of degenerative subchondral cysts (Figure 1). In some patients, there is clinically significant inflammation, including effusions and synovitis (14). When osteoarthritis of the knee becomes severe, joint deformities occur, most commonly as a varus or valgus deformity (14).

Women suffer more frequent from severe radiographic knee OA than men, particular following the menopause (2,3,9); however, the greatest risk factors are age and obesity (15). The populations of developed countries are ageing and rates of obesity are rising, hence an increase in rates of knee osteoarthritis is inevitable.

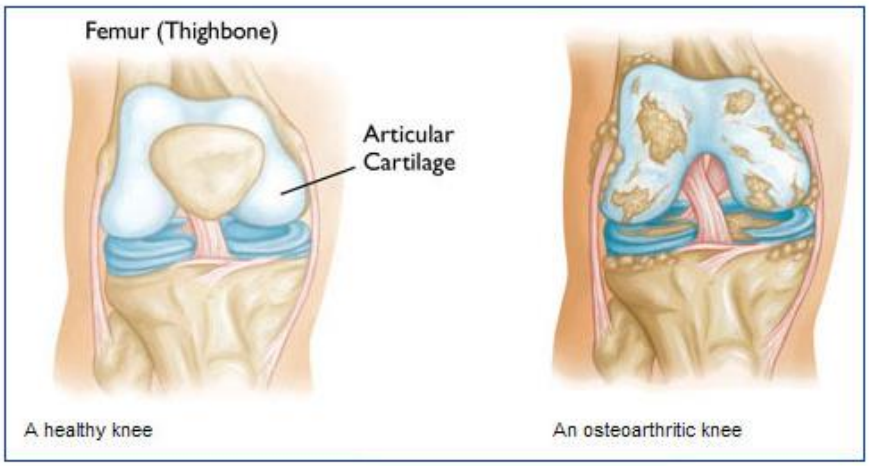


Figure 1. Normal knee anatomy and severe knee osteoarthritis (16)

4.2 Knee osteoarthritis and muscle strength

Deficits in muscle strength, activation, and proprioception are common in patients with knee OA and can occur as a consequence of disuse due to pain. However, studies have shown that muscle weakness may predispose to the onset of the disease and may potentially accelerate its progression (1,17,18). Deficits in isometric knee extensor muscle strength in subjects with knee OA range from 10% to 56% (19). Moreover, concentric isokinetic tests have revealed strength deficits ranging from 11% to 56% in subjects with knee OA compared with healthy controls (19). The largest deficits (76%) compared with healthy controls were seen in eccentric muscle strength (19). Although focus in the literature is largely on the knee extensor muscles, knee flexor strength deficits have been reported in patients compared with healthy controls, with isometric deficits ranging from 4% to 35% and concentric isokinetic deficits from 7% to 38% (19). Reduced muscle strength of other muscle groups in the involved leg has also been demonstrated (19).

4.3 Knee osteoarthritis, muscle mass, and neuromuscular mechanisms

Reduced muscle strength and changes in the skeletal muscle structure are normal consequences of the ageing process (20,21) . Muscle mass is lost at a rate of approximately 1% per year (20,21), whereas muscle strength is lost at a rate of 1.5–2.5% per year after the age of 60 (20,22). A possible

mechanism that could account for the apparent greater loss of strength than muscle mass is failure of voluntary muscle activation. This activation failure may result from either impairment in motor unit recruitment or motor unit firing rates (23,24).
In patients with knee OA, these changes are magnified (25). Voluntary activation deficits range from 4–30% in persons with various stages of knee OA (25). Quadriceps weakness in individuals with end-stage knee OA is more predominantly attributed to failure in muscle activation than to muscle atrophy (26).

4.4 Total knee arthroplasty

In end-stage OA not responding to non-surgical therapy, total knee arthroplasty (TKA) is a safe and cost-effective intervention (27-29). The main clinical indication for TKA is OA, which accounts for 94–97% of the operations (30,31).

Approximately 8,000 TKA operations per year are performed in Denmark. The number of operations increased from the 2000 to 2010, then decreased in 2011, and thereafter, the numbers have been approximately stationary (32). The overall 10-year implant survival is 92.6% for primary surgery (32).

The most commonly used surgical procedure is performed using a midline incision and a parapatellar approach. The damaged cartilage surfaces at the end of the femur and the tibia and the posterior surface of the patella are removed and replaced with cemented or uncemented tri-compartmental prostheses (14). However, no resurfacing of the patella is performed if the cartilage is intact (Figure 2).

Replacement of knee joints generally leads to pain reduction, correcting of joint alignment, improvement of physical function, and a high satisfaction rate (33,34). However, patients may not fully regain muscle strength and functional performance after surgery (35-39), and impairments of muscle strength and functional capacity remain below the level of a healthy age- and gender-matched population for years after TKA (40,41). Furthermore, about 20% of the patients may continue to endure knee pain or other knee problems after TKA (42-44).

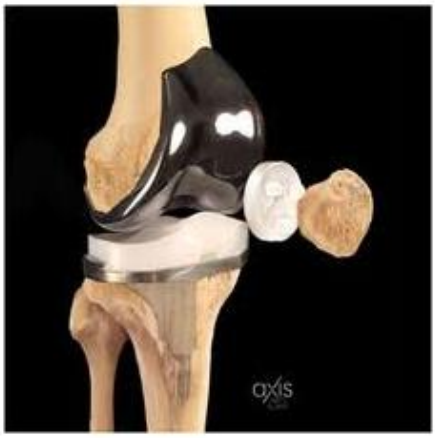


Figure 2. Artificial joint components of total knee arthroplasty and position in the tibia and femoral bone (45)

4.5 Fast track surgery

During the past 15 years, the fast-track surgery concept has been developed across surgical procedures (46-48), and the concept has during the past decade been successfully introduced in patients undergoing total hip arthroplasty (THA) and TKA (47-50). Fast track surgery aims at giving the patients the best available treatment at all times, being an evolving, dynamic entity, with clinical enhancements and concomitant organizational optimization constantly interacting (49). The goal is to reduce morbidity, mortality, and functional convalescence and to obtain an earlier achievement of functional milestones, including functional discharge criteria, with subsequent reduced length of hospital stay and high patient satisfaction (48,49). This multimodal intervention includes all areas of the patients' management, preoperative assessment, information and optimization, attenuation of surgical stress, pain treatment, mobilization and exercises, and oral nutrition (48,49). Decrease hospital stay to about 2 to 4 days in contrast to previously 4 to 12 days has been a consequence of fast-track surgery, without increasing the readmission rate (49,50).

4.6 Physical exercises before TKA

In 2003, the National Institute of Health convened a consensus development conference to compile the scientific evidence surrounding TKA to enhance guidelines for clinical decision making and patient clinical outcomes. One of the primary conclusions was that "the use of rehabilitation services was one of the most understudied aspects of the perioperative management of patients

following total knee replacement" and "there is no evidence supporting the generalized use of specific preoperative or postoperative rehabilitation interventions" (51).

Subsequently, different exercise programs have been applied before TKA, with the aim of optimizing functional performance after surgery (52-58) (Table 1), but none of the studies demonstrated improvements following the interventions. A systematic review and meta-analyses have furthermore demonstrated that therapeutic exercise was not associated with observed functional recovery during the hospital stay, observed recovery within 3 month of surgery, and self-reported recovery within 3 month of surgery compared with control participants (59). Moreover, a recent systematic review and meta-analysis including studies on preoperative rehabilitation concluded, that for all outcomes, none was consistently favorable toward preoperative rehabilitation compared with the alternative (60). However, another meta-analysis found low to moderate evidence from mainly small randomized controlled trials that pre-operative interventions, particularly exercise, reduce pain for patients with knee OA prior to TKA (61).

4.7 Progressive resistance training

Dr. Thomas DeLorme, a US army physician, experimented in 1945 with a new strength training rehabilitation technique. Delorme refined the system by 1948 to include three progressively heavier sets of 10 repetitions, and he referred to the program as "Progressive Resistance Exercise". The high-intensity program was markedly more successful than older training protocols (62). The concept has been further developed since (63). The effects of progressive resistance training (PRT) in increasing muscle strength and functional performance in healthy older adults is well documented (64,65). In recent years PRT is frequently applied in musculoskeletal rehabilitation studies, such as multiple sclerosis, cancer, and before and after orthopedic surgery (66-68).

4.8 Progressive resistance training before TKA

Two studies applying progressive resistance training before TKA were identified (Table 2). McKay et al. performed a pilot work evaluating 6 weeks of pre-operative PRT in TKA patients and found that PRT was feasible. Statistically insignificant improvements in strength and functional

Table 1. Schematic overview of randomized trials investigating efficacy of preoperative exercise interventions on recovery after total knee arthroplasty

Trials	Sample size (n)	Subjects diagnoses for TKA Age	Duration & frequency	Training regimen	Outcome (vs. control)
Beupre et al. (52) 2004	131	Non-inflammatory arthritis ~ 67 years	4 weeks 3 sessions/ week	Resistance training	Muscle strength NS Patient-reported outcomes NS
D'Lima et al. (53) 1996	20	Osteoarthritis and rheumatoid arthritis ~ 69 years	6 weeks 3 sessions/ week	Resistance training	HSS score NS Patient-reported outcomes NS
Rodgers et al. (54) 1998	23	Osteoarthritis 67.6 years	6 weeks 3 sessions/ week	Resistance training	Muscle strength NS Functional performance NS HSS score NS
Rooks et al. (55) 2006	45	Non-inflammatory arthritis ~ 67 years	6 weeks 3 sessions/ week	Resistance training	Muscle strength NS Functional performance NS Patient-reported outcomes NS
Topp et. al. (56) 2009	54	Osteoarthritis 63.8 years	3 sessions/ week until surgery	Resistance training	Muscle strength NS Functional performance NS
Williamson et al. (57) 2007	121	Non-inflammatory arthritis 69.8 years	6 weeks 1 session/ week	Resistance training	Functional performance NS Patient-reported outcomes NS
D'Lima et al. (53) 1996	20	Osteoarthritis and rheumatoid arthritis ~ 69 years	6 weeks 3 sessions/ week	Aerobic training	HSS score NS Patient-reported outcomes NS
Villadsen et al. (58) 2012	81	Osteoarthrits ~ 66 years	8 weeks 2 sessions/ week	Neuromus-cular exercise program	Patient-reported outcomes NS

Abbreviations: HSS: Hospital for Special Surgery knee rating, NS: non-significant

performance before surgery were demonstrated, but the improvements did not translate into post-TKA improvements when compared to a control group (69). The study was, however, limited by a small sample size, and because the training program was performed bilaterally, applying low loading. Van Leeuwen et al. found no effect of PRT added to standard training compared to standard training alone, either before or after TKA (70). Also this study had a small sample size.

Table 2. Schematic overview on randomized trials investigating efficacy of preoperative progressive resistance training interventions on recovery after total knee arthroplasty

Trials	Sample Size	Subjects diagnoses for TKA Age/Sex Start	Duration & frequency	Training regimen	Outcome (vs. control)
McKay et al. (69) 2012	RT: 10, UBT: 12 Total dropout: 6/22 = 27% RT dropout: 3/10 = 30% UBT dropout: 3/12 = 25% RT adherence: 98% UBT adherence: 93%	Osteoarthritis ~70 years +/-6 9M/13W 6 weeks before surgery	6 weeks 30 min/ session, 3 sessions/ week 18 sessions	RT: 4 leg exercises: Quadriceps, hamstrings, leg press, triceps surae (performed bilaterally) 2*8 reps Exercises progressed from 60% of 1RM with 1–2 kg per week as tolerated UBT: 4 exercises upper body training: Latissimus dorsi, chest press, biceps brachii, triceps brachii 2*8 reps Exercises progressed from 60% of 1RM with 1–2 kg per week as tolerated Supervised	**After intervention** KE (isom): NS 50 FOOT WT: NS Stair climbing test: NS WOMAC: NS HRQOL (SF-36): NS **At 6 weeks postop. follow-up** KE (isom): NS 50 FOOT WT: NS Stair climbing test: NS WOMAC: NS HRQOL (SF-36): NS **At 12 weeks postop. follow-up** KE (isom): NS 50 FOOT WT: NS Stair climbing test: NS WOMAC: NS HRQOL (SF-36): NS
Van Leeuwen et al. (70) 2014	RT: 11, Con: 11 Total dropout: 6/22 = 27% RT dropout: 2/11 = 18% Con dropout: 4/11 = 36% RT adherence: 100%	Osteoarthritis ~ 71 years 12M/10W 6 weeks before surgery	6 weeks 2-3 sessions/ week	RT: 4 leg exercises: Leg press, step-up, squat, leg extension (performed unilaterally) Exercises progressed from 3*15 reps 15RM to 4*8 reps 8RM Supervised	**After intervention** KE (isom): NS KF (isom): NS VA: NS CST: NS SCT: NS 6MWT: NS WOMAC: NS **At 6 weeks postop. follow-up** KE (isom): NS KF (isom): ↑ VA: NS CST: NS SCT: NS 6MWT: NS WOMAC: NS

(*Continued)*

Table 2 *(Continued)*

		At 12 weeks postop. fo **llow-up** KE (isom): NS KF (isom): NS VA: NS CST: NS SCT: NS 6MWT: NS WOMAC: NS

Abbreviations: RT, resistance training; Con, control group; UBT, upper body training; M, men; W, women; NS, non-significant; KE, knee extension; OP, operated leg; NOP, non-operated leg; Isom, isometric; CAR, central activation ratio; RM, repetition maximum; WT, walk test; HRQOL, health-related quality of life; VA, voluntary activation; CST, chair stand test; SCT, stair climbing test; 6MWT, 6 minute walk test; WOMAC, Western Ontario and McMasters Osteoarthritis Index; Rep, reptitions; ↑ indicates increase

4.9 Rehabilitation after TKA

Several studies have been performed to investigate the effect of different rehabilitation modalities aiming at reducing the strength loss and functional impairments after TKA. In a recent systematic review that included 19 studies investigating physical exercise after TKA (71), four categories of postoperative intervention were discussed: 1) strengthening exercises (72-76); 2) aquatic therapy (77-80); 3) balance training (81-83); and 4) clinical environment (84-90). The review concluded that not only should postoperative strengthening exercises be a primary component of postoperative care, but the exercise programs should be supervised and progressed as the patients meet clinical and strength milestones (71).

Several studies have been identified applying PRT after TKA (72,73,87,91) (Table 3). In one study the PRT intervention started early after TKA (within the first week), in three other studies the intervention started late (3–8 weeks postoperative). Only Petterson et al. demonstrated a long-term effect of PRT in comparison with an embedded group that had performed standard care rehabilitation (72).

Table 3. Schematic overview on randomized trials investigating efficacy of postoperative progressive resistance training interventions on recovery after total knee arthroplasty.

Trials	Sample size Dropouts Adherence %	Subjects Diagnoses for TKA Age/Sex Start	Duration & frequency	Training regimen	Outcome (vs. control)
Petterson et al. (25,72) 2009	RT: 100, RT+es: 100, Con: 41 Total dropout: 19/200 = 10% RT dropout: 3/100 = 3% RT+es dropout: 16/100 = 16% Adherence: mean 16.9+/1.3 visits	All diagnoses for TKA ~65yr +/- 8 122M/119W 3-4 weeks after TKA	6 weeks 2-3 sessions/ week 12-18 sessions	6 leg exercises Quadriceps, hamstrings, gastrocnemius, soleus, hip abductors and flexors (performed unilateral) Week 1-6: 10 RM 2-3 sets of 10 reps. Supervised ES group: +NMES RT group: -NMES Patients of 1 referring surgeon from the pooled RT and ES group Con. group: Patients of the referring surgeon represent the standard of care in the community	**At 3-month follow-up** KE-OP (isom): NS CAR: NS Timed Up and Go: NS 6MWT: NS Stair climbing test: NS HRQOL (SF-36): NS **At 12-month follow-up** KE-OP (isom): NS CAR: NS Timed Up and Go: NS 6MWT: NS Stair climbing test: NS HRQOL (SF-36): NS **At 12-month follow-up** KE-OP (isom) ↑ CAR: NS Timed Up and Go ↑ 6MWT ↑ Stair climbing test ↑ HRQOL (SF-36): NS
Johnson et al. (73) 2010	RT: 10 WBV: 11 Total dropout: 5/21 = 24% RT dropout: 2/10 = 20% Required to complete at least 10 out of 12 sessions.	Osteoarthritis ~68yr +/- 10 No information about sex between the dropouts 3–6 weeks after surgery	4 weeks 3 sessions/ week 12 sessions	2 leg exercises Knee extension, hip flexion 1-3 sets of 10 reps. Exercises were progressed once the patient could complete the exercise and extra weight (0.454–4.54 kg) were added. Supervised	**After intervention** KE-OP (isom): NS KE-NOP (isom): NS CAR-OP: NS CAR-NOP: NS Timed Up and Go: NS

Continued

Table 3. *(Continued)*

Madsen et al. (87) 2013	RT: 40 Con: 40 Total dropout: 12/80 = 15% RT dropout: 4/40 = 10% Con dropout: 8/40 = 20% Adherence: 87%	Osteoarthritis ~67yr 4-8 weeks after surgery	6 weeks 2 session/ week	4 leg exercises: Squat, leg press, leg extension, seated curls 1 set 10-12RM progressed to 3 sets 6-8RM Supervised	**At 3 months** Peak LEP: NS Sit-to-stand: NS 10m walk test: NS OKS: NS SF-36: NS **At 6 months** Peak LEP: NS Sit-to-stand: NS 10m walk test: NS OKS: NS SF-36: NS
Jakobsen et al. (91) 2014	RT: 40 Con: 39 Total dropout: 7/79 = 9% RT dropout: 5/40 = 13% Con dropout: 2/39 = 5%	All diagnoses ~65yr Within the first week after surgery	7 weeks 2 session/ week	2 leg exercises: Leg press, leg extension 2 sets 12 RM progressed to 2 sets 8RM Supervised	**At 8 weeks** KE-OP (isom): NS Leg press power: NS 6MWT: NS KOOS: NS OKS: NS EQ-5D: NS **At 26 weeks** KE-OP (isom): NS Leg press power: NS 6MWT: NS KOOS: NS OKS: NS EQ-5D: NS

Abbreviations: RT, resistance training; RT+es, resistance training combined with electrical stimulation; WBV, whole body vibration; Con, control group; M, men; W, women; NS, non-significant; KE, knee extension; OP, operated leg; NOP, non-operated leg; Isom, isometric; CAR, central activation ratio; RM, repetition maximum; WT, walk test; HRQOL, health related quality of life; LEP leg extension power; KOOS, Knee injury and osteoarthritis outcome score; OKS, Oxford Knee Score; 6MWT, 6 minute walk test; EQ-5D, Euroqol questionnaire-5 dimensions; ↑ indicates increase.

5. Objectives and hypothesis

The overall objective of this PhD thesis was to investigate the efficacy of preoperative PRT on postoperative functional performance and muscle strength in patients undergoing TKA.

Paper I

The purpose of this study was in a systematic review to investigate the effect of PRT on muscle strength and functional capacity before and/or after total hip or knee arthroplasty. The review also includes an analysis of the effects of PRT on the patients' quality of life and the rate of adverse events.

Paper II

The purposes of this study were to test the hypotheses that in patients scheduled for TKA knee extensor and knee flexor strength would be 1) weaker in the affected leg than in the non-affected leg; 2) strongly associated with both measured functional performance and patient-reported measures; 3) more closely associated with functional performance when measured during concentric than during isometric contractions and; 4) more strongly related to the 30-s chair stand test (30sCST) than to the timed-up-and-go (TUG) test and walking measures.

Paper III

The purpose of this study was to investigate the efficacy of 4 weeks of preoperative and 4-week post-operative PRT compared to 4 weeks of post-operative PRT only on functional performance, muscle strength, and patient-reported outcomes in patients undergoing TKA. A secondary purpose was to evaluate the safety profile and feasibility of PRT in terms of drop-out rate, exercise adherence, and adverse events.

Hypothesis: It was hypothesized that 4 weeks of preoperative PRT would be safe and feasible and would improve functional performance, knee extensor and flexor muscle strength, and patient-reported outcomes preoperatively and at 6 weeks postoperatively when compared to controls.

Paper IV

The purpose of this study was to examine whether PRT initiated 5 weeks prior to TKA 1) would exacerbate pain and knee effusion and 2) would allow an increase in the training load throughout the training period and subsequently increase muscle strength.

Hypothesis: We hypothesized that PRT before TKA 1) would not exacerbate knee joint pain and effusion, and 2) would increase the training load and subsequently the muscle strength.

6. Methods

The study methods applied are described in detail in the original manuscripts. This section summarizes the general study design, the most important methods applied, and some methodological considerations not mentioned in the manuscripts.

6.0 Paper I

A systematic literature search of nine different databases was performed to identify articles on progressive resistance training conducted before and/or after total hip and knee arthroplasty.

Studies were included if 1) the effect of a PRT intervention was compared with no intervention or another type of intervention; 2) the outcomes included muscle strength and/or functional capacity; 3) all participants were scheduled for or had just undergone THA or TKA; 4) they were randomized, controlled trials (RCT); and 5) papers were presented as full-length papers in English. Data on patient characteristics, training regimen, controls, and outcome measures were extracted.

The methodological quality of the studies was evaluated using the original 11-item Physiotherapy Evidence Database (PEDro) scale (92). Each satisfied item, except item 1, contributes one point to the total PEDro score (range = 0–10 point). Points are achieved when a criterion is clearly satisfied and reported (92) The PEDro scale has been shown to have sufficient reliability (92) and is a valid measure of the methodological quality of clinical trials (92,93). Three investigators independently scored all included studies (IM, UD, and BS) according to the PEDro operational definitions (92), and afterwards consensus was achieved in the few cases of disagreement. A meta-analysis could not be performed due to the large heterogeneity of the studies in terms of time point and duration of the intervention, different control groups and outcome measures. Consequently, the results of each individual study was reported and interpreted.

6.1 Paper II

6.1.0 Study design and patients

This cross-sectional study is part of the RCT that investigated the effect of preoperative PRT on functional performance and muscle strength after TKA (Paper 3). Fifty-nine patients scheduled for

TKA were included from the Orthopedic Department at Aarhus University Hospital and Silkeborg Regional Hospital, Denmark.

Included were patients who were: 1) scheduled for primary unilateral TKA; 2) diagnosed with OA; 3) resident in the Aarhus municipality; 4) able to transport themselves to training; and 5) willing to give informed consent. Excluded were patients who were: 1) age < 18 years; 2) suffering from heart disease or uncontrolled hypertension; 3) suffering from neuromuscular or neurodegenerative conditions; and 4) unable to comprehend the protocol instructions.

6.1.1 Testing procedure

The assessment of the patients included tests of muscle strength and functional performance and measurements of height, body mass, and range of knee joint motion. Furthermore, patients completed questionnaire items on pain, functional performance, and quality of life. All patients were tested according to the protocol 6 weeks before TKA by the same assessor (BS) at Section of Sport Science, Department of Public Health, Aarhus University.

6.1.2 Muscle strength

Maximal isokinetic and isometric knee extension and flexion were measured in an isokinetic dynamometer (Humac Norm, Computer Sports Medicine Inc., MA, USA) (94). Patients performed three maximal isometric contractions of the knee extensors at a knee joint angle of 70^0 (0^0 = full knee extension) and of the knee flexors at a knee joint angle of 20^0. These angles were chosen because the greatest strength is demonstrated at these degrees (95). Rest periods of 60 seconds were allowed between attempts. The trial with the highest peak torque (Nm) was selected for further analysis. Isometric testing was performed on both legs.

The concentric knee extensor and knee flexor muscle strength of the affected knee was evaluated at 60^0/sec (peak moment, Nm). The patients performed six maximal concentric contractions in full possible range of motion (ROM); the trial with the highest peak torque was selected for further analysis.

Dynamometry is considered the gold standard of muscle strength assessment, and dynamometry tests of knee extensor muscles in knee OA have proven reliable (94).

6.1.3 Patient-reported outcomes

The Knee Injury and Osteoarthritis Outcome Score (KOOS) has been developed as a health status instrument for measuring patient-perceived outcomes in patients with osteoarthritis of the knee (96). The patient-reported questionnaire consists of five subscales: pain, other symptoms, function of daily living, function in sport and recreation, and knee-related quality of life (96). KOOS is a reliable and valid tool in patients with knee OA. However, the subscale function in sport and recreation has shown weak-to-moderate reliability and weak construct validity (97,98).

Knee pain ratings were recorded on an 11-point numerical rating scale from 0 ('no pain') to 10 ('worst pain imaginable'). Current pain, the worst pain during the past 14 days, and the average pain during the past 14 days were rated. Numerical rank scale is a reliable and valid tool for pain assessment (99).

Health-related quality of life was recorded on a rating scale from 0 ("worst health related quality of life imaginable") to 100 ("best health related quality of life imaginable").

6.1.4 Statistical analyses

To calculate the association between functional performance, patient-reported outcomes, and knee muscle strength, linear regression analyses were applied. Pitman's test was applied to identify which functional performance test had the closest relationship with muscle strength and whether concentric or isometric strength had the closest relationship with functional performance.

6.2 Paper III

The main study of this PhD thesis is an assessor-blinded two arm randomized controlled study that included 12 weeks of follow-up following TKA (as well as at 52 weeks following TKA, which is outside the timeframe of the current thesis).

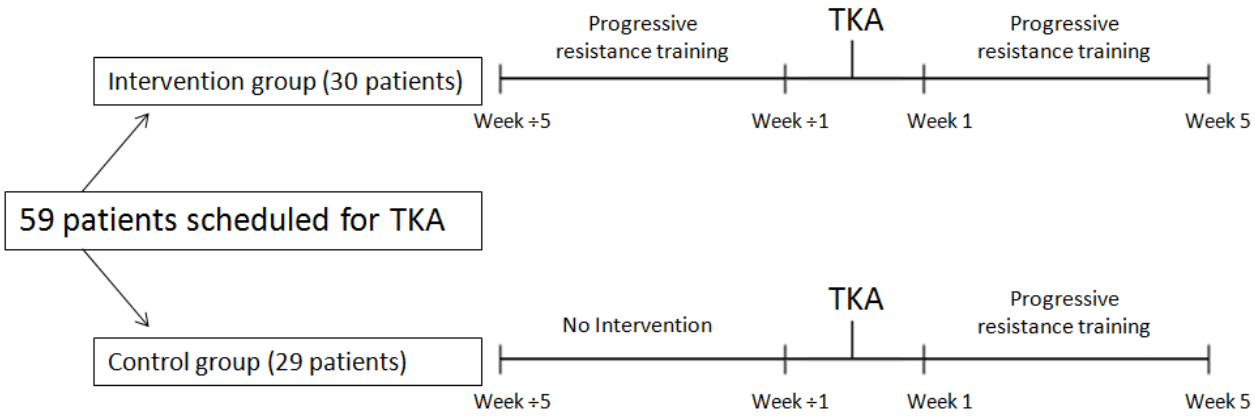


Figure 3: Study design

6.2.0 Patients and ethics

Fifty-nine patients scheduled for TKA were included from the Orthopedic Department at Aarhus University Hospital and at Silkeborg Regional Hospital, Denmark (Figure 3). In- and exclusion criteria are described under Paper II (Figure 4).

The study followed the Declaration of Helsinki, was approved by the regional Ethics Committee (Journal no. M-20110191), and was registered with the Danish Data Protection Agency (Registration no. 1-16-02-191-11) and at ClinicalTrials.gov (NCT01647243).

6.2.1 Sample size

An a priori power calculation was performed on the primary outcome, the 30sCST, and an expected difference between the intervention and control group of at least 10.7%, based on a prior pilot study, at the test 6 weeks postoperatively; $\alpha = 0.05$, $\beta = 0.80$. The power calculation indicated that 31 patients should be needed in each study arm to demonstrate a treatment effect. Due to possibly drop-out, it was planned to include 70 patients.

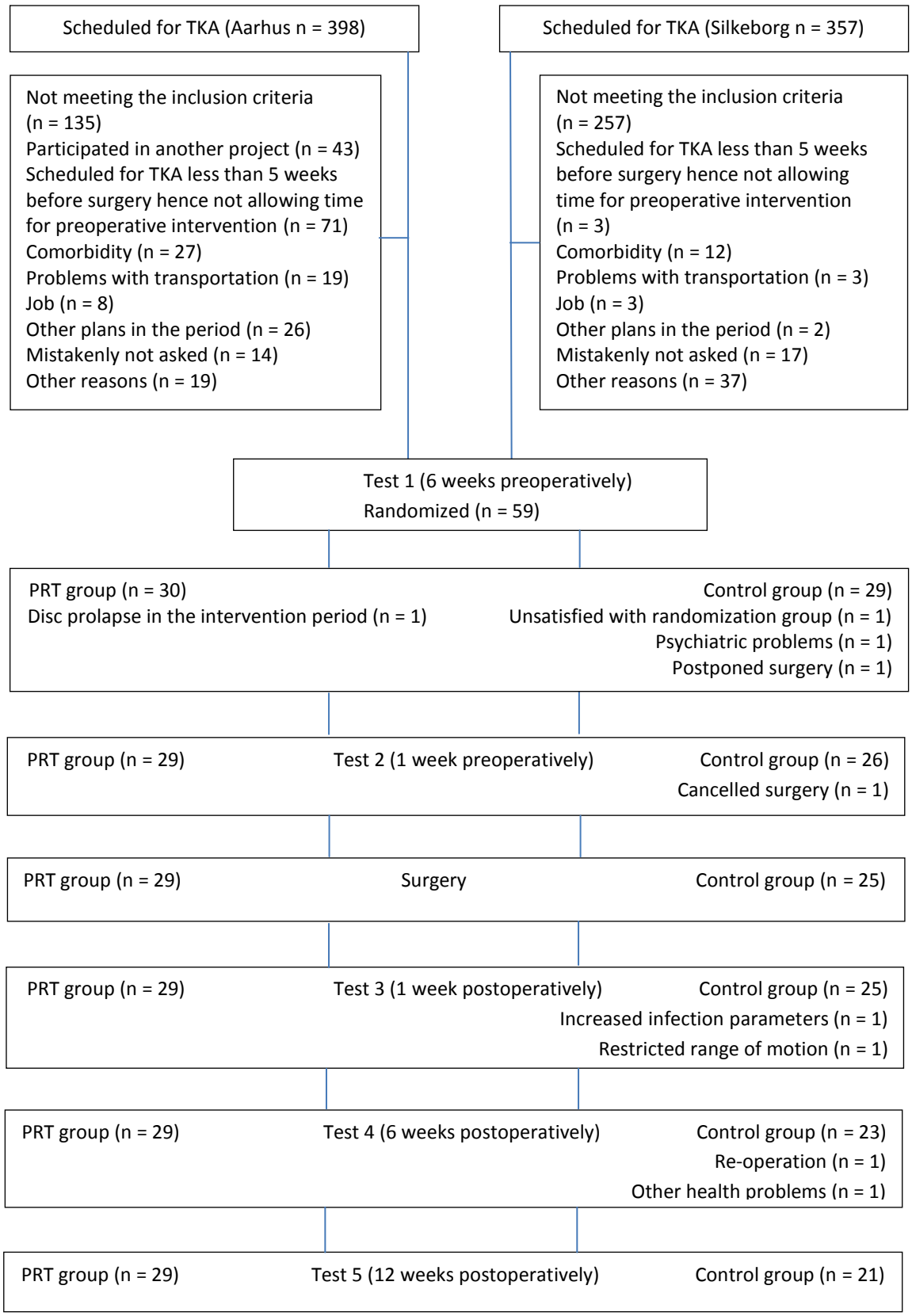


Figure 4. Flow diagram

6.2.2 Randomization

Patients were randomly assigned to preoperative PRT or to the control group with use of concealed, opaque envelopes prepared by the assessor. The randomization was stratified by hospital and randomized in blocks of 10. The envelopes were placed in bags, 10 in each bag, and separate bags for the two hospitals. After the first test, the patients drew an envelope from the bag. The envelopes were administrated by the physiotherapists that provided the PRT intervention.

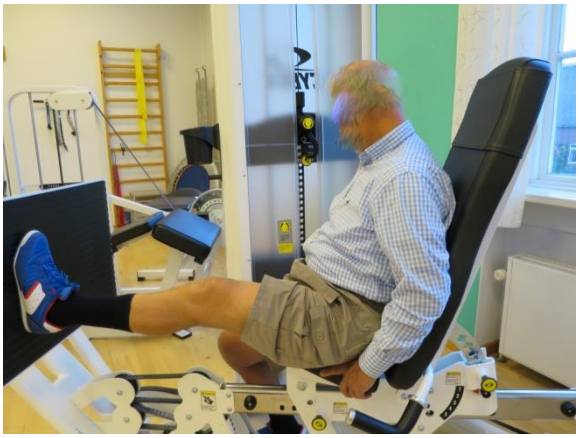
6.2.3 Intervention

The intervention group performed supervised progressive resistance training three sessions per week for 4 weeks pre-operatively, and completed a further three sessions per week for 4 weeks postoperatively.

Progressive resistance training was defined in accordance with the 2009 guidelines of the American College of Sports Medicine (63) as a concentric/eccentric muscle contraction against a variable or constant external resistance at a constant or variable velocity, where loading is continuously adjusted to ensure progression.

The training protocol was described in terms of sets, repetitions, and load. A set is a group of exercise repetitions performed without rest and load is expressed as the repetition maximum (RM, e.g. 10 RM, indicating the heaviest load that can be lifted at 10 repetitions). Rest periods between set and exercise were controlled (63).

Patients exercised in groups of three at Aarhus University Hospital (Figure 5). Each session was supervised by one of three physiotherapists specifically trained in progressive resistance training. The duration of each session was approximately 60 minutes. The training intensity started with 12 repetition maximum (RM) with progression during weeks toward 8 RM (Table 4 and 5). Three sets of each exercise were performed with a rest length of 2 minutes between sets and exercises (Table 4 and 5). Following a 10-minute warm up on a stationary bike, the same six exercises were executed unilaterally during all planned sessions pre- and postoperatively. Exercises included leg press, knee extension, knee flexion, hip extension, hip abduction, and hip adduction in standard strength training machines (Cybex, Owatonna, MN, USA). Patients were instructed to perform all exercises with a fast concentric phase followed by a slow eccentric phase. The load in each exercise should be



Leg press

Knee flexion

Knee extension

Hip abduction

Hip adduction

Hip extension

Figure 5. Six exercises comprising the PRT program

adjusted so that the prescribed number of repetitions in each set led to failure. If more repetitions than prescribed could be made, the load was to be increased. The session ended with 3 x 30 sec. stretching of knee extensors, knee flexors, and ankle flexors. If a participant missed a training session, it was attempted to substitute the session on an alternative day.

Table 4. Pre-operative progression

Week	Sets	Repetitions	Load	Rest between sets and exercises
1	3	12	12 RM	2 min.
2	3	10	10 RM	2 min.
3	3	8	8 RM	2 min.
4	3	8	8 RM	2 min.

6.2.4 Control

Patients in the control group were instructed to "live as usual" for 4 weeks pre-operatively. Post-operatively they followed the same PRT protocol as the intervention group.

Table 5. Post-operative progression

Week	Sets	Repetitions	Load	Rest between sets and exercises
1	3	12	12 RM	2 min.
2	3	10	10 RM	2 min.
3	3	10	10 RM	2 min.
4	3	8	8 RM	2 min.

6.2.5 Perioperative care

All patients followed a standardized, optimized fast-track surgical program for TKA including patient information, spinal anesthesia, optimized pain management, enforced mobilization on the day of surgery, and nutritional advice (49). All patients were invited to an information day prior to TKA, where they were informed about a planned hospital stay of 2 days with pre-defined functional discharge criteria: independency in gait, transfer, personal care, and sufficient pain treatment. During hospitalization patients were instructed to perform a home-based training program that included exercises to improve functional performance, muscle strength, range of motion, and management of knee joint effusion.

6.2.6 Outcome measures

The outcome measures were collected at baseline (6 weeks) and 1 week preoperatively, and again at 1 week, 6 weeks, and 12 weeks after TKA (and 52 weeks postoperatively that is outside the time frame of this PhD thesis) (Figure 6). All outcome measures were blindly assessed in a standardized order at each test by the principal investigator at the Department of Public Health, Section of Sport Science, Aarhus University. The outcome measures are described under Paper II and in the original Paper III.

Figure 6. Test points and time for TKA

Primary outcome

Changes in performance in the 30sCST from baseline to 6 weeks postoperatively were defined as the primary outcome. The test is reliable in patients with knee OA (100,101). The 30sCST was chosen for the primary outcome because it is a functional test associated with muscle strength (102-106). Furthermore, it is an activity most people perform many times a day.

Secondary outcomes

6.2.6.a. *Functional performance*

To ensure a variety of functional activities of daily life, the following four functional performance measures challenging the lower extremity were assessed: 30sCST (primary outcome) (100,101,107), the TUG (100,108,109), 10-m walk test (10 mWT) (110), and 6 minute walk test (6MWT) (111-113). Description of the tests can be found under Paper II.

6.2.6.b. *Muscle strength, range of motion and knee joint effusion*

Maximal isokinetic and isometric knee extension and flexion were measured in an isokinetic dynamometer. A description of the tests can be found in Paper II, section xx and in the original Papers II and III. The advantage of using a dynamometer for evaluating maximal muscle strength is that the patients were tested on the same standardized equipment on which they had not trained. This minimized the variation in strength changes caused by a learning effect based upon improved involvement of assessor muscles, improved coordination of prime-movers, and/or reduced antagonist co-contraction (114-116).

Active and passive knee joint flexion and extension range of motion (ROM) of the affected knee were measured by goniometry. The fulcrum of the goniometer was placed over the lateral epicondyle with the one 30-cm arm pointed toward the major trochanter of the femur and the other toward the lateral malleolus (117). The method is reliable and valid in patients with knee restrictions (117).

Knee joint effusion was assessed by measuring the knee joint circumference (118,119). The patient was placed on a couch in a supine position. Knee joint circumference was measured 1 cm above the bases of patella with a non-elastic measure. The measurements were performed bilaterally. Measurement of the knee joint effusion is reliable in patients with TKA (118).

6.2.6.c ***Safety and feasibility*** was measured at reporting of drop-out rate, exercise adherence (exercise adherence (%) = (no. of completed sessions / no. of planned sessions) * 100) and adverse events.

6.2.6.d *Patient-reported outcomes*

KOOS, knee pain ratings, and health-related quality of life are described under Paper II.

6.2.7 Statistical analyses

A series of repeated-measures analyses of variance, multilevel mixed-effects linear regression, were conducted to investigate the differences between changes from baseline to all test points in the intervention group and the control group on pre- and postoperative outcomes. The statistical analyses followed the intention-to-treat principle and were performed in Stata 12.1 (StataCorp, College Station, TX, USA). For further details please see Paper III.

6.3 Paper IV

The present study was a part of a clinical randomized controlled trial (Paper III).

6.3.0 Patients

In total 30 patients were randomly assigned to 4 weeks of preoperative PRT (intervention group).

6.3.1. Outcome measures

Before and after each training session, the patients' pain level and knee joint circumference at rest were recorded by the training physiotherapist. Furthermore, the weight load (kg) and number of repetitions in each set for leg press, knee extension, knee flexion, hip extension, hip abduction, and hip adduction were recorded during each training session.

6.3.1.a *Knee pain ratings and knee joint effusion* are described under Paper II.

6.3.1.b *Muscle strength (1RM)*

The first and last preoperative PRT sessions were initiated by a one repetition maximum (1RM) testing (120) of unilateral leg press, knee extension, and knee flexion. After a 10-minute warm up on a stationary bike, the patients conducted a few repetitions at approximately 50% of 1 RM. Then the load increased step-wise until failure. The tests were performed on the training machines.

6.3.2 Statistical analyses

Knee pain at rest after each training session during the training period was assessed using Kruskal-Wallis test. Changes of knee joint effusion before and after each training session during the training period were assessed using repeated measures analyses of variance (ANOVA). Student's paired t-test was applied to evaluate the difference between maximal muscle strength before and after the training period. Spearman's test was applied to calculate the correlation between the change in muscle strength and knee joint pain and effusion.

7. Results

The study results are described in detail in the original manuscripts (Papers I–IV). This section summarizes the main results.

7.0 Paper I

7.0.0 Study characteristic

Four RCT studies on PRT and THA that included 136 patients and 3 RCT studies on PRT and TKA that included 284 patients were identified and rated according to the PEDro scale. The general methodological quality of the studies was low to moderate.

7.0.1 Intervention characteristic

The PRT intervention was targeted solely at the lower extremity in all studies (25,69,73,121-131) except one, which also included upper body exercises (121). The total number of sessions was generally higher in THA than in TKA. All studies applied supervised PRT, and none reported any side effects or adverse events related to PRT.

7.0.2 Muscle strength, functional capacity, and patient-reported outcomes

The THA studies consistently reported strength improvement of the muscles trained during PRT. The effects of PRT on muscle strength reported in the TKA studies were inconsistent. No effect of PRT on isometric strength of the knee extensors assessed as peak force (Nm) was reported (69); nor was any effect of postoperative PRT of isometric strength of knee flexors or on the central activation ratio achieved (73). However, an improvement of the normalized maximum voluntary isometric contraction was reported (25,72) (Table 6).

Weak evidence of a beneficial effect of pre- and postoperative progressive resistance interventions was reported on functional capacity in THA patients. However, the results were inconsistent in TKA studies (Table 6).

Studies show improved patient-reported function in THA patients, (121,122) but not in TKA patients (69), while no differences in health-related quality of life were found in either THA or TKA patients (Table 6).

Table 6. Schematic overview of included TKA studies

Trials	Sample Size Dropouts Adherence % PEDro score	Subjects Diagnoses for TKA Age/Sex Start	Duration & frequency	Training regime	Outcome (vs. control)
Pre TKA interventi-ons					
McKay et al.(69)	RT: 10, UBT: 12 Total dropout: 6/22 = 27% RT dropout: 3/10 = 30% UBT dropout: 3/12 = 25% RT adherence: 98% UBT adherence: 93% Total score: 6/10	Osteoarthritis ~70yr +/- 6 9M/13W 6 weeks before surgery	6 weeks 30 min/session, 3 sessions/week 18 sessions	PT: 4 leg exercises Quadriceps, hamstrings, leg press, triceps surae (performed bilaterally) 2*8 reps Exercises progressed from 60% of 1RM with 1-2 kg per week as tolerated UBT: 4 exercises upper body training Latissimus dorsi, chest press, biceps brachii, triceps brachii 2*8 reps Exercises progressed from 60% of 1RM with 1-2 kg per week as tolerated Supervised	**After intervention** KE (isom): NS 50 FOOT WT: NS Stair climbing test: NS WOMAC: NS HRQOL (SF-36): NS **At 6 weeks postop. follow-up** KE (isom): NS 50 FOOT WT: NS Stair climbing test: NS WOMAC: NS HRQOL (SF-36): NS **At 12 weeks postop. follow-up** KE (isom): NS 50 FOOT WT: NS Stair climbing test: NS WOMAC: NS HRQOL (SF-36): NS
Post TKA interventi-ons					

Continued

Petterson et al.(25,72)	RT: 100, RT+es: 100, Con: 41 Total dropout: 19/200 = 10% RT dropout: 3/100 = 3% RT+es dropout: 16/100 = 16% Adherence: mean 16.9+/1.3 visits Total score: 6/10	All diagnoses for TKA ~65yr +/- 8 122M/119W 3-4 weeks after TKA	6 weeks 2-3 sessions/week 12-18 sessions	6 leg exercises Quadriceps, hamstrings, gastrocnemius, soleus, hip abductors and flexors (performed unilateral) Week 1-6: 10 RM 2-3 sets of 10 reps. Supervised ES group: +NMES RT group: -NMES Patients of 1 referring surgeon from the pooled RT and ES group Con. group: Patients of the referring surgeon represent the standard of care in the community	**At 3 month follow-up** KE-OP (isom): NS CAR: NS Timed Up and Go: NS 6MWT: NS Stair climbing test: NS HRQOL (SF-36): NS **At 12 month follow-up** KE-OP (isom): NS CAR: NS Timed Up and Go: NS 6MWT: NS Stair climbing test: NS HRQOL (SF-36): NS **At 12 month follow-up** KE-OP (isom) ↑ CAR: NS Timed Up and GO ↑ 6MWT ↑ Stair climbing test ↑ HRQOL (SF-36): NS
Johnson et al.(73)	RT: 10, WBV: 11 Total dropout: 5/21 = 24% RT dropout: 2/10 = 20% Required to complete at least 10 out of 12 sessions. Total score: 4/10	Osteoarthritis ~68yr +/- 10 No information about sex between the dropouts 3-6 weeks after surgery	4 weeks 3 sessions/week 12 sessions	2 leg exercises Knee extension, hip flexion 1-3 sets of 10 reps. Exercises were progressed once the patient could complete the exercise and extra weight (0.454-4.54 kg) were added. Supervised	**After intervention** KE-OP (isom): NS KE-NOP (isom): NS CAR-OP: NS CAR-NOP: NS Timed Up and Go: NS

Abbreviations: TKA, total knee arthroplasty; Pre, preoperative; Post, postoperative; PEDro, Physiotherapy Evidence Database; RT, resistance Training; UBT, upper body training; RT+es, resistance training combined with electrical stimulation; ERT, eccentric resistance training; WBV, whole body vibration; Con, control group; M, men; W, women; NS, non-significant; KE, knee extension; OP, operated leg; NOP, non-operated leg; RFD, rate of force development; Isom, isometric; CAR, central activation ratio; RM, repetition maximum; 6MWT, 6 minute walk test; HRQOL, health related quality of life; ↑ indicates increase.

7.1 Paper II

In total 59 patients, 70.4 ± 6.8 years, 61% women, body mass index median 30.3 (range 22.6–42.5) were included in the study during the inclusion period from January 2012 to December 2013.

7.1.0 Muscle strength in affected and non-affected leg

The knee extensors were significantly weaker in the affected leg than in the non-affected leg *($p < 0.01$)*, whereas for knee flexors the difference between the two legs was insignificant *($p = 0.51$)*. The average strength of the knee extensors in the affected leg corresponded to 89.1% (SD 30.2) of that of the non-affected leg.

7.1.1 Muscle strength vs. functional performance / patient-reported measures

An overall association between functional performance and concentric and isometric knee extensor and knee flexor muscle strength in the affected and non-affected leg was found, except for the 6MWT (Table 7). Furthermore, we found no association between knee injury and osteoarthritis score (KOOS) subscales and any knee muscle strength parameters. In contrast, an overall association was found between the KOOS subscales and pain.

Table 7**.** Associations between functional performance measures and muscle strength*

	CST (rep.)‡		**TUG (sec)‡**		**10mWT (sec)‡**		**6MWT (m)‡**	
Muscle strength	Crude	Adjusted †	Crude	Adjusted †	Crude	Adjusted †	Crude	Adjusted †
Affected leg	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*
Concentric extension	0.29	0.49	-0.23	-0.26	-0.17	-0.18	0.17	0.13
peak torque (Nm) ‡	***(0.01)***	***(<0.01)***	***(<0.01)***	***(<0.01)***	***(<0.01)***	***(0.01)***	***(0.03)***	*(0.18)*
Concentric flexion peak	0.28	0.32	-0.21	-0.18	-0.17	-0.16	0.20	0.16
torque (Nm) ‡	***(<0.01)***	***(<0.01)***	***(<0.01)***	***(0.01)***	***(<0.01)***	***(<0.01)***	***(0.01)***	***(0.02)***
Isometric extension peak	0.28	0.58	-0.21	-0.21	-0.17	-0.19	0.18	0.19
torque (Nm) ‡	***(0.05)***	***(<0.01)***	***(<0.01)***	*(0.06)*	***(<0.01)***	***(0.02)***	***(0.03)***	*(0.09)*
Isometric flexion peak	0.28	0.43	-0.14	-0.04	-0.12	-0.06	0.14	0.00
torque (Nm) ‡	***(0.02)***	***(<0.01)***	*(0.09)*	*(0.73)*	***(0.05)***	*(0.46)*	*(0.12)*	*(0.97)*
Non-affected leg								
Isometric extension peak	0.23	0.55	-0.24	-0.27	-0.16	-0.17	0.14	0.06
torque (Nm) ‡	*(0.08)*	***(<0.01)***	***(<0.01)***	***(0.03)***	***(<0.01)***	*(0.07)*	*(0.10)*	(0.65)
Isometric flexion peak	0.27	0.34	-0.21	-0.16	-0.15	-0.10	0.21	0.15
torque (Nm) ‡	*(0.06)*	*(0.06)*	***(0.02)***	*(0.19)*	***(0.03)***	*(0.25)*	***(0.03)***	(0.21)

* Analysed by linear regression; † Adjusted for age, sex, height, and weight; ‡ Log-transformed data; β, Regression coefficient.
Abbreviations: CST, 30-s chair stand test; TUG, timed-up-and-go; 10mWT, 10m walk test; 6MWT, 6-m walk test; rep, repetitions.

7.1.2 Concentric vs. isometric muscle strength

Generally, the concentric knee flexor muscle strength was more strongly associated with functional performance than the isometric knee flexor strength. Concentric knee flexor strength was more closely associated with the TUG, 10mWT, and the 6MWT than isometric knee flexor strength, but no difference was found between concentric and isometric knee extensor strength in any test of functional performance.

7.1.3 30sCST vs. TUG and walking

The 30sCST was the test that was most strongly associated with all parameters of muscle strength. 30sCST was more closely associated with both concentric and isometric knee extensor and knee flexor than the TUG and the walking tests (Table 8).

Table 8. Comparison of associations between functional performance and muscle strength measures

	CST vs. TUG	**CST vs. 10mWT**	**CST vs. 6MWT**	**TUG vs. 10 mWT**	**10mWT vs. 6MWT**
Affected leg					
Concentric knee extension	CST>TUG	CST>10 mWT	CST>6MWT	TUG>10mWT	10mWT>6MWT
peak torque (Nm)	*p<0.01*	*p<0.01*	*p<0.01*	*p<0.01*	*p<0.01*
Concentric knee flexion	CST>TUG	CST>10 mWT	CST>6MWT	TUG<10mWT	10mWT>6MWT
peak torque (Nm)	*p<0.01*	*p<0.01*	*p<0.01*	*p<0.01*	*p<0.01*
Isometric knee extension	CST>TUG	CST>10 mWT	CST>6MWT	TUG<10mWT	10mWT>6MWT
peak torque (Nm)	*p<0.01*	*p<0.01*	*p<0.01*	*p<0.01*	*p<0.01*
Isometric knee flexion	CST>TUG	CST>10 mWT	CST>6MWT	---	---
peak torque (Nm)	*p<0.01*	*p<0.01*	*p<0.01*		
Non-affected leg					
Isometric knee extension	CST>TUG	CST>10 mWT	CST>6MWT	TUG>10mWT	---
peak torque (Nm)	*p<0.01*	*p<0.01*	*p<0.01*	*p<0.01*	
Isometric knee flexion	---	---	---	---	---
peak torque (Nm)					

* Analysed by Pitman's test. CST, 30-s chair stand test; TUG, timed-up-and-go; 10mWT, 10-m walk test; 6MWT, 6 minute walk test; >, indicates stronger association; <, indicates weaker association.

7.2 Paper III

7.2.0 Baseline findings and adherence

In total 30 patients were randomized to the intervention group and 29 to the control group. No significant differences between the randomization groups were seen at baseline (Table 9). In total one patient (3.3%) dropped out of the intervention group, while seven patients (24.1%) dropped out of the control group. None of the patients missed training sessions or were discontinued from the study due to adverse events related to the intervention. The adherence was 94.0% (SD 8.4) preoperatively and 100% postoperatively in the intervention group and 94.2% (SD 21.2) postoperatively in the control group.

Table 9. Baseline characteristics of the intervention and control group

Characteristics	**PRT group**	**Control group**
Sex (female/male) (no.)	19/11	17/12
Age (years)	70.7 (7.3)	70.1 (6.4)
Height (m)*	1.67 [1.45-1.84]	170.0 [1.46-1.97]
Weight (kg)*	83.6 [56.8-117.2]	91.9 [66.2-137.4]
Body mass index (kg/m^2)*	30.0 [22.6-42.5]	31.8 [24.3-42.2]
Pain medication (non-prescribed)		
0 days/1-4 days/5-7 days per week (n)	8/6/16	11/7/11
Pain medication (prescribed)		
0 days/1-4 days/5-7 days per week (n)	22/1/7	18/2/9
Knee arthroplasty of opposite leg (n)	3	4
Smoker (n)	3	4
Job (n)	4	4

Values are means (standard deviation) or * median [range]. † Measured on 11-point numerical rating scale. £ Measured 1 cm above basis of patella

7.2.1 Comparison of changes from baseline to 6 weeks post-TKA

Primary outcome

An overall time*group interaction was found. At the primary time-point of interest, a significant difference between changes of the 30sCST performance from baseline to 6 weeks postoperatively in the intervention group vs. the control group was found, 2.5 (0.9;4.1) and -1.1 (-2.8;0.7), respectively, $p < 0.004$ (Figure 6A).

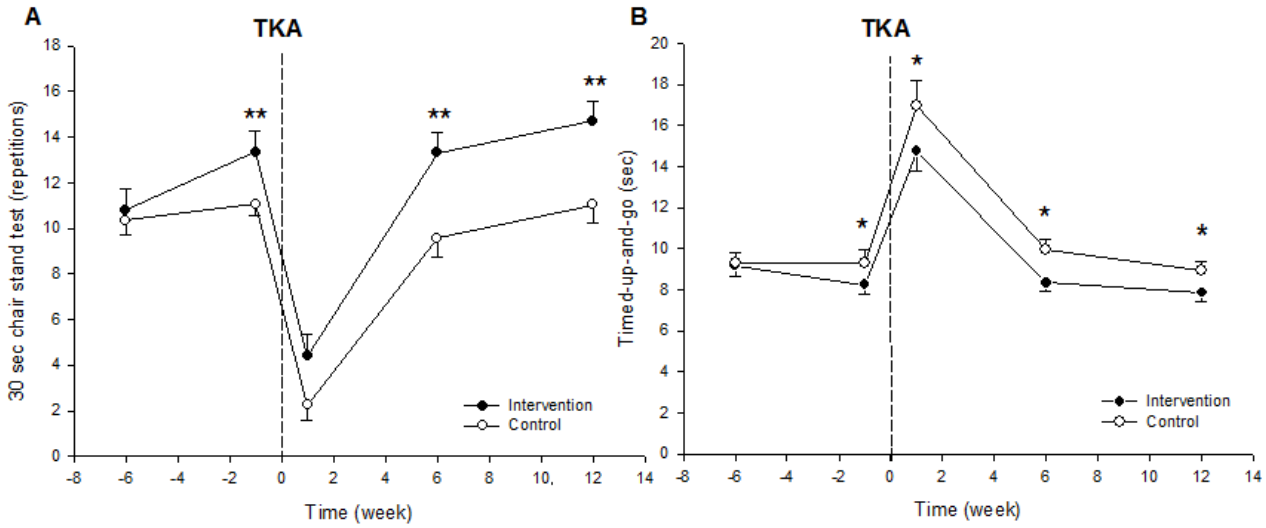


Figure 6 A. 30-s chair stand test between groups (mean (standard error of the mean (SEM))) B. Timed-up-and-go between groups (mean (SEM)). * $p \leq 0.05$; ** $p < 0.01$.

Secondary outcomes

An overall time*group interaction was found for the TUG (Figure 6B). At the primary time-point of interest, the TUG showed a significant difference between changes from baseline to 6 weeks post-TKA between groups, whereas the walking tests did not (Table 10). At the time-point 6 weeks post-TKA all muscle strength parameters showed significant improvements in the intervention group compared to the control group of the involved leg (Figure 7A and 7B), and this also was the case in

the knee extensors in the non-involved leg (Table 11). No differences were found between the groups in any patient-reported outcomes, except for the KOOS sport subscale.

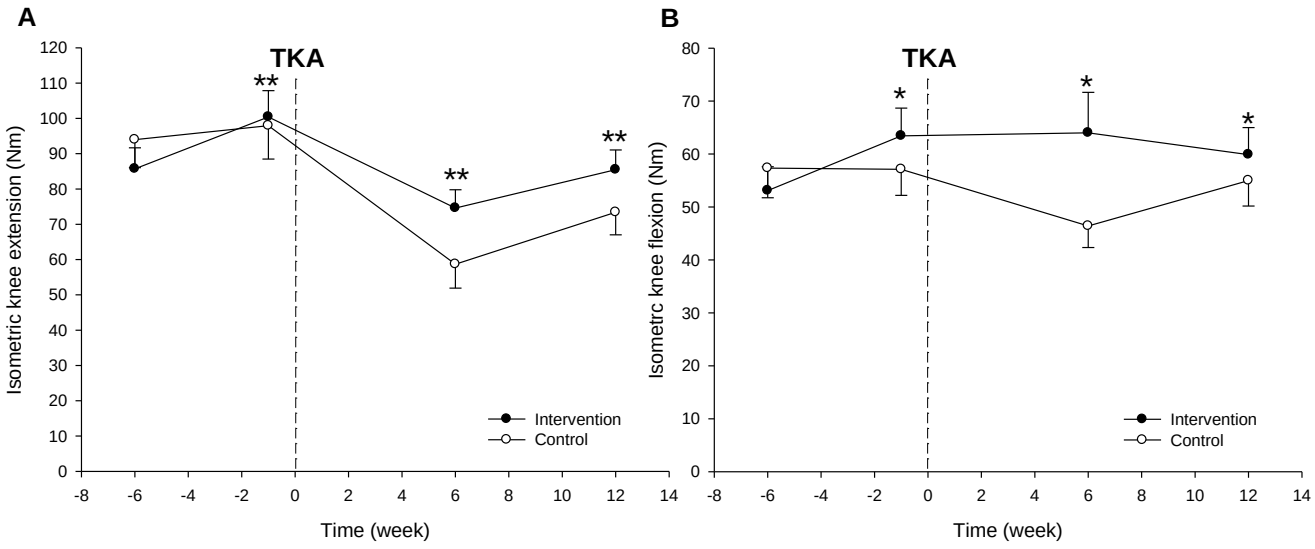


Figure 7 A. Isometric extension between groups (mean (SEM)) B. Isometric flexion between groups (mean (SEM)). ** $p \leq 0.05$; ** $p < 0.01$.*

Table 10. Mean and differences between intervention and control group at each test points in functional capacity outcomes

Outcome	Baseline Mean (SD)	Test 2 Mean (SD)	Δ test 2 Mean (CI) *p*	Test 3 Mean (SD)	Δ test 3 Mean (CI) *p*	Test 4 Mean (SD)	Δ test 4 Mean (CI) *p*	Test 5 Mean (SD)	Δ test 5 Mean (CI) *p*
30sCST (rep)									
PRT	10.8 (5.1)	13.3 (5.1)	2.5 (1.6;3.4)	4.4 (5.1)	-6.4 (-8.0;-4.9)	13.3 (5.0)	2.5 (0.9;4.1)	14.7 (4.7)	3.9 (2.5;5.3)
Control	10.4 (3.3)	11.1 (2.9)	0.3 (-0.6;1.3)	2.2 (3.5)	-8.2 (-9.9;-6.6)	9.6 (4.4)	-1.1 (-2.8;0.7)	11.0 (4.4)	0.2 (-1.4;1.7)
			0.001		*0.116*		***0.004***		***0.001***
TUG (sec)									
PRT	9.1 (2.6)	8.2 (2.3)	-0.8 (-1.4;-0.2)	14.8 (5.2)	5.8 (4.2;7.4)	8.3 (2.3)	-0.7 (-1.6;0.1)	7.9 (2.3)	-1.2 (-1.9;-0.5)
Control	9.3 (3.0)	9.3 (3.1)	0.2 (-0.5;0.9)	17.0 (5.6)	8.3 (6.4;10.1)	10.0 (2.4)	0.8 (-0.1;1.7)	8.9 (2.1)	-0.1 (-0.9;0.7)
			0.034		***0.044***		***0.015***		***0.050***
10mWT (sec)									
PRT	7.7 (1.8)	7.3 (1.6)	-0.3 (-0.7;0.1)	12.5 (4.9)	5.0 (3.3;6.7)	7.6 (1.8)	<0.01 (0.6;0.6)	7.1 (1.5)	-0.6 (-1.1;-0.1)
Control	7.9 (1.5)	8.0 (2.0)	0.2 (-0.2;0.7)	14.4 (5.6)	6.6 (4.6;8,5)	8.6 (1.6)	0.7 (0.1;1.4)	7.7 (1.2)	-0.1 (-0.6;0.5)
			0.114		*0.225*		*0.119*		*0.216*
6MWT (m)									
PRT	404 (119)	434 (101)	23.2 (4.7;41.6)	258 (93)	-156.5 (-194.5;-118.5)	424 (103)	16.8 (-20.4;54.0)	449 (94)	41.2 (7.1;75.3)
Control	408 (63)	427 (76)	9.4 (-11.1;30.0)	226 (82)	-183.1 (-222.6;-143.7)	376 (83)	-33.5 (-74.1;7.1)	433 (74)	8.4 (-29.5;46.3)
			0.330		*0.341*		*0.074*		*0.208*

Δ, changes from baseline to; 30sCST, 30-s chair stand test; TUG, Timed-up-and-go test; 10MWT, 10-m walk test; 6MWT, 6 minute walk test

Table 11. Mean and differences between intervention and control group at each test points in muscle strength outcomes

Outcome	**Baseline Mean (SD)**	**Test 2 Mean (SD)**	**Δ test 2 Mean (CI) *p***	**Test 3 Mean (SD)**	**Δ test 3 Mean (CI) *p***	**Test 4 Mean (SD)**	**Δ test 4 Mean (CI) *p***	**Test 5 Mean (SD)**	**Δ test 5 Mean (CI) *P***
Involved leg									
Isokinetic ext. (Nm)									
Intervention	71.0 (35.4)	80.0 (40.7)	8.5 (2.7;14.3)	---	---	61.6 (23.5)	-10.5 (-19.1;-1.9)	71.6 (26.8)	0.3 (-8.1;8.7)
Control	80.9 (37.0)	87.6 (40.8)	3.5 (-3.0;10.1)			53.6 (25.6)	-29.8 (-39.0;-20.6)	64.1 (25.3)	-21.1 (-30.3;-11.8)
			0.267				***0.003***		***0.001***
Isokinetic flex. (Nm)									
Intervention	37.9 (25.3)	47.0 (25.3)	8.8 (3.5;14.1)	---	---	41.2 (22.2)	2.3 (-5.0;5.7)	45.7 (21.2)	7.7 (0.6;14.8)
Control	45.5 (23.9)	51.0 (26.4)	4.1 (-1.8;9.9)			33.5 (22.6)	-13.7 (-21.8;-5.7)	38.6 (19.9)	-9.9 (-17.7;-2.1)
			0.241				***0.004***		***0.001***
Isometric ext. (Nm)									
Intervention	85.7 (32.6)	100.4 (40.1)	14.3 (8.1;20.5)	---	---	74.6 (26.4)	-15.2 (-24.4;-6.0)	85.5 (29.5)	0.3 (-8.3;8.9)
Control	94.0 (41.8)	97.9 (46.2)	-3.7 (-10.5;3.0)			58.7 (30.2)	-38.0 (-48.3;-27.7)	73.4 (28.6)	-25.7 (-35.5;-16.0)
			<0.001				***0.001***		***<0.001***
Isometric flex. (Nm)									
Intervention	53.1 (24.4)	63.4 (27.7)	10.4 (3.9;16.9)	---	---	64.0 (39.0)	8.7 (-3.6;21.0)	60.0 (27.0)	8.4 (-0.6;17.5)
Control	57.34 (29.7)	57.1 (24.1)	-1.5 (-8.3;5.4)			46.4 (17.8)	-12.1 (-26.2;1.9)	55.0 (20.4)	-5.8 (-16.3;4.6)
			0.014				***0.029***		***0.043***

Continued

Table 11 *Continued*

Non-involved leg									
Isometric ext. (Nm)									
Intervention	103.8 (43.6)	116.2 (39.5)	11.2 (3.0;19.4)	117.7 (39.3)	12.8 (5.7;19.8)	122.0 (40.9)	13.0 (4.7;21.4)	113.9 (44.2)	9.5 (2.1;16.9)
Control	108.0 (50.6)	117.8 (50.8)	2.9 (-6.0;11.8)	116.6 (46.3)	3.9 (-4.0;11.7)	114.7 (46.0)	0.1 (-9.0;9.3)	120.1 (54.5)	-1.6 (-10.2;7.1)
			0.178		*0.100*		***0.041***		*0.058*
Isometric flex. (Nm)									
Intervention	52.6 (21.9)	61.8 (28.1)	8.6 (1.6;15.7)	60.0 (22.7)	6.3 (-2.2;14.8)	59.9 (20.3)	5.7 (-1.1;12.6)	60.0 (23.4)	7.0 (1.0;12.9)
Control	55.3 (23.0)	62.3 (28.6)	6.7 (-1.0;14.5)	61.7 (35.2)	7.0 (-2.6;16.7)	54.5 (22.2)	0.2 (-7.4;7.8)	61.0 (27.7)	2.9 (-4.1;9.8)
			0.721		*0.912*		*0.293*		*0.381*

Δ, Difference between changes from baseline to; ext., extension; flex., flexion.

7.3 Paper IV

Of the 30 included patients, one patient dropped out of the study due to a herniated disc during the training period. No drop-outs and adverse events related to the training intervention were recorded. Table 12 shows knee joint pain at rest before and after each training session. At many test points, the patients stated no pain. Median differences of the pain from before to after each training session varied from 0 to 2. Pain after training was unchanged over time *(p = 0.99).*

Table 12. Pain at rest measured on a numeric rating scale before and after each training session.

	Before training		After training	
Session	**Median**	**IQR[#]**	**Median**	**IQR[#]**
1	0.5	0–2	0	0–2
2	1	0–2	0	0–2
3	0	0–2	0	0–1
4	0	0–1	0	0–1
5	0	0–1	0	0–1
6	0	0–2	0	0–2
7	0	0–1	0	0–2
8	0	0–1	0	0–2
9	0	0–1.5	0.5	0–2
10	1	0–2	0	0–2
11	0	0–1	0	0–1
12	0	0–1	0	0–1

[#]IQR, interquartile range

Mean differences of the knee joint circumference from before to after a single session varied from 0–0.4 cm (Figure 8), and was statistically unchanged throughout all training sessions *(p = 0.99).*

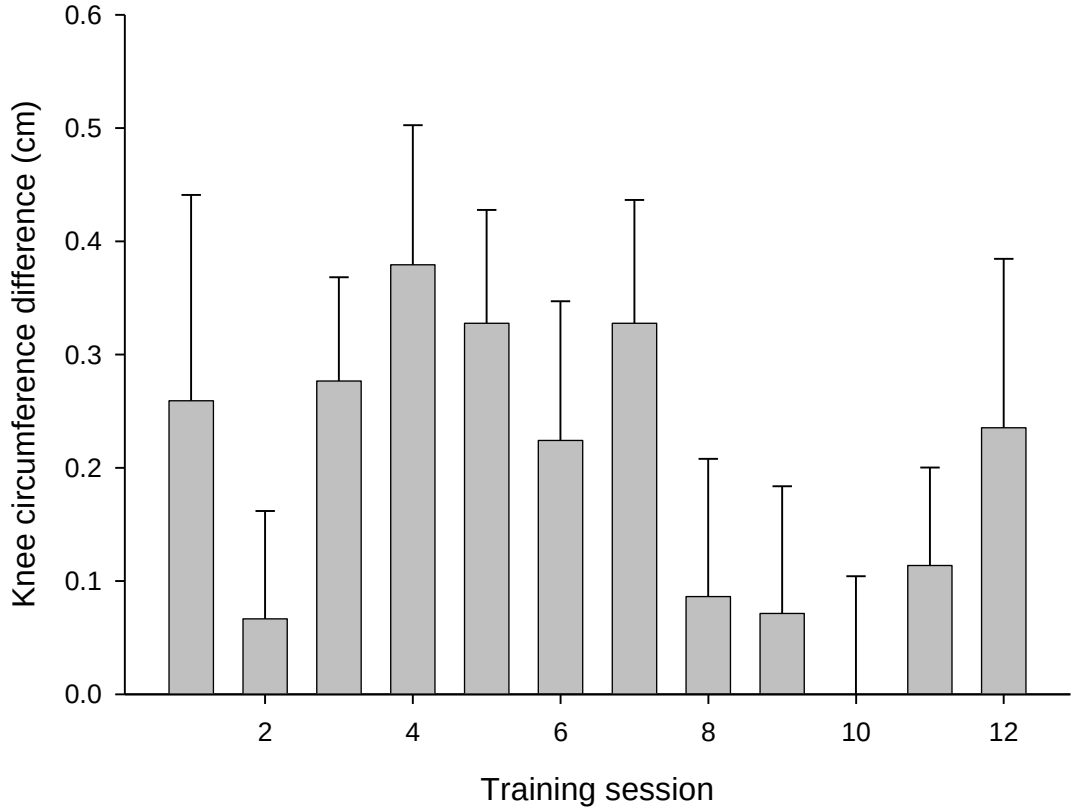


Figure 8 Difference in knee circumference from before to after each training sessions. Bars indicate (means (SEM)). At training session 10, the mean difference is 0. Effusion after training was unchanged over time, $p = 0.99$ (repeated measures (ANOVA)).

Maximal muscle strength improved: unilateral leg press mean 18% ± 30 *($p = 0.03$)*, knee extension mean 81% ± 156 *($p < 0001$)* and knee flexion mean 53% ± 57 *($p < 0.001$).*

There was no significant correlation between maximal muscle strength and knee joint pain and effusion *($p > 0.07$).*

8. Discussion

The main findings of the present PhD thesis were that supervised pre- and postoperative PRT improved functional performance and increased knee extensor and knee flexor muscle strength when compared to postoperative PRT alone at 6 weeks postoperatively. The improvements were achieved without increasing pain or causing knee effusion. However, in contrast to our hypothesis, no significant improvement was found in preoperative PRT in patient-reported functional performance and health-related quality of life except for the KOOS subscale "sports". PRT was safe when performed both preoperatively and postoperatively in terms of no observed adverse events and an excellent adherence rate (Paper III and Paper IV).

At baseline, 6 weeks before TKA, the knee extensors were weaker in the affected leg than in the non-affected leg; whereas no statistical difference was found between the knee flexor muscles. In general, knee extensor and knee flexor muscle strength were associated with functional performance test outcomes, except for the 6MWT. However, no association between patient-reported knee function and muscle strength was observed. Isokinetic muscle strength generally showed a closer association with functional performance test outcomes than isometric muscle strength. Finally, the 30sCST was the functional performance test that was most closely associated with the various parameters of muscle strength investigated in this PhD thesis (Paper II).

Only three randomized controlled trials evaluating the effects of PRT before and after TKA were found after a systematic literature search in nine databases for our review (Paper I). The large heterogeneity of the studies limits the strength of any conclusions that may be drawn from this review and excludes further application of meta-analytical procedures. Nonetheless, some important points may be made. TKA patients tolerated PRT without suffering side effects or adverse events, and their adherence was consistently excellent in studies reporting adherence outcomes.

Only two studies have specifically investigated the effect of preoperative PRT (69,70), one included in the review, and a recent study published later (16). In the study by McKay et al. 6-week bilateral lower-body PRT intervention was compared to an upper-body PRT intervention, and the findings demonstrated a statistically significant time*group effect on the SF-36 mental component score and non-significant improvements of quadriceps strength and walking speed immediately before TKA. However, 6 weeks postoperatively, the improvements were lost as compared to the control group (69). In the study by Leeuwen et al., a 6-week standard training program with additional PRT was

not more efficacious than standard training alone when assessed on muscle strength and functional performance immediately before TKA and 6 and 12 weeks after TKA (70). The significant improvements in our study may be a result of a higher training intensity, application of unilateral vs. bilateral training, involvement of more muscle groups around the knee, or caused by a larger sample size that increased the power of the study.

A recent systematic review and meta-analysis identified seven studies of preoperative rehabilitation before TKA. It was concluded that no outcome was consistently improved following preoperative interventions as compared to controls, with the exception of a trend toward the length of hospital stay being shorter (60). Another systematic review concluded that there is low-to-moderate evidence from mostly small randomized controlled trials demonstrating that pre-operative exercise interventions may reduce pain in TKA patients (61). However, none of the studies included in the reviews have applied high-intensity resistance training programs.

The impact of the preoperative PRT intervention on postoperative recovery in our study was not the same as reported in previous exercise studies. The reason for this may be attributed to several factors. The training protocol in our study differs from previous studies because we applied high exercise intensity according to the progressive overload principle. The training physiotherapist supervised and ensured that patients continually trained close to the maximum of their capability and followed the plan of progression. The patients trained unilaterally, and the training volume (the summation of the total number of repetitions performed during a training session multiplied by the load) of each muscle group within each training session was high compared to previous studies. Since the training took place in small groups, the competitive element might also have optimized the training intensity.

In a recent review by Hoogeboom et al., studies investigating the effect of preoperative exercises on functional performance after TKA and THA was evaluated on a therapeutically validity scale (132). It was concluded that studies scored low on the therapeutic validity scale, evaluated in terms of e.g. whether the exercise programs were in line with the latest research, had sufficient volume and were tailored to the potential of the participants. Hence, the poor therapeutic validity of the exercise programs may have hampered potentially beneficial effects. Regarding therapeutic validity, we consider that our study has a high score on the therapeutic validity scale as the training protocol was designed according to the principles recommended by the American College of Sports Medicine

(63), e.g. high training intensity and volume of all weak muscles around the involved knee, plan for progression ensured by special trained physiotherapists, and a high training frequency.

Calculation of the minimal detectable change of the 30sCST was not the aim of the current study and has not been identified elsewhere in patients with knee OA or TKA patients. However, in older adults with type 2 diabetes, a change of 3.35 repetitions was reported as the minimal detectable change (133). Hence, the efficacy in our study at the primary test point exceeds this value, suggesting that the results can be considered reliable. No data exist on the minimal clinical relevant change of the 30sCST, but the substantial change of 35.2% between the intervention group and the control group from baseline to 6 weeks after TKA indicates that the improvement is clinically relevant.

The observed discrepancy between the results of objectively assessed functional performance and patient-reported functional performance is in accordance with other studies concluding that measured functional performance is associated with muscle strength and patient-reported functional performance to pain (134,135). It could be argued that this would limit the clinical relevance of the intervention, but it could also reflect poor responsiveness of the patient-reported scales or the patients' ability to cope with their deficits.

Interesting, a recent systematic review that included 48 studies investigated the effect of exercise programs on pain and patient-reported disability in knee OA. It was concluded that exercise programs focusing on a single type of exercise were more efficacious in reducing pain and patient-reported disability than those mixing several types of exercise with different goals within the same session (134). This conclusion supports our exercise approach and ought to be taken into account when planning exercise interventions before and after TKA.

All patients followed the same postoperative PRT protocol; hence, we get no answers on the impact of postoperative PRT. However, it seems plausible that muscles that are stimulated and conditioned through PRT preoperatively are more responsive to the high-intensity exercise program performed postoperatively.

We included two studies in our review that investigated PRT after surgery (Paper I). Johnson et al. investigated PRT in comparison with a group receiving whole body vibration initiated 3 to 6 weeks after surgery and found no difference between groups on any of the outcomes. Petterson et al. found improved functional performance and increased muscle strength of PRT compared to a control

group following standard care 12 months after TKA (72). However, the control group was not randomized (72). Two recent studies have been published subsequently (87,91). Madsen et al. investigated supervised group-based rehabilitation including PRT compared to supervised, home-based rehabilitation with late intervention start (4–8 weeks postoperatively) and Jakobsen et al. investigated 7 weeks of physical rehabilitation (with PRT) early after TKA (within the first week after TKA) and compared it to physical rehabilitation without PRT. None of the studies found an effect of adding PRT to standard rehabilitation. Only one of the four PRT studies showed an effect of PRT, even though a review had concluded that high-intensity exercise programs were more effective than low-intensity (71).

At discharge from hospital, up to 80% of quadriceps muscle strength is lost, despite fast-track surgery that includes early mobilization and exercises (136). From a logical point of view and supported by this study, a preoperative PRT optimization program may prevent some of this massive strength loss. We failed to obtain muscle strength measurements 1 week after surgery, but we found a statistically significant difference between groups in the TUG and a trend toward improved 30sCST, 10mWT, and 6MWT in comparison to the control group.

Generally, the patients experienced none to mild knee pain at rest both before and after the training sessions. It is possible that the patients had experienced higher levels of pain during the exercises, but even so, the pain sensation is a temporary phenomenon that is normalized when the training exercises end. Only limited swelling was observed after each training session (from 0 to 0.4 cm), and this did not increase over the training period. We consider this minor increase of knee circumference after training to have no clinical relevance since the patients managed to increase muscle strength substantially (Paper IV).

The 30sSTS was chosen as the primary outcome because it is a functional performance test associated with muscle strength (102-106). We confirmed this association, and found additionally that 30sCST was more strongly associated with muscle strength than the TUG and walking tests (Paper II).

Methodological consideration and limitations

The greatest limitation of the work in this PhD thesis is that we failed to include the planned 70 patients, increasing the risk of a type 2 error. Due to the time schedule for this PhD thesis, we had to stop inclusion before reaching the planned 70 patients. However, the efficacy of the preoperative PRT on the primary outcome at the primary time point was greater than expected, and thus we demonstrated a significant effect even though the 70 patient target was not reached.

Selection bias may have occurred because the patients had to accept participation in a training intervention and transport to the training site. The patients with few physical and mental resources may not be interested in participating in such a study. However, the group of patients denying participation due to problems with transport was only a small group.

Another limitation was that only the assessor was blinded in relation to the patients' group affinities. It is, however, very difficult to blind patients and training physiotherapists to an exercise intervention because a placebo intervention is easily revealed by both patients and physiotherapists.

Due to knee pain and restricted range of motion, it was not possible to obtain useful measurements of the operated leg at the test 1 week postoperatively. Moreover, several further measurements would have been relevant to assess, e.g. isokinetic muscle strength measures of the non-involved leg and hip abductor and adductor muscle strength, but since the duration of each test session was 2½ hours, it was not feasible to perform further measurements.

A 3-arm design with the third arm as a genuine control group would clarify a possible effect of the postoperative training intervention. However, the patient population was not large enough to allow for three groups.

Despite a comprehensive literature search (Paper I), we only found a few studies about PRT before and/or after TKA. Furthermore, the studies were heterogenic and the methodological quality generally low, which prevented clear conclusions.

9. Conclusion

Paper I

PRT is safe and feasible before and/or after THA. PRT is safe, but the methodological quality of existing evidence permits no conclusion on the effectiveness of PRT before and/or after TKA.

Paper II

Future rehabilitation programs should include both the knee extensor muscles and the knee flexor muscles to improve functional performance. The 30sCST is a proxy measure of the knee extensors and the knee flexors.

Paper III

Supervised preoperative PRT is an efficacious and safe intervention for improving postoperative functional performance and muscle strength, but not for improving patient-reported functional performance and health-related quality of life.

Paper IV

PRT of the affected leg initiated shortly before TKA does not exacerbate knee joint pain and effusion despite a substantial increase in muscle strength.

10. Perspectives and future research

The findings of the present PhD thesis have shown that a short pre-operative PRT program is efficient in regard to improving recovery after surgery. This should be considered by the knee surgeons when planning TKA surgeries. TKAs are mainly performed on older people for whom it is very important to remain as independent as possible.

Therapists and clinicians can extract practical inspiration regarding intensity, duration, and volume from the study and apply this to their patients. Knee flexor muscle strength is shown to be important in functional performance and should be included in future rehabilitation programs. The 30sCST is shown to be closely associated with muscle strength and could be applied as an easy and fast tool in the evaluation of strength training programs.

The study has also raised new questions for future research. 1) In the present study, the preoperative intervention was short and efficient. An extended intervention period might improve functional performance even further. 2) The efficacy of the postoperative PRT intervention is not clear from the current study. A randomized study with the postoperative PRT intervention from this study compared with a control group receiving home-based training would clarify this issue. 3) We have investigated the training program's impact on knee extensor and flexor muscle strength and the associations with functional performance. However, the training program's impact on the hip abductor, adductor and extensor muscle strength and its association with functional performance would be of interest to investigate. 4) Since preoperative training programs are not a part of usual care before TKA in Denmark, health economic analyses of a preoperative intervention would be highly relevant to carry out. 5) Since the onset and progression of knee OA is associated with decreased knee extensor muscle strength, it would be of interest to investigate whether the PRT program applied in an earlier phase would postpone the progression of the OA.

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List of appendices

Appendix 1: Paper 1

Skoffer B, Dalgas U, Mechlenburg I. Progressive resistance training before and after total hip and knee arthroplasty: A systematic review. Clin Rehabil. 2015 Jan;29(1):14-29.

Appendix 2: Paper 2

Skoffer B, Dalgas U, Mechlenburg I, Søballe K, Maribo T. Functional capacity is associated with both extensor and flexor strength in patients scheduled for Total Knee Arthroplasty: a cross-sectional study. Journal of Rehabilitation Medicine 2014. Accepted for publication

Appendix 3: Paper 3

Skoffer B, Maribo T, Mechlenburg I, Hansen PM, Søballe K, Dalgas U. Efficacy of preoperative progressive resistance training on postoperative functional performance and muscle strength in patients undergoing total knee arthroplasty. A randomized controlled study. *Submitted*

Appendix 4: Paper 4

Skoffer B, Dalgas U, Maribo T, Søballe K, Mechlenburg I. No exacerbation of knee joint pain and effusion following preoperative progressive resistance training in patients scheduled for total knee arthroplasty. *Submitted*

Appendix 5: List of theses from the orthopedic research group

Appendix 1: Paper 1

Article

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Progressive resistance training before and after total hip and knee arthroplasty: a systematic review

Birgit Skoffer[1,2], Ulrik Dalgas[3] and Inger Mechlenburg[4]

Abstract

Objective: To investigate the effect of progressive resistance training (PRT) on muscle strength and functional capacity before and/or after total hip arthroplasty (THA) and total knee arthroplasty (TKA). The effects of THA and TKA upon quality of life and the rate of adverse events were also investigated.

Data sources: Literature from nine databases.

Review methods: Studies were included if 1) the effect of a PRT intervention was compared with no intervention or another type of intervention; 2) the outcomes included muscle strength and/or functional capacity; 3) all participants were scheduled for or had just undergone THA or TKA; 4) they were randomized, controlled trials (RCT); and 5) only full-length papers in English were studied. Data on patient characteristics, training regime, controls, and outcome measures were extracted.

Results: Four RCT studies on PRT and THA including 136 patients and three RCT studies on PRT and TKA including 284 patients were identified and rated according to the PEDro scale. The general methodological quality of the studies was low. No adverse events were reported in any of the studies. Weak evidence of a beneficial effect of PRT before and/or after THA on muscle strength and functional capacity was found. No effect of PRT before TKA on muscle strength and functional capacity was found. The results of postoperative PRT were too heterogeneous to allow conclusions.

Conclusion: PRT is safe and feasible before and/or after THA. PRT is safe, but the methodological quality of existing evidence permits no conclusion on the effectiveness of PRT before and/or after TKA.

Keywords

Exercise therapy, functional capacity, hip replacement, knee replacement, muscle strength, weight training

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Introduction

Total hip arthroplasty and total knee arthroplasty are the two most common surgeries performed in people with osteoarthritis.[1] Both are safe and cost-effective in patients with end-stage osteoarthritis who do not respond to non-surgical therapy.[1–3] Replacement of a hip or knee joint generally leads to pain reduction, correction of joint alignment, improvement of physical function and high satisfaction.[4,5] However, patients may not fully regain muscle strength and functional capacity after surgery,[6–10] and impairments of muscle strength and functional capacity remain below levels seen in a healthy-matched population for years after total hip and knee arthroplasty.[11,12] Total hip arthroplasty patients recover more quickly from surgery than total knee arthroplasty patients,[13–15] presumably because their pain levels are generally lower than those experienced by total knee arthroplasty patients.[16]

Patients scheduled for total hip or knee arthroplasty typically have reduced muscle strength due to sarcopenia, impaired neuromuscular function and pain-induced disuse of the affected leg.[17–19] The approach to rehabilitation has become more aggressive over the past decade. Progressive resistance exercises effectively elicit strength gains, and both training volume and intensity are strongly associated with the level of physiological adaptations in healthy aging adults.[20] Intensive progressive resistance training protocols have been applied in the early post-operative phase after total hip or knee arthroplasty. More recently, progressive resistance training has also been applied before surgery.

Nonetheless, existing reviews[21,22] have not systematically summarised the literature regarding the effect of progressive resistance training before and/or after total hip and knee arthroplasty. The purpose of the present study was therefore to systematically review the effect of progressive resistance training on muscle strength and functional capacity before and/or after total hip or knee arthroplasty. The review also includes an analysis of the effects of progressive resistance training on the patients' quality of life and the rate of adverse events.

Methods

Data sources and searches

This study was performed in accordance with the PRISMA guidelines.[23] A systematic literature search of nine different databases (PubMed, Embase, Cochrane Library, Web of Knowledge, PEDro, Cinahl, SveMed+, SPORTDiscus and Bibliotek.dk) was performed to identify articles on progressive resistance training conducted before and/or after total hip or knee arthroplasty published from 1980 until 11 February 2013. The literature search was performed by two investigators (UD and BS) and a research librarian. The search was performed using the subject headings "resistance training" or "exercise therapy" in combination with "total hip arthroplasty" or "total knee arthroplasty". The exact search terms used in the databases are shown in Appendix 1 (online supplementary material). Also, a regular text search in PubMed with the terms "total hip arthroplasty" or "total knee arthroplasty" in combination with "resistance training" was performed to identify studies not yet categorised in the MeSH database.

Study selection

Studies were included in this review if 1) the effect of a progressive resistance training intervention was compared with the effect of no intervention or with the effect obtained from use of another type of intervention; 2) the outcomes included muscle strength and/or functional capacity; 3) all study participants had performed progressive resistance training before and/or after total hip or knee arthroplasty; 4) they were randomized, controlled trials; and 5) only full-length papers in English were studied. Progressive resistance training was defined in accordance with the 2009 guidelines of the American College of Sports Medicine[24] as a concentric/eccentric muscle contraction against a variable or constant external resistance at a constant or variable velocity, where loading is continuously adjusted to ensure progression. Consequently, a study was excluded if 1) the training intervention was not progressive according to the above

definition; 2) the study included participants who had undergone surgery other than total hip or knee arthroplasty; 3) it was a review, a cohort study or a case-control study.

Data extraction and quality assessment

The methodological quality of the studies was evaluated using the original 11-item Physiotherapy Evidence Database (PEDro) scale.[25,26] (Appendix 2, online supplementary material). All 14 papers were evaluated according to the PEDro scale, but only one score was assigned for each unique study. For example, five papers by Suetta et al.[27–31] were published on the basis of a single study, but assigned only one PEDro score. Three investigators independently scored all included studies (IM, UD and BS) according to the PEDro operational definitions,[25] and afterwards consensus was achieved in the few cases of disagreement. A meta-analysis could not be performed due to large heterogeneity of the studies in terms of time point and the duration of the intervention, different control groups and outcome measures. Consequently, the results of each individual study are reported and interpreted.

Data synthesis and analysis

Data extraction and analysis included patient characteristic, training regime, controls and outcome measures (e.g. muscle strength and functional capacity). The first author (BS) extracted data from all the studies, while the second (UD) and the third author (IM) verified the data from the THA and TKA studies, respectively. The benefit of progressive resistance training was calculated as a percentage change over time. Percentage changes at each time point in the intervention group were compared with the corresponding percentage changes in the control group. However, data were not available for this calculation in the studies by Gilbey et al. and Wang et al.[32–34], and for the imbedded group in the study by Petterson et al.[35]

Results

The search identified four randomized controlled trials on progressive resistance training and total hip arthroplasty including 136 patients and three randomized controlled trials on progressive resistance training and total knee arthroplasty including 284 patients (Figure 1). The subjects included in the study by Wang et al.[34] form a subset of the subjects included in the study by Gilbey et al., and they are therefore not included in the total numbers.[32,33,36] However, these papers reported different outcome measures, and both were therefore included in the review where they are interpreted separately. The reference lists of the included 14 papers were checked for further relevant publications, but no further studies were found.

Study characteristics

The identified studies scored 4 to 7 of a total of 10 points on the PEDro scale, mean 5.5 (1.3) in total hip arthroplasty studies and mean 5.3 (1.2) in knee arthroplasty studies (Table 1, 2 and 3). None of the studies achieved points in relation to blinding of subjects or therapist, and only one study[35] applied blinded assessment. In one study, isometric quadriceps strength was reported as the primary outcome measure,[37] while another study[35] applied the quadriceps strength and the central activation ratio (a ratio between the maximal voluntary isometric contraction and the maximal voluntary isometric contraction with superimposed electrical stimulation)[38] as its primary outcome measures. None of the studies reported power calculations.

Patient characteristic

Most of the patients had undergone surgery due to osteoarthritis. The body mass index was generally higher in total knee arthroplasty patients than in total hip arthroplasty patients (Table 1, 2 and 3). The total dropout rate ranged from 0% to 25% in total hip arthroplasty patients and from 10% to 27% in knee arthroplasty patients in those studies where dropout rates were reported.

Intervention characteristic

The progressive resistance training intervention was targeted solely at the lower extremity in all

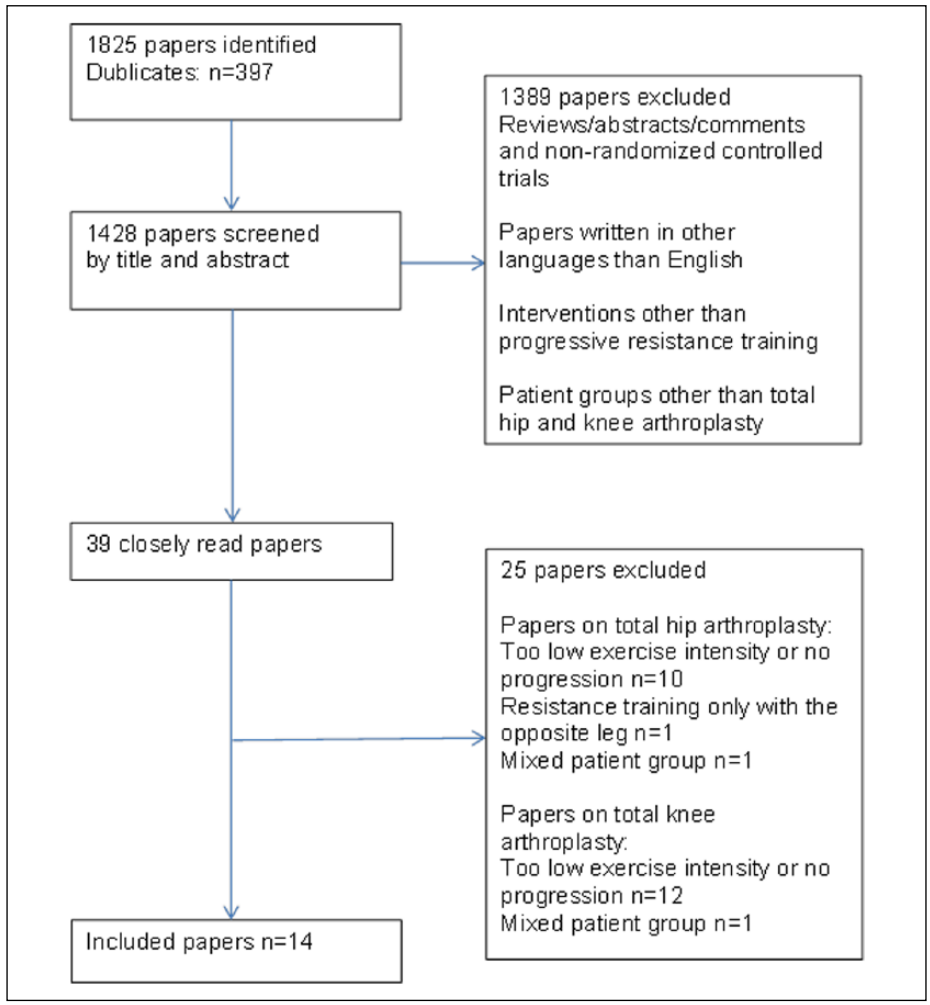

Figure 1. Flow diagram.

studies except one which also included upper body exercises.[32] The intensity of the training was generally reported in two different ways; it was expressed either as a percentage of 1 repetition maximum (1 repetition maximum is the heaviest load that can be lifted one time using proper technique) or as the load that can be lifted for a given number of repetitions, i.e. 10 repetition maximum. The total number of sessions was generally higher in total hip arthroplasty than in knee arthroplasty. All studies applied supervised progressive resistance training, and none reported any side effects or adverse events related to progressive resistance training (Table 1, 2 and 3).

Characteristic of the control groups

All the total hip arthroplasty studies included a control group whose subjects followed a home-based exercise program.[33,34,39] In the studies by McKay et al. and by Johnson et al. another exercise intervention was applied as control. [35,37,38,40] Finally, Petterson et al. randomized patients into two groups and compared progressive resistance

Table 1. Schematic overview of included pre and post intervention THA studies.

Trials	Sample size Dropouts Adherence % PEDro score	Subject diagnoses for THA Age/Sex Start	Duration and frequency	Training regime	Outcome (vs. control)
Gilbey et al.[32,33]	Total included: 76. Total dropout: 19/76 = 25% Adherence RT: 97%. Adherence home-based: 95%. Total score: 4/10.	Osteoarthritis, osteonecrosis of the femoral head, posttraumatic osteoarthritis, inflammatory arthritis, Padget's disease ~67yr 8 weeks before THA and 3 weeks after.	Before THA 8 weeks 2 supervised sessions/week 2 home-based sessions/ week 16 + 16 sessions. After THA 10 or 20 weeks 2 supervised sessions/ week 2 home-based sessions/ week 20 + 20 or 40 + 40 sessions.	6 leg exercises: hip abduction, hip flexion, hip extension, knee extension, knee flexion, plantar flexion. Performed unilateral 1-3*10 reps. When 3*10 reps could be performed 5kg was added in all exercises. Supervised +hydrotherapy and aerobic training.	1 week pre THA. Composite hip strength score ↑. WOMAC total ↑. WOMAC stiffness ↑. WOMAC physical functions ↑. 3 weeks post THA WOMAC total ↑. WOMAC physical functions ↑. Usual gait speed ↑. 12 weeks post THA composite hip strength score ↑. WOMAC total ↑. WOMAC stiffness ↑. WOMAC physical functions ↑. 24 weeks post THA composite hip strength score ↑. WOMAC total ↑. WOMAC physical functions ↑. Usual gait speed ↑. Walking distance ↑.
Wang et al.[34] *	RT: 15, Con: 13. Total dropout: 0/28 = 0%. RT dropout: 0/15 = 0%. Adherence: 97%. Total score: 6/10.	Osteoarthritis, inflammatory arthritis, osteonecrosis of the hip ~67yr 10M/18W. 8 weeks before THA and 3 weeks after THA.	Before THA 8 weeks 2 supervised sessions/ week 2 home-based sessions/ week 16+16 sessions. After THA 10 or 20 weeks 2 supervised sessions/ week 2 home-based sessions/ week 20 + 20 or 40 + 40 sessions.	6 leg exercises: hip abduction, hip flexion, hip extension, knee extension, knee flexion, plantar flexion. Performed unilateral 1-3*10 reps. When 3*10 reps could be performed 5kg was added in all exercises. Supervised +hydrotherapy and aerobic training.	3 weeks post THA. Usual gait speed ↑. 12 weeks post THA. Usual gait speed ↑. Walking distance ↑. 24 weeks post THA. Usual gait speed ↑. Walking distance ↑.

THA, total hip arthroplasty; PEDro, Physiotherapy Evidence Database; RT, resistance training; M, men; W, women; Con, control group; WOMAC, Western Ontario and McMasters Osteoarthritis; ↑ indicates increase; ↓ indicates decrease; *the subjects included in the study of Wang et al. are a subset of the subjects included in the study of Gilbey et al. and, consequently, not counted in the total numbers.

Table 2. Schematic overview of included post intervention THA studies.

Trials	Sample size Dropouts Adherence % PEDro score	Subject diagnoses for THA Age/Sex Start	Duration and frequency	Training regime	Outcome (vs. control) Difference (%)
Suetta et al.[27–31]	RT: 13, RT+es: 11, Con: 12. Total dropout: 6/36 =17% RT dropout: 2/13 = 15%. Total score: 5/10.	Osteoarthritis ~70y (60-86y) / 18M /18W. Within few days of THA	12 weeks 3 sessions/ week 36 sessions	2 leg exercises: knee extension and leg press. Performed unilateral. Week 1: 20RM. Week 2-4: 15RM. Week 5-6: 12RM. Week 7-12: 8RM. 3-5 sets supervised.	After 5 weeks of intervention. Strength KE-OP (60deg/sec) ↑ (19.8%). Strength KE-OP (180deg/sec): NS (14.8%). Strength (isom) ↑ (28.7%). Maximal gait speed: NS (0.9%). Stair climbing test: NS (-5.8%). Sit to stand: NS (-9.7%). After 12 weeks of intervention. Strength KE-OP (60deg/sec) ↑ (4.5%). Strength KE-OP (180deg/sec) ↑ (4.6%). Strength KE-OP (isom) ↑ (-10.5). Maximal gait speed: NS (6.6%). Stair climbing test: NS (-7.8%). Sit to stand ↑ (-16.9%)
Husby et al.[39,62]	RT: 12, Con: 12. Total dropout: 0/24 = 0%. RT dropout: 0/12 = 0%. Total score: 7/10.	Osteoarthritis ~57y (<70y) 9M/15W 1 week after THA.	4 weeks 5 sessions/ week 20 sessions.	2 leg exercises. Leg press and hip abduction. Performed unilateral. 4 sets at 5-6RM supervised.	After intervention. Leg press OP (1RM) ↑ (74.9%). Leg press both legs (1RM) ↑ (33.4%). Strength hip abduction OP (1RM) ↑ (268.7%). RFD OP ↑ (-142.4%) Step length OP: NS (-1.7%). Stance time OP: NS (-10.7%). HRQOL (SF36 PCS): NS (-11.0%). At 6 months follow up leg press OP (1RM): NS, (-53.3%) leg press both legs (1RM) ↑ (-24.8%). Strength hip abduction OP (1RM) ↑ (-66.3%). RFD OP: NS (-8.6%). Step length OP: NS (-3.3%). Stance time OP: NS (5.5%). HRQOL (SF36 PCS): NS (0.8%).

Table 2. (Continued)

Trials	Sample size Dropouts Adherence % PEDro score	Subject diagnoses for THA Age/Sex Start	Duration and frequency	Training regime	Outcome (vs. control) Difference (%)
					At 12 months follow up leg press OP (1RM): NS (-0.8%), leg press both legs (1RM): NS (12.4%). Hip abduction OP (1RM): NS (8.1%) RFD OP 12 months ↑ (14.9%). Step length OP: NS (7.0%). Stance time OP: NS (7.2%). HRQOL (SF36 PCS): NS (-0.0%).

THA, total hip arthroplasty; PEDro, Physiotherapy Evidence Database; RT, resistance training; RT+es, resistance training combined with electrical stimulation; Con, control group; M, men; W, women; RM, repetition maximum; NS, non-significant; KE, knee extension; OP, operated leg; RFD, rate of force development; Isom, isometric; HRQOL, health related quality of life ↑ indicates increase ↓ indicates decrease.

training with progressive resistance training with neuromuscular electrical stimulation. After one year, a pooled group of the two progressive resistance training groups was compared with an embedded prospective cohort receiving standard rehabilitation[35,41] (Table 1, 2 and 3).

Muscle strength

The total hip arthroplasty studies consistently reported strength improvement of the muscles trained during progressive resistance training. Isometric and isokinetic muscle strength was assessed as peak torque (Nm) in two studies[27,31] whereas Husby et al. reported improved 1 repetition maximum (kg) leg press strength. Gilbey et al. reported significant improvement of a composite hip strength score (including muscle strength during thigh flexion, extension and abduction). The thigh flexor and extensor musculature were measured as peak torque (Nm), and the thigh abduction strength (kg) was measured in a tensiometer.[33] The ability to develop a rapid rise in muscle force, i.e. the contractile rate of the force development, was increased in the progressive resistance group.[31,39] The effects of progressive resistance training on muscle strength reported in the total knee arthroplasty studies are inconsistent. No effect of preoperative progressive resistance training on isometric strength of the knee extensors assessed as peak force (Nm) was reported[37]; nor was any effect of postoperative progressive resistance training of isometric strength of knee flexors or on the central activation ratio achieved.[40] However, an improvement of the normalized maximum voluntary isometric contraction has been reported[35,41] (Table 1, 2 and 3).

Functional capacity

Weak evidence of a beneficial effect of pre- and postoperative progressive resistance interventions is reported on functional capacity in total hip athroplasty patients (Table 1 and 2). However, the results were inconsistent in total knee arthroplasty studies, which limit definite conclusions (Table 3).

Table 3. Schematic overview of included TKA studies.

Trials	Sample size Dropouts Adherence % PEDro score	Subject diagnoses for TKA Age/Sex Start	Duration and frequency	Training regime	Outcome (vs. control) Difference (%)
Pre TKA interventions					
McKay et al.[37]	RT: 10, UBT: 12. Total dropout: 6/22=27%. RT dropout: 3/10=30%. UBT dropout: 3/12=25%. RT adherence: 98%. UBT adherence: 93%. Total score: 6/10	Osteoarthritis ~70yr +/- 6 9M/13W 6 weeks before surgery.	6 weeks 30 min/session, 3 sessions/week 18 sessions.	PT: 4 leg exercises: quadriceps, hamstrings, leg press, triceps surae (performed bilaterally). 2*8 reps exercises progressed from 60% of 1RM with 1-2 kg per week as tolerated. UBT: 4 exercises upper body training: latissimus dorsi, chest press, biceps brachii, triceps brachii. 2*8 reps exercises progressed from 60% of 1RM with 1-2 kg per week as tolerated supervised.	After intervention KE (isom): NS (10.9%) 50 FOOT WT: NS (-21.5%). Stair climbing test: NS (7.9%). WOMAC pain: NS (5.1%). WOMAC function: NS (8.8%) HRQOL PCS (SF-36): NS (4.8%) HRQOL MCS (SF-36): NS (10.7%). At 6 weeks postop. follow up KE (isom): NS (-12.1%). 50 FOOT WT: NS (21.2%) stair climbing test: NS (-1.1%). WOMAC pain: NS (9.7%) WOMAC function: NS (0.7%). HRQOL PCS (SF-36): NS (-9.2%). HRQOL MCS (SF-36): NS (-16.9%). At 12 weeks postop, follow up KE (isom): NS (-1.5%). 50 FOOT WT: NS (-7.2%). Stair climbing test: NS (5.4%). WOMAC pain: NS (5.8%). WOMAC function: NS (-2.4%). HRQOL PCS (SF-36): NS (12.9%). HRQOL MCS (SF-36): NS (-12.9%).

Table 3. (Continued)

Trials	Sample size Dropouts Adherence % PEDro score	Subject diagnoses for TKA Age/Sex Start	Duration and frequency	Training regime	Outcome (vs. control) Difference (%)
Post TKA interventions					
Petterson et al.[3,5,41]	RT: 100, RT+es: 100, Con: 41. Total dropout: 19/200 = 10%. RT dropout: 3/100 = 3%. RT+es dropout: 16/100 = 16% Adherence: mean 16.9+/1.3 visits. Total score: 6/10	All diagnoses for TKA ~65yr +/- 8 122M/119W 3-4 weeks after TKA.	6 weeks 2-3 sessions/week 12-18 sessions.	6 leg exercises: quadriceps, hamstrings, gastrocnemius, soleus, hip abductors and flexors (performed unilateral). Week 1-6: 10 RM 2-3 sets of 10 reps. supervised. ES group: +NMES RT group: -NMES.	At 3 month follow up KE-OP (isom): NS (-18.8%) CAR: NS (-1.1%). Timed Up and Go: NS (-1.9%) 6MWT: NS (1.2%). Stair climbing test: NS (-2.3%). HRQOL (SF-36 PCS): NS (6.4%). HRQOL (SF-36 MCS): NS (1.5%). At 12 month follow up KE-OP (isom): NS (-1.1%). CAR: NS (-3.4%). Timed Up and Go: NS (-1.6%) 6MWT: NS (0.7%). Stair climbing test: NS (-3.44%). HRQOL (SF-36 PCS): NS (1.1%). HRQOL (SF-36 MCS): NS (1.6%).
				Patients of 1 referring surgeon from the pooled. RT and ES group Con. group: patients of the referring surgeon represent the standard of care in the community.	At 12 month follow up KE-OP (isom) ↑ CAR: NS Timed Up and GO ↑ 6MWT ↑. Stair climbing test ↑ HRQOL (SF-36): NS.

(Continued)

Table 3. (Continued)

Trials	Sample size Dropouts Adherence % PEDro score	Subject diagnoses for TKA Age/Sex Start	Duration and frequency	Training regime	Outcome (vs. control) Difference (%)
Johnson et al.[40]	RT: 10, WBV: 11. Total dropout: 5/21 = 24%. RT dropout: 2/10 = 20%. Required to complete at least 10 out of 12 sessions. Total score: 4/10.	Osteoarthritis ~68yr +/- 10. No information about sex between the dropouts 3-6 weeks after surgery.	4 weeks 3 sessions/week 12 sessions.	2 leg exercises: knee extension, hip flexion. 1-3 sets of 10 reps. Exercises were progressed once the patient could complete the exercise and extra weight (0.454-4.54 kg) was added. Supervised.	After intervention KE-OP (isom): NS (-7.0%). KE-NOP (isom): NS (-16.1%). CAR-OP: NS (-6.8%). CAR-NOP: NS (-4.2%). Timed Up and Go: NS (-1.3%).

TKA, total knee arthroplasty; PEDro, Physiotherapy Evidence Database; RT, resistance Training; UBT, upper body training; RT+es, resistance training combined with electrical stimulation; ERT, eccentric resistance training; WBV, whole body vibration; Con, control group; M, men; W, women; NS, non-significant; KE, knee extension; OP, operated leg; NOP, non-operated leg; RFD, rate of force development; Isom, isometric; CAR, central activation ratio; RM, repetition maximum; WT, walk test; HRQOL, health related quality of life; ↑ indicates increase; ↓ indicates decrease.

Muscle morphological and neural adaptations

An increased cross sectional area of the quadriceps femoris muscle (obtained by computed tomography) and an increased neural drive (surface EMG) to the knee extensors were seen following 12 weeks of postoperative progressive resistance training in total hip arthroplasty patients compared with values obtained immediately before surgery.[27] Furthermore, muscle fibre hypertrophy of the type IIa and IIx fibres (biopsies from m. vastus lateralis), improvement of muscle pennation angle (ultrasound) and muscle thickness (ultrasound) of the knee extensors were reported 12 weeks postoperatively compared with the group receiving standard rehabilitation.

Self-reported function and health-related quality of life

Studies show improved self-reported function in total hip arthroplasty patients,[32,33] but not in total knee arthroplasty patients,[37] while no differences in health-related quality of life were found in either total hip arthroplasty or total knee arthroplasty patients (Table 1, 2 and 3).

Discussion

The systematic literature search revealed seven randomized controlled trials evaluating the effects of progressive resistance training before and/or after total hip arthroplasty or total knee arthroplasty. Their large heterogeneity limits the strength of any conclusions that may be drawn from this review and excludes further application of meta-analytical procedures. Nonetheless, some important points can be made. Total hip and knee arthroplasty patients tolerated progressive resistance training without suffering from side effects or adverse events, and their adherence was consistently excellent in studies reporting adherence outcomes. Furthermore, there is weak-to-moderate evidence of a beneficial effect of pre- and postoperative progressive resistance training interventions on muscle strength and functional capacity in total hip arthroplasty patients, while findings in total knee arthroplasty patients are generally inconsistent.

None of the studies exclusively investigated preoperative progressive resistance training in total hip arthroplasty. According to the studies in which interventions were applied before and after total hip arthroplasty,[33,34] it cannot be determined whether the improvement was achieved owing to the pre- and/or the postoperative training. However, significant improvements in functional capacity were found immediately before the post total hip arthroplasty interventions. This indicates that preoperative progressive resistance training did, indeed, contribute to the effects reported postoperatively. We identified only one study exclusively investigating preoperative progressive resistance training in total knee arthroplasty patients. The general lack of improvements reported in this study is in accordance with the results of several other studies that applied other types of preoperative exercise interventions in total knee arthroplasty.[42–45] Rooks et al. demonstrated improvements of a 6-week exercise program compared with an educational program in total hip arthroplasty patients, but not in total knee arthroplasty patients.[46] A review by Gill et al. demonstrated benefits on pain and self-reported function from preoperative exercise programs before total hip arthroplasty, whereas no such benefits were found from preoperative exercise programs implemented before total knee arthroplasty.[47]

This collectively suggests that exercise interventions before total hip arthroplasty may be beneficial, whereas exercise interventions before total knee arthroplasty seem to be inefficient. The lack of positive effects of exercise interventions performed before total knee arthroplasty may be explained by severe pain, which limits the exercise intensity that can be obtained in total knee arthroplasty patients. Consequently, one could speculate whether an efficient preoperative total knee arthroplasty exercise intervention should be one that only induces short-interval pain while at the same time being intensive. Progressive resistance training could be such an intervention, and the fact that McKay et al. reported no improvement may be

owed to the moderate intensity and/or the bilateral exercises applied in their study. Future studies should therefore test more intensive unilateral protocols. Interestingly, a recent review conducted by Wallis et al. concluded that there is low-to-moderate evidence from mostly small randomized controlled trials demonstrating that pre-operative exercise interventions may reduce pain in patients with hip and knee osteoarthritis prior to joint replacement, which suggests a possible role of exercise in pre surgery pain management.[48]

Muscle strength and functional capacity consistently improved in total hip arthroplasty patients postoperatively exposed to progressive resistance training. Furthermore, the study by Suetta et al. showed both beneficial morphological and neural adaptations following postoperatively progressive resistance training.[27,30] Such studies provide knowledge of the underlying mechanisms furthering improvements of muscle strength. These aspects should be considered when designing future studies since a better understanding of these mechanisms may optimise progressive resistance training protocols.

Studies evaluating low-intensity exercise interventions have shown improved hip muscle strength and maximal walking after physiotherapist-supervised exercises;[49,50] and they have shown improved postural stability, increased strength of hip muscles and the knee extensors after an intervention consisting of weight bearing exercises.[51] However, Vissers et al. recently reviewed 31 studies and concluded that physical functioning was generally recovered to only about 80% of the expected level at 6 to 8 month postoperatively.[52] This clearly highlights the need for further development of effective interventions for use in total hip arthroplasty patients.

The studies included in the present review suggest that progressive resistance training is more effective in terms of achieving muscle strength and functional capacity in total hip arthroplasty than in total knee arthroplasty patients. However, in two of the three total knee arthroplasty studies, the progressive resistance training intervention was compared with another kind intervention rather than with no intervention. Furthermore, the interventions in the total hip arthroplasty studies generally lasted longer (12 to 28 weeks) than in the total knee arthroplasty studies (4 to 6 weeks). The greater volume of training therefore at least partly explains the superior effect of training in total hip arthroplasty patients. Previous studies have shown that total knee arthroplasty patients have a slower and less complete recovery of function than total hip arthroplasty patients.[13,53,54] Furthermore, two recent studies showed a 30% reduction of knee extensor strength of the preoperative level in total hip arthroplasty patients,[55] while a reduction of 80% was seen in total knee arthroplasty patients[56] at discharge. This difference was seen despite implementation of fast-track surgery with mobilisation and rehabilitation immediately after surgery.

Another aspect to consider when designing progressive resistance training protocols to total hip arthroplasty and total knee arthroplasty patients is the asymmetry between the affected and the non-affected leg. In total hip arthroplasty patients, the affected leg is characterised by reduced preoperative muscle strength of hip flexors, extensors, abductors, adductors, knee extensors and flexors compared with the non-affected leg.[57] In total knee arthroplasty patients, reduced muscle strength of the knee extensors, knee flexors, hip abductors and plantar flexors has been reported.[58,59] When trying to re-establish symmetry, a unilateral approach to progressive resistance training would intuitively seem superior, but no studies have so far clarified whether this is, indeed, the case. A further consideration concerns the choice of exercises. Optimally, the selected exercises should take the above-mentioned muscle strength deficits into account if the goal is to re-establish muscle strength symmetry between the two legs.

Future studies should clarify whether total knee arthroplasty patients will benefit from longer and more intense unilateral pre- and postoperative progressive resistance training interventions.

The general methodological quality of the included studies in terms of the PEDro total score was low to moderate ranging from 4 to 7 out of 10 points. In particular, therapist and subject blinding was a problem, and bias cannot be disregarded. However, in most clinical trials examining rehabilitation/physiotherapy interventions, it is very difficult or even impossible to blind the therapist

providing the intervention and the participants receiving it. Blinding of assessors is more implementable and is strongly recommended for future trials within this field. Interestingly, a review of trials evaluating primarily medical treatments[60] demonstrated that trials without blinding and concealed allocation tended to report a higher treatment effect than trials including these design features, which clearly emphasises the importance of these aspects. Thus, Schultz et al. found that trials not applying double-blinding, generally reported higher treatment effects in the order of 17%.[61] Finally, sample size calculation is not reflected in the PEDro scale despite its importance for the methodological quality. Several of the included studies have small sample sizes, and none had performed a priori power calculation based on the primary study outcome. This increases the risk of type 2 errors,[37,39,40] which should be kept in mind when interpreting the results.

Additional research determining the preoperative effects of progressive resistance training on muscle strength and functional capacity is required in both total hip arthroplasty and total knee arthroplasty. Moreover, attention should be paid to the great reduction in muscle strength observed immediately after surgery. Future total knee arthroplasty studies should include genuine control groups to allow comparison with standard rehabilitation. Further investigation of underlying mechanisms explaining changes in muscle strength (and pain) is also warranted, especially in total knee arthroplasty studies. More attention should be given to the design of (unilateral) progressive resistance training interventions in terms of choice of exercises (optimizing the symmetry between the legs), intensity (as intensive as possible) and duration and frequency to optimise the effectiveness. Finally, future studies should implement defined primary outcome measures, power calculations and blinded assessment. Consensus on a set of core outcome measures would also greatly improve comparison across studies. For example, the effect of preoperative progressive resistance training could be investigated in a randomized controlled study applying an intensive (~8-10RM) unilateral exercise protocol for 2-3 times per week lasting at least 4 weeks.

Some study limitations have to be borne in mind when interpreting the results of the present review. Despite a comprehensive literature search, we only identified seven relevant studies. Furthermore, the heterogeneity of these studies prevented us from completing a meta-analysis. In some of the studies, the sample sizes were relatively small, and the studies were therefore potentially underpowered to demonstrate a possible effect of the PRT intervention. Also, the general lack of concealed allocation and blinded assessors may increase the risk of overestimation of the effects of the PRT interventions. Finally, we have not assessed the possibility of unpublished as well as non-English studies, so a publication bias may exist.

Clinical messages

- Progressive resistance training is safe and feasible before and/or after total hip arthroplasty.
- The methodological quality of existing evidence permits no conclusion on the effectiveness of progressive resistance training before and/or after total knee arthroplasty.
- There is an evident need for research into the effect of progressive resistance training before and/or after total knee arthroplasty.

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Conflict of interest

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Appendix 1. Detailed list of retrieved articles and applied search terms in nine different databases

Database	Articles retrieved	Search Terms (subject headings etc.)
Pubmed	853	((“Arthroplasty, Replacement, Hip”[MESH] OR“Hip Prosthesis”[Mesh]) OR (“Arthroplasty, Replacement, Knee”[MESH] OR “Knee Prosthesis”[Mesh])) AND (“Exercise Therapy”[Mesh])
Embase	624	(“Hip arthroplasty”/exp OR “Knee arthroplasty”/exp) AND “Exercise”/exp
Cochrane	127	(“Arthroplasty, Replacement, Hip”[MESH] OR “Arthroplasty, Replacement, Knee”[MESH]) AND (“Exercise”[Mesh] OR “Exercise Therapy”[Mesh] OR “Exercise Movement Techniques”[Mesh])
Web of Knowledge	0	(“Hip arthroplasty” OR “Knee arthroplasty”) AND (“Exercise” OR “Resistance training” OR “Stength training”)
PEDro	90	(“Hip arthroplasty” OR “Knee arthroplasty”) AND (“Exercise” OR “Resistance training” OR “Strength training”)
Cinahl	77	(“Hip arthroplasty” OR “Hip replacement” OR “Knee arthroplasty” OR “Knee replacement”) AND (“Exercise” OR “Resistance training” OR “Strength training”)
SveMed+	7	(“Arthroplasty, Replacement, hip” OR “Arthroplasty, Replacement, knee”) AND (“Exercise” OR “Resistance training”)
SPORTDiscus	47	(“Total hip replacement” OR “Total knee replacement”) AND (“Exercise”)
Bibliotek.dk	0	(“Hoftealloplastik” eller “Knæalloplastik”) OG (”Genoptræning” ELLER ”Fysioterapi” ELLER ”Styrketræning”)

Appendix 2. Included studies rated according to the Physiotherapy Evidence Database (PEDro) scale*

	Trials	PEDro criteria											Total score
		1	2	3	4	5	6	7	8	9	10	11	
THA	Gilbey et al.[16,17]	√	√	-	√	-	-	-	-	-	√	√	4/10
	Wang et al.[67]	√	√	-	√	-	-	-	√	√	√	√	6/10
	Suetta et al.[54-58]	√	√	√	√	-	-	-	-	-	√	√	5/10
	Husby et al.[23,24]	√	√	√	√	-	-	-	√	√	√	√	7/10
TKA	McKay et al.[36]	√	√	√	√	-	-	-	-	√	√	√	6/10
	Petterson et al.[40,41]	√	√	-	√	-	-	√	-	√	√	√	6/10
	Johnson et al.[27]	√	√	-	√	-	-	-	-	-	√	√	4/10

Criteria 1: Specified eligibility criteria (not included in the total score)
Criteria 2: Randomized allocation
Criteria 3: Concealed allocation
Criteria 4: Similarity between groups at baseline
Criteria 5: Blinding of subjects
Criteria 6: Blinding of therapists
Criteria 7: Blinding of assessors
Criteria 8: Outcome measures obtained from at least 85% of initially allocated subjects
Criteria 9: All received treatment, or key outcome was analyzed by “intention to treat”
Criteria 10: Between-group statistical comparisons
Criteria 11: Both point and variability measures provided
Criteria scoring: √ = present - = absent
* All 14 papers were evaluated according to the PEDro scale, but only one score was assigned for each unique study

Appendix 2: Paper 2

Running title: Functional performance and knee muscle strength

Functional performance is associated with both knee extensor and flexor muscle strength in patients scheduled for total knee arthroplasty:

A cross-sectional study

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Abstract

Objective: To test in patients scheduled for total knee arthroplasty if muscle strength would be 1) strongly associated with both measured functional performance and patient-reported measures; 2) more closely associated with functional performance when measured during concentric than during isometric contractions and; 3) stronger related to the 30s chair stand test than to the timed-up-and-go and walking measures.

Design: Cross-sectional-study.

Patients: Fifty nine patients, mean age 70.4 years.

Methods: Associations between muscle strength and measured functional performance and patient-reported measures were calculated.

Results: Both knee extensor and knee flexor strength were associated with performance-based measures. Generally, the concentric knee flexor muscle strength was more strongly associated with functional performance than the isometric knee flexor strength. Concentric and isometric knee extensor strength were of equal importance. The 30s chair stand test was better than the timed-up-and-go and the walking tests at determining muscle strength.

Conclusion: Future rehabilitation programs should include both the knee extensor muscles and the knee flexor muscles to improve functional performance. The 30s chair stand test is a valid and clinical relevant proxy measure of knee extensor and the knee flexor muscle strength.

Key words: Osteoarthritis, knee, muscle strength, functional capacity

INTRODUCTION

Knee osteoarthritis (OA) is a frequent health problem in older adults (1). The most prominent symptoms in knee OA are pain, reduced functional performance, decreased muscular strength and reduced quality of life (2-5). Pain and reduced functional performance in combination with radiographically confirmed severe OA are the main indications for total knee arthroplasty (TKA) (6).

Impairment of the knee extensor muscle strength in patients with knee OA is well-documented (3), and decreased knee extensor muscle strength is the only significant determinant of reduced functional performance in patients with severe knee OA (7). Furthermore, knee extensor muscle weakness is a primary risk factor for developing knee pain, disability and progression of joint damage in persons with knee OA (8,9). Although focus in the literature is largely on the knee extensors, substantial knee flexor strength deficits have been reported (3). The importance of knee muscle strength is evident, but valid and reliable tests of muscle strength require expensive and complex laboratory equipment and hence transferability to a clinical setting is sparse.

Patients awaiting TKA perform poorer in performance-based measures such as the timed-up-and-go (TUG) test, the 6 minutes walk test (6MWT) and the single-limb stance test (10) when compared to healthy controls. Even so, it is still unknown how these performance-based measures relate to knee muscle strength. This is important to know for clinicians who monitors the results of a rehabilitation intervention with performance-based measures in patients with knee OA in a clinical setting and who needs to know which performance-based measure is to be preferred.

Most of the studies on knee muscle strength are based on isometric muscle tests (3)**.** Isometric tests of the muscle groups reflect the work of the prime mover, whereas the results of concentric muscle tests probably better reveal the complex activation of muscle groups exhibited in physical function.

Knowledge on the association between isometric and concentric muscle strength and performance-based measures may help determine the best clinical relevant method for testing knee muscle strength. Moreover, a better understanding of the relationship between knee extensor and knee flexor muscle strength and performance-based measures may improve rehabilitation programs before and after TKA (11,12).

We aimed to test the hypotheses that in patients scheduled for TKA, knee extensor and knee flexor strength would be 1) weaker in the affected leg than in the non-affected leg; 2) strongly associated with both measured functional performance and patient-reported measures; 3) more closely associated with functional performance when measured during concentric than during isometric contractions and; 4) stronger related to the 30s chair stand test (30sCST) than to the TUG test and walking measures.

METHODS

Study design and patients

This cross-sectional study is part of a randomized, controlled study that investigates the effect of preoperative progressive resistance training on functional performance and muscle strength after TKA. Fifty-nine patients scheduled for TKA were included from the Orthopaedic Department at Aarhus University Hospital and Silkeborg Regional Hospital, Denmark (Figure 1).

Included were patients who were: 1) scheduled for primary unilateral TKA; 2) diagnosed with OA; 3) resident in the Aarhus municipality; 4) able to transport them-selves to training; and 5) willing to give informed consent. Excluded were patients who were: 1) age < 18 years; 2) suffering from heart

disease or uncontrolled hypertension; 3) suffering from neuromuscular or neurodegenerative conditions; and 4) unable to comprehend the protocol instructions.

The study followed the Declaration of Helsinki, was approved by the regional Ethics Committee (Journal no. M-20110191) and was registered with the Danish Data Protection Agency (Registration no. 1-16-02-191-11) and at ClinicalTrials.gov (NCT01647243).

Testing procedure

The assessment included tests of muscle strength and functional performance and measurement of height, body mass and range of knee joint motion. Furthermore, patients completed questionnaire items on pain, functional performance and quality of life. All patients were tested according to the protocol 6 weeks before TKA by the same assessor (BS).

Muscle strength was measured using an isokinetic dynamometer (Humac Norm, Computer Sports Medicine Inc., Massachusetts, USA). Patients were in a seated position with a 90^0 hip flexion. The body and the tested thigh were fastened with straps. The anatomic axis of the knee was aligned with the axis of the dynamometer, and the ankle cuff was 3 cm proximal to the medial malleolus. Moment values were corrected for the gravity of the lower limb and were measured by the dynamometer at a knee joint angle of 45^0.

Patients performed three maximal isometric contractions of the knee extensors at a knee joint angle of 70^0 (0^0 = full knee extension) and of the knee flexors at a knee joint angle of 20^0 (13). Rest periods of 60 seconds were allowed between attempts. The trial with the highest peak torque (Nm) was selected for further analysis. Isometric testing was performed bilaterally.

The concentric knee extensor and knee flexor muscle strength of the affected knee was evaluated at 60^0/sec (peak moment, Nm). The patients performed six maximal concentric contractions in full

possible range of motion (ROM); the trial with the highest peak torque was selected for further analysis.

Dynamometry is considered the gold standard of muscle strength assessment, and dynamometry tests of knee extensor muscles in knee OA have proven reliable (14).

30sCST measures the total number of full rise to standing position patients were able to perform in 30 sec. Patients were seated in a standard chair with their arms folded across their chest (15). The best of two test trials was selected for further analysis. The test is reliable in patients with knee OA (16,17).

TUG measures (in seconds) the time taken to rise from a standard armed chair, walk 3 m, turn, walk back to the chair and sit down again. Patients were instructed to walk as fast as they felt was safe, and the use of an assistive device was allowed if necessary (18). The fastest time of two test trials was selected for further analysis. The test is valid in patients with knee OA (16,19).

Ten-meter walk test (10mWT) measures maximal walking speed. Patients were instructed to walk 12 m between two marked lines. Time was stopped when the first foot touched or passed the 10-m line. Patients were instructed to walk as fast as they felt was safe using an assistive device if necessary (20). The fastest time of two test trials was selected for further analysis.

6MWT measures the maximal walking distance in 6 min. Subjects were instructed to walk as far as possible in 6 min in a safe manner in an undisturbed 30-m long corridor. The use of assistive devices was allowed if necessary (21). The test is reliable in patients with knee OA (22).

Active and passive knee joint flexion and the extension ROM of the affected knee were measured by goniometry. The patient was placed in the supine position. The fulcrum of the goniometer was placed over the lateral epicondyle with the one 30-cm arm pointed towards the major trochanter of

the femur and the other towards the lateral malleolus (23). During active ROM, patients flexed and extended the knee as much as possible. During passive ROM, the assessor flexed and extended the knee until the patient said "stop". The method is reliable and valid in patients with knee restrictions (23).

The Knee Injury and Osteoarthritis Outcome Score (KOOS) is a patient-reported questionnaire consisting of five subscales: pain, other symptoms, function of daily living, function in sport and recreation, and knee-related quality of life (24). KOOS is a reliable and valid tool in patients with knee OA (25,26). However, in sport and recreation the subscale function has shown weak-to-moderate reliability and weak construct validity (25,26).

Knee pain ratings were recorded on an 11-point numerical rating scale from 0 ('no pain') to 10 ('worst pain imaginable'). Current pain, the worst pain during the past 14 days and the average pain during the past 14 days were rated. Numerical rank scale is a reliable and valid tool for pain assessment (27).

Statistical analyses

Descriptive statistics were calculated with mean and standard deviation (SD) for normally distributed data and median and range if data showed non-normal distribution. Normal distribution of data was checked with box-plots, q-q plots, histograms and dot-plots. To compare muscle strength between the affected and the non-affected leg, paired t-test was applied. To calculate the association between functional performance, patient-reported outcomes and knee muscle strength, linear regression analyses were applied. Logarithmic transformation was applied on the non-normally distributed data to achieve an approximate, normal distribution. Pitman's test was applied to identify which functional performance test had the closest relationship with muscle strength and

whether concentric or isometric strength had the closest relationship with functional performance. Statistical analyses were performed in Stata version 12.1 (StataCorp LP, USA).

RESULTS

In total 59 patients accepted to participate in the study during the inclusion period (Figure 1). The patients' demographics are listed in Table 1. Median values and range for functional performance tests and muscle strength are shown in Table 2.

Muscle strength in affected and non-affected leg

The median values and the range of concentric and isometric knee muscle strength are shown in Table 2. The knee extensors were significantly weaker in the affected leg than in the non-affected leg *($p < 0.01$),* whereas for knee flexors the difference between the two legs was insignificant *($p = 0.51$).* The average strength of the knee extensors in the affected leg corresponded to 89.1% (SD 30.2) of that of the non-affected leg.

Muscle strength vs. functional performance / self-reported measures

An overall association between functional performance and concentric and isometric knee extensor and knee flexor muscle strength in the affected and non-affected leg was found, except for the 6MWT. The association was generally strongest for the affected leg (Table 3).

Scores of the KOOS subscales are shown in Table 1. Using linear regression, we found no association between subscales and any knee muscle strength parameters, either for crude or for adjusted scores (supplemental material Table s1, available online). In contrast, an overall association was found between the KOOS subscales and pain (supplemental material Table s2, available online).

Concentric vs. isometric muscle strength

Generally, both concentric and isometric knee extensor and knee flexor muscle strength were associated with functional performance-based measures. However, concentric knee flexor strength was closer associated with the TUG, 10mWT and the 6MWT than isometric knee flexor strength, but no difference was found between concentric and isometric knee extensor strength in any test of functional performance (Table 4).

30sCST vs. TUG and walking

The 30sCST was the test strongest associated with all parameters of muscle strength. 30sCST was closer associated with both concentric and isometric knee extensor and knee flexor than the TUG and the walking tests (Table 5).

DISCUSSION

This study shows that knee extensors were weaker in the affected leg than in the non-affected leg, whereas knee flexor muscle strength was similar in the two legs. In general, knee extensor and knee flexor muscle strength were associated with performance-based measures, except for the 6MWT. However, no association between patient-reported measures and muscle strength was observed. Concentric muscle strength was generally closer associated with performance-based measures than isometric muscle strength. Finally, the 30sCST test was the performance-based measures most closely associated with the various parameters of muscle strength.

Muscle strength in affected and non-affected leg

Concentric and isometric knee extensor muscle strength were higher than the corresponding knee flexor strength in both legs. The isometric knee extensor muscle strength was lower in the affected leg than in the non-affected leg, while the muscle strength of the knee flexor was similar in the two legs. These results are in accordance with the findings of Stevens-Lapsley et al. who found that isometric knee extensor strength was lower in the affected than in the non-affected leg (21%; $p = 0.03$), whereas the strength of the knee flexors was similar in the two legs in patients scheduled for TKA ($p = 0.70$) (28). Brown et al. found that the concentric knee extensor and flexor strength of the affected knee was 24-30% lower than the strength of the unaffected leg in patients scheduled for TKA (29). The latter finding cannot be directly compared with ours, since we did not investigate the concentric strength of the non-affected leg. Still, Brown et al.'s finding suggests that knee OA affects concentric muscle strength more than isometric muscle strength.

Muscle strength vs. functional performance / patient-reported measures

Overall, the present study showed associations between performance-based measures and knee extensor and knee flexor muscle strength, except for the 6MWT. The strongest was generally found for the affected leg, but the functional performance was also affected by the muscle strength of the

non-affected leg. These results are in agreement with those presented in a study of Mizner et al. which showed an association between functional performance and quadriceps muscle strength in patients scheduled for TKA (31). In their study, a weaker relationship was observed between muscle strength and the TUG as compared to the stair climbing test. Furthermore, Brown et al. demonstrated that knee flexor strength in the involved leg was the best predictor of the 30sCST in patients scheduled for TKA (26). The 6MWT is often used to assess functional performance in different patient groups, for example in patients before and after TKA (10,19). We found a positive association only with concentric knee flexor strength. In contrast, a negative association between the 6MWT and body mass was found which shows that patients of low body mass perform better in this test than heavier patients. This should be taken into account when the results of the 6MWT are interpreted.

This study found no associations between patient-reported measures and muscle strength. This is in agreement with Brown et al. (29); whereas Kennedy et al. (5) demonstrated low-to-moderate correlation between patient-reported and performance-based measures. Furthermore, other studies have shown that patient-reported measures of knee function are strongly influenced by pain (32), which the results in our study confirmed.

Concentric vs. isometric muscle strength

The present study generally demonstrated a stronger association between performance-based measures and concentric knee flexor muscle strength than between performance-based measures and isometric knee flexor strength. With regard to knee extensors, the concentric and the isometric strength seemed to be equally associated with performance-based measures. The concentric knee flexor muscle strength was stronger associated with the TUG and walking tests than the isometric knee flexor strength.

TUG was closely associated with both concentric and isometric muscle strength of both legs. The TUG was reviewed by the Osteoarthritis Research Society International (OARSI) (16), and it is one of five performance-based measures recommended for research and clinical practice (33).

30sCST vs. TUG and walking

30sCST was the performance-based measure that most accurately measured muscle strength. To rise from a chair is a strength demanding task and the strong association was expected. Laboratory research of movement analysing kinetic and kinematic parameters demonstrated that the chair stand movement was both selective and showed functional content validity in TKA (32). Furthermore, chair stand movement has been recognised as a biomechanical instrument identifying how the knee function is affected (32). In line with our findings, the 30sCST was one of the best rated tests in a review evaluating the properties of performance-based measures to assess physical function in hip and knee OA (16), and one of the three core tests recommended by the OARSI (33).

Clinical implications

Much attention has been paid to knee extensor muscle strength in clinical research and rehabilitation programs in clinical practice. However, along with results obtained in other OA patients (34) and healthy controls (3), the results of the present study suggest that it is equally important to include the knee flexor muscles in rehabilitation programs to improve or maintain functional performance. Furthermore, the 30sCST test was found to be the best proxy measure of muscle strength when more advanced equipment for measurement of knee extensor and knee flexor muscle strength is not available.

Study limitations

As this study is a cross-sectional study, we cannot comment on causality, but only on associations between functional performance, patient-reported measures and muscle strength. The impact of the strength of other muscles in the lower extremity may be relevant to investigate, e.g. the strength of hip and ankle muscles. Furthermore, the sample size did not allow numerous adjustments in the regression analysis.

CONCLUSIONS

Future rehabilitation programs should address both the knee extensor muscles and the knee flexor muscles to improve functional performance in patients with knee OA. The 30sCST is a valid and clinical relevant proxy measure of knee extensor and the knee flexor muscle strength.

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Figure 1. Flow diagram

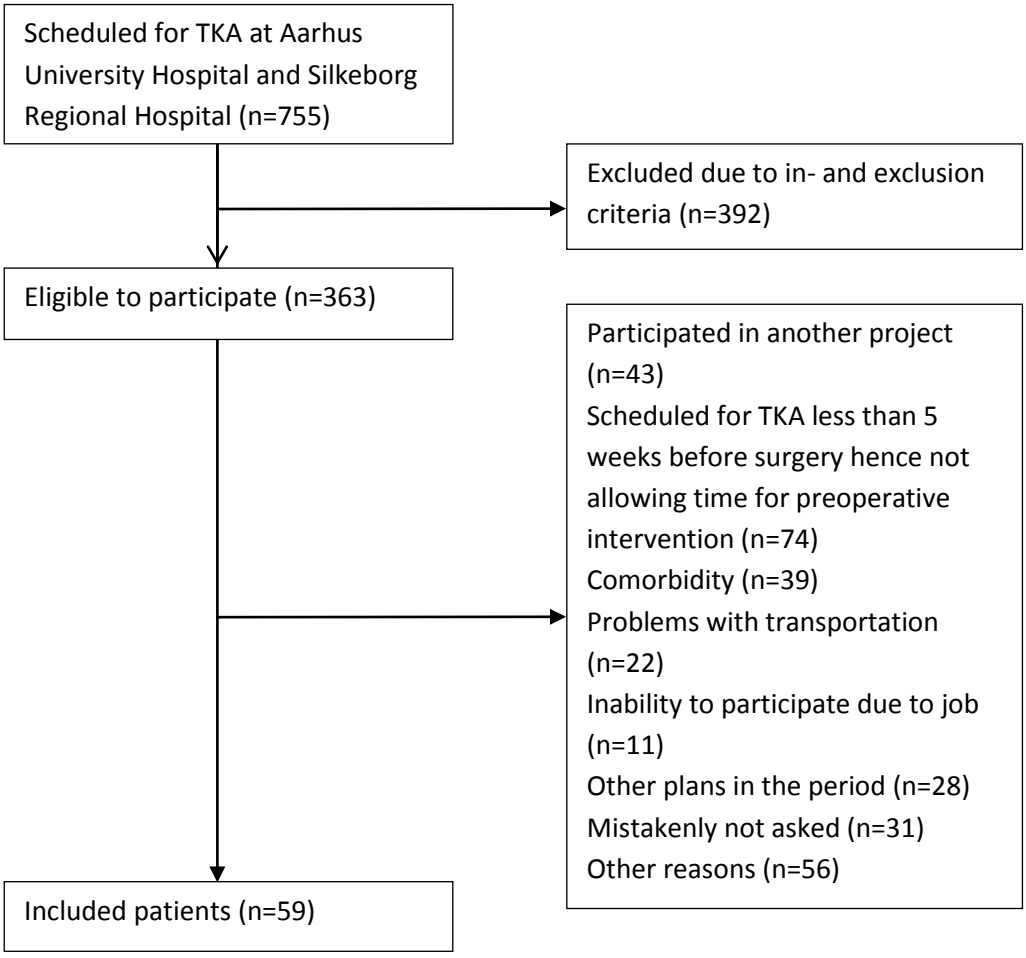

Table 1. Characteristics of included patients scheduled for total knee arthroplasty

Sex (female/male) (n)	36/23
Age (years)	70.4 (6.8)
Height (m)*	1.68 [1.45-1.97]
Body mass (kg)*	84.0 [56.8-137.4]
Body mass index (kg/m^2)*	30.3 [22.6-42.5]
Range of motion	
Knee flexion AROM (deg.)	119.7 (10.1)
Knee flexion PROM (deg.)	124.2 (9.7)
Knee extension AROM (deg.)‡	5.9 (3.1)
Knee extension PROM (deg.)‡	4.1 (3.4)
Patient-reported outcomes	
KOOS pain*	50.0 [27.8-88.9]
KOOS other symptoms*	53.6 [21.4-96.4]
KOOS function of daily living *	55.9 [29.4-88.2]
KOOS sport & recreation*	20.0 [00.0-75.0]
KOOS quality of life *	37.5 [6.3-81.3]
Current pain†	4.3 (2.8)
Worst pain during the past 14 days†	6.7 (2.0)
Average pain during the past 14 days†	5.5 (2.0)

AROM: Active range of motion; PROM: Passive range of motion.

Values are means (standard deviation) or * median [range].

Table 2. Functional performance and knee extension and flexion muscle strength in included patients

Functional performance	
30s CST (rep)	11 [0-23]
TUG (sec.)	8.6 [5.6-21.2]
10mWT (sec.)	7.6 [4.8-13.6]
6MWT (m)	420 [120-592]
Normalized muscle strength	
Affected leg	
Concentric extension peak torque (Nm/kg)	0.9 [0.3-1.8]
Concentric flexion peak torque (Nm/kg)	0.4 [0.1-1.3]
Isometric extension peak torque (Nm/kg)	1.0 [0.3-1.7]
Isometric flexion peak torque (Nm/kg)	0.6 [0.2-1.8]
Non-affected leg	
Isometric extension peak torque (Nm/kg)	1.1 [0.5-2.6]
Isometric flexion peak torque (Nm/kg)	0.5 [0.3-1.4]

Values are median [range].

Table 3. Associations between functional performance measures and muscle strength*

	CST (rep.)‡		TUG (sec)‡		10mWT (sec)‡		6MWT (m)‡	
Muscle strength	Crude	Adjusted †	Crude	Adjusted †	Crude	Adjusted †	Crude	Adjusted †
Affected leg	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*
Concentric extension peak torque (Nm) ‡	0.29 ***(0.01)***	0.49 ***(<0.01)***	-0.23 ***(<0.01)***	-0.26 ***(<0.01)***	-0.17 ***(<0.01)***	-0.18 ***(0.01)***	0.17 ***(0.03)***	0.13 *(0.18)*
Concentric flexion peak torque (Nm) ‡	0.28 ***(<0.01)***	0.32 ***(<0.01)***	-0.21 ***(<0.01)***	-0.18 ***(0.01)***	-0.17 ***(<0.01)***	-0.16 ***(<0.01)***	0.20 ***(0.01)***	0.16 ***(0.02)***
Isometric extension peak torque (Nm) ‡	0.28 ***(0.05)***	0.58 ***(<0.01)***	-0.21 ***(<0.01)***	-0.21 (0.06)	-0.17 ***(<0.01)***	-0.19 ***(0.02)***	0.18 ***(0.03)***	0.19 *(0.09)*
Isometric flexion peak torque (Nm) ‡	0.28 ***(0.02)***	0.43 ***(<0.01)***	-0.14 *(0.09)*	-0.04 *(0.73)*	-0.12 ***(0.05)***	-0.06 *(0.46)*	0.14 *(0.12)*	0.00 *(0.97)*
Non-affected leg								
Isometric extension peak torque (Nm) ‡	0.23 *(0.08)*	0.55 ***(<0.01)***	-0.24 ***(<0.01)***	-0.27 ***(0.03)***	-0.16 ***(<0.01)***	-0.17 *(0.07)*	0.14 *(0.10)*	0.06 *(0.65)*
Isometric flexion peak torque (Nm) ‡	0.27 *(0.06)*	0.34 *(0.06)*	-0.21 ***(0.02)***	-0.16 *(0.19)*	-0.15 ***(0.03)***	-0.10 *(0.25)*	0.21 ***(0.03)***	0.15 *(0.21)*

* Analysed by linear regression; † Adjusted for age, sex, height, and weight; ‡ Log-transformed data; β, Regression coefficient.
Abbreviations: CST, 30s chair stand test; TUG, timed-up-and-go; 10mWT, 10m walk test; 6MWT, 6 minute walk test; rep, repetitions.

Table 4. Comparison of associations between functional performance and muscle strength measures of the affected leg; concentric vs. isometric

	30sCST	**TUG**	**10 mWT**	**6MWT**
Knee extension peak torque (Nm)	NS	NS	NS	---
Knee flexion peak torque (Nm)	NS	concentric > isometric *p <0.01*	concentric > isometric *p <0.01*	concentric > isometric *p = 0.04*

* Analysed by Pitman's test. 30sCST, 30s chair stand test; TUG, timed-up-and-go; 10mWT, 10m walk test; 6MWT, 6 minutes walk test; NS, non-significant;
>, indicates stronger association; <, indicates weaker association

Table 5. Comparison of associations between functional performance and muscle strength measures

	CST vs. TUG	**CST vs. 10mWT**	**CST vs. 6MWT**	**TUG vs. 10 mWT**	**10mWT vs. 6MWT**
Affected leg					
Concentric knee extension	CST>TUG	CST>10 mWT	CST>6MWT	TUG>10mWT	10mWT>6MWT
peak torque (Nm)	*p<0.01*	*p<0.01*	*p<0.01*	*p<0.01*	*p<0.01*
Concentric knee flexion	CST>TUG	CST>10 mWT	CST>6MWT	TUG<10mWT	10mWT>6MWT
peak torque (Nm)	*p<0.01*	*p<0.01*	*p<0.01*	*p<0.01*	*p<0.01*
Isometric knee extension	CST>TUG	CST>10 mWT	CST>6MWT	TUG<10mWT	10mWT>6MWT
peak torque (Nm)	*p<0.01*	*p<0.01*	*p<0.01*	*p<0.01*	*p<0.01*
Isometric knee flexion	CST>TUG	CST>10 mWT	CST>6MWT	---	---
peak torque (Nm)	*p<0.01*	*p<0.01*	*p<0.01*		
Non-affected leg					
Isometric knee extension	CST>TUG	CST>10 mWT	CST>6MWT	TUG>10mWT	---
peak torque (Nm)	*p<0.01*	*p<0.01*	*p<0.01*	*p<0.01*	
Isometric knee flexion	---	---	---	---	---
peak torque (Nm)					

* Analysed by Pitman's test. CST, 30s chair stand test; TUG, timed-up-and-go; 10mWT, 10m walk test; 6MWT, 6 minute walk test; NS, non-significant; >, indicates stronger association; <, indicates weaker association.

Supplemental material Table S1. Associations between KOOS subscales and muscle strength*

KOOS subscales / Muscle strength	Pain		Other symptoms		Function of daily living		Sport and recreation		Quality of life	
	Crude	Adjusted†	Crude	Adjusted†	Crude	Adjusted†	Crude	Adjusted†	Crude	Adjusted†
	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*
Affected leg										
Isokinetic extension	0.01	0.08	0.12	0.05	0.05	0.06	0.27	0.45	0.03	-0.02
peak torque (Nm) ‡	*(0.90)*	*(0.35)*	*(0.16)*	*(0.65)*	*(0.43)*	*(0.53)*	*(0.22)*	*(0.18)*	*(0.84)*	*(0.89)*
Isokinetic flexion	0.07	0.05	0.11	0.05	0.11	0.13	0.24	0.31	0.08	0.08
peak torque (Nm) ‡	*(0.21)*	*(0.50)*	*(0.14)*	*(0.51)*	*(0.05)*	*(0.06)*	*(0.22)*	*(0.21)*	*(0.45)*	*(0.52)*
Isometric extension	-0.02	-0.06	0.09	0.07	0.05	0.11	0.33	0.76	0.10	0.28
peak torque (Nm) ‡	*(0.78)*	*(0.52)*	*(0.33)*	*(0.58)*	*(0.54)*	*(0.28)*	*(0.17)*	***(0.03)***	*(0.50)*	*(0.15)*
Isometric flexion	0.03	0.06	0.19	0.16	0.02	0.01	0.11	0.16	0.03	-0.09
peak torque (Nm) ‡	*(0.67)*	*(0.52)*	*(0.06)*	*(0.18)*	*(0.76)*	*(0.90)*	*(0.65)*	*(0.62)*	*(0.87)*	*(0.63)*
Non-affected leg										
Isometric extension	0.02	-0.02	0.07	0.05	0.05	0.16	0.22	0.68	0.02	0.02
peak torque (Nm) ‡	*(0.76)*	*(0.85)*	*(0.45)*	*(0.72)*	*(0.49)*	*(0.17)*	*(0.35)*	*(0.07)*	*(0.90)*	*(0.93)*
Isometric flexion	-0.03	-0.11	0.09	<0.01	-0.04	-0.10	-0.08	0.10	-0.13	-0.22
peak torque (Nm) ‡	*(0.73)*	*(0.30)*	*(0.42)*	*(0.98)*	*(0.62)*	*(0.37)*	*(0.77)*	*(0.78)*	*(0.44)*	*(0.29)*

* Analysed by linear regression; † Adjusted for age, sex, height, and weight; ‡ Log-transformed data; β, Regression coefficient. Abbreviations: KOOS: Knee injury and osteoarthritis outcome score

Supplemental material Table S2. Associations between KOOS subscales and pain*

KOOS subscales / Pain	Pain		Other symptoms		Function of daily living		Sport and recreation		Quality of life	
	Crude	Adjusted†	Crude	Adjusted†	Crude	Adjusted†	Crude	Adjusted†	Crude	Adjusted†
	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*	β *(p)*
Current pain	-0.04	-0.03	-0.04	-0.03	-0.05	-0.04	-0.06	-0.07	-0.05	-0.04
	(<0.01)	*(<0.01)*	*(0.01)*	*(0.04)*	*(<0.01)*	*(<0.01)*	*(0.10)*	*(0.10)*	*(0.03)*	*(0.09)*
Worst pain‡	-0.06	-0.05	-0.03	-0.02	-0.04	-0.03	-0.06	-0.06	-0.06	-0.05
	(<0.01)	*(<0.01)*	*(0.15)*	*(0.32)*	*(0.02)*	*(0.04)*	*(0.31)*	*(0.31)*	*(0.06)*	*(0.14)*
Average pain‡	-0.06	-0.05	-0.04	-0.03	-0.05	-0.06	-0.08	-0.09	-0.06	-0.05
	(<0.01)	*(<0.01)*	*(0.09)*	*(0.19)*	*(<0.01)*	*(<0.01)*	*(0.17)*	*(0.15)*	*(0.04)*	*(0.09)*

* Analysed by linear regression; † Adjusted for age, sex, height, and weight; ‡ Log-transformed data; β, Regression coefficient. Abbreviations: KOOS: Knee injury and osteoarthritis outcome score

Appendix 3: Paper 3

Efficacy of preoperative progressive resistance training on postoperative functional performance and muscle strength in patients undergoing total knee arthroplasty

A randomized controlled trial

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Running title: Progressive resistance training

Abstract

Objectives: To investigate the efficacy of 4 weeks of pre-operative and 4-week post-operative progressive resistance training (PRT) compared to 4 weeks of post-operative PRT only on functional performance, muscle strength and patient-reported outcomes in patients undergoing total knee arthroplasty (TKA).

Methods: In total 59 patients were randomized to 4 weeks of pre-operative PRT (intervention group) or to a group who "lived as usual" (control group). Both groups performed 4 weeks of PRT after TKA. At 6 and 1 weeks before TKA, and at 1, 6 and 12 weeks after TKA performance-based measures (30s chair stand test (30sCST), timed-up-and-go (TUG) and walking tests), knee extensor and flexor muscle strength (dynamometry), patient-reported functional performance, health related quality of life and, pain scores were evaluated.

Results: A significant group difference in favor of the intervention group was found for the 30sCST (2.5 rep. (0.9;4.1) vs. -1.1 rep. (-2.8;0.7), $p<0.004$), the TUG (-0.7 sec (-1.6;0.1) vs. 0.8 sec (-0.1;1.7), $p=0.015$**),** knee extensor muscle strength (-15.2 Nm (-24.4;-6.0) vs. -38.0 Nm (-48.3;-27.7), $p=0.001$) and knee flexor muscle strength (8.7 Nm (-3.6;21.0) vs. -12.1 Nm (-26.2;1.9), $p=0.029$) when evaluated at the predefined primary test point 6 weeks after TKA. No differences were found between groups on patient-reported outcomes, e.g. no differences in pain level or medication were found.

Conclusions: Pre-operative PRT is an efficacious intervention improving post-operative recovery of functional performance and muscle strength but not patient-reported outcomes, without worsening pain or increasing medication in patients undergoing TKA.

Key words: Knee replacement, knee osteoarthritis, rehabilitation, strength training

INTRODUCTION

Reduced knee extensor muscle strength is a common clinical finding in subjects with knee osteoarthritis (OA) and the strength deficit appears to play a key role in the development and progression of the disease [1,2]. Subjects with knee OA show reductions in knee extensor muscle strength of 10-56% compared to age-matched healthy controls, and the strength deficit is associated with reduced functional performance and increased pain [3-5]. An additional surgery-induced loss of knee extensor muscle strength of 60-80% has been demonstrated at discharge following total knee arthroplasty (TKA) [6-9]. Even several years after TKA, the knee extensor muscle strength is reduced by 19-37% [10], and patients do not reach the level of functional performance seen in healthy adults.

The preoperative knee extensor muscle strength in patients undergoing (TKA) is a strong predictor of functional performance one year after surgery [11]. This has led several studies to evaluate the efficacy of pre-operative interventions targeting predominately knee extensor muscle strength. However, muscle strength impairments also include knee flexors, hip abductors, hip adductors and hip extensors of the involved leg, suggesting the need to target these muscle groups as well [5]. From a clinical point of view it is therefore highly relevant to identify pre-operative interventions that can improve recovery of knee muscle strength and functional performance after TKA.

A recent systematic review concluded that pre-operative progressive resistance training (PRT) is a promising intervention in subjects undergoing total hip arthroplasty, showing positive effects on post-operative recovery [12]. At the same time no solid conclusions could be drawn on the effects of PRT performed preoperatively in patients undergoing TKA [12], because only one minor study

could be located [13]. Moreover, it remains to be clarified whether pre-operative training can increase knee muscle strength to such an extent that it has clinical implications for the post-operative recovery of muscle strength and functional performance.

Consequently, the purpose of this study was to investigate the efficacy of 4 weeks of preoperative and 4-week post-operative PRT compared to 4 weeks of post-operative PRT only on functional performance, muscle strength and patient-reported outcomes in patients undergoing TKA. A secondary purpose was to evaluate the safety profile and feasibility of PRT in terms of drop-out rate, exercise adherence and adverse events.

It was hypothesized that 4 weeks of preoperative PRT would be safe and feasible, and would improve functional performance, knee extensor and flexor muscle strength, and patient-reported outcomes preoperatively and at 6 weeks postoperatively when compared to controls.

METHODS

Study design and patients

The present study was an assessor-blinded, clinical randomized controlled trial. Patients scheduled for TKA from January 2012 to December 2013 were recruited from the orthopedic department at Aarhus University Hospital and Silkeborg Regional Hospital.

Included were patients who were: 1) scheduled for primary unilateral TKA; 2) diagnosed with OA; 3) resident in the Aarhus municipality; 4) able to transport them-selves to training; and 5) willing to give informed consent. Excluded were patients who were: 1) age <18 years; 2) suffering from heart disease or uncontrolled hypertension; 3) suffering from neuromuscular or neurodegenerative conditions; and 4) unable to comprehend the protocol instructions.

The study followed the Declaration of Helsinki and was approved by the regional Ethics Committee (Journal no. M-20110191), and registered with the Danish Data Protection Agency (Registration no. 1-16-02-191-11) and at ClinicalTrials.gov (NCT01647243).

Procedures

The outcome measures were collected at baseline (six weeks) and one week preoperatively, one week, six weeks and 12 weeks after TKA. All outcome measures were blindly assessed by the principal investigator.

Randomization

Patients were randomly assigned to preoperative PRT or to the control group applied by concealed, opaque envelopes prepared by the assessor (Figure 1). The randomization was stratified by hospital and randomized in blocks of 10. The envelopes were placed in bags, 10 in each bag and separate

bags for the two hospitals. After the first test, the patients drew an envelope from the bag. The envelopes were administrated by the physiotherapists that provided the PRT intervention.

Intervention

All PRT training sessions took place at Aarhus University Hospital and were handled by three physiotherapists specially trained in the applied training concept. Patients performed three training sessions per week for four weeks preoperatively, and completed a further three sessions per week for four weeks postoperatively. The duration of each session was approximately 60 minutes. Patients were trained in groups of three under supervision by a physiotherapist. The training intensity started with 12 repetition maximum (RM) with progression towards 8 RM. Three sets of each exercise were performed with a rest length of two minutes between sets and exercises. Following a ten minute warm up on a stationary bike the same 6 exercises were executed unilaterally during all planned sessions pre- and postoperatively. Exercises included leg press, knee extension, knee flexion, hip extension, hip abduction and hip adduction in strength training machines (Cybex, Owatonna, USA). The session ended with 3x30 seconds stretching of knee extensors, knee flexors and ankle flexors.

Control group

Patients in the control group were instructed to "live as usual" for four weeks preoperatively. Postoperatively they followed the same PRT protocol as the intervention group, also exercising three days per week for four weeks.

Perioperative care

All patients followed a standardized, optimized fast track surgical program for TKA including patient information, spinal anesthesia, optimized pain management, enforced mobilization on the day of surgery, nutrition and a home-based training program [14-17]. A hospital stay of two days with pre-defined functional discharge criteria was planned. The TKA was performed using midline incision, parapatellar approach, and insertion of cemented or uncemented tricompartmental prostheses [18]. However, no resurfacing of patella was performed if the cartilage was intact.

Outcome measures

Changes in performance in the *30s chair stand test (30sCST)* from baseline to six weeks postoperatively were defined as the primary outcome. 30sCST measures the total numbers of full raises patients were able to perform in 30 seconds. Patients were seated in a standard chair with the arms folded across the chest [19]. The test is reliable in patients with knee OA [20,21].

Timed-up-and-go (TUG) measures (in seconds) the time taken to rise from a standard armed chair, walk three meters, perform a 180^0 turn, and then walk back to the chair, and sit down again. Patients were instructed to walk as fast as they felt safe, and use of an assistive device was allowed if necessary [22]. The test is valid in patients with knee OA [20,23,24].

Ten-meter walk test (10mWT) measures maximal walking speed. Patients were instructed to walk 12 meters between two marked lines. Time was stopped when the front foot touched or passed the 10-meters line. Patients were instructed to walk as quickly as they felt safe, with an assistive device if necessary [25].

Six minute walk test (6MWT) measures the maximal walking distance covered in six minutes. Subjects were instructed to walk as far as possible in 6 minutes in a safe manner in an undisturbed 30-meters corridor according to the guidelines published by the American Thoracic Society [26,27]. The use of assistive devices was allowed if necessary [26]. The test is reliable in patients with knee OA and after TKA [28-30].

Muscle strength was measured using an isokinetic dynamometer (Humac Norm, Computer Sports Medicine Inc., Massachusetts, USA). Patients were in a seated position with 90^0 hip flexion. The anatomic axis of the knee was aligned with the axis of the dynamometer, and the ankle cuff was placed three centimetres proximal to the medial malleolus. Moment values were corrected for the gravity of the lower limb and were measured by the dynamometer at a knee joint angle of 45^0.

Patients performed three maximal isometric contractions of the knee extensors at a knee joint angle of 70^0 (0^0 = full knee extension) and of the knee flexors at a knee joint angle of 20^0 [31]. Rest periods of 60 seconds were allowed between attempts. The trial with the highest peak torque (Nm) was selected for further analysis. Both legs underwent isometric testing.

The concentric knee extensor and knee flexor muscle strength of the affected knee was evaluated at 60^0/sec (peak moment, Nm). The patients performed six maximal concentric contractions in full possible range of motion (ROM); the trial with the highest peak torque was selected for further analysis.

Dynamometry is considered the gold standard of muscle strength assessment, and dynamometry tests of knee extensor muscles in knee OA have proven reliable [32].

Active and passive knee joint flexion and extension ROM of the affected knee were measured by goniometry. The patient was positioned supine. The fulcrum of the goniometer was placed over the lateral epicondyle with one 30-centimeter arm pointed towards the major trochanter of the femur and the other towards the lateral malleolus [33]. This method is reliable and valid in patients with knee restrictions [33].

Knee joint effusion was assessed by measuring the knee joint circumference [34,35] with the patient lying supine on a couch. Knee joint circumference was measured one centimeter above the base of

the patella with a non-elastic measure. Measurement of the knee joint effusion is reliable in patients with TKA [34].

The Knee Injury and Osteoarthritis Outcome Score (KOOS) is a patient-reported questionnaire consisting of five subscales: pain, other symptoms, function of daily living, function in sport and recreation, and knee-related quality of life [36]. KOOS is a reliable and valid tool in patients with knee OA [37,38].

Knee pain ratings were recorded on an 11-point numerical rating scale from 0 (‘no pain’) to 10 (‘worst pain imaginable’). Current pain, the worst pain during the past 14 days and the average pain during the past 14 days were rated. Numerical rank scale is a reliable and valid tool for pain assessment [39]. Use of prescribed and non-prescribed medication was recorded.

Health related of quality of life was recorded on a rating scale from 0 (“worst health related quality of life imaginable”) to 100 (“best health related quality of life imaginable”).

Safety and feasibility was measured with reporting of drop-out rate, exercise adherence (exercise adherence (%) = (no. of completed sessions / no. of planned sessions) * 100) and adverse events.

Information on *length of hospital stay (LOS)* was registered from the medical records.

Sample size

An a priori power calculation was performed on the primary outcome, the 30sCST, using an expected difference between the intervention and control group of at least 10.7%, based on a prior pilot study, at the test six weeks postoperatively; $\alpha = 0.05, \beta = 0.80$. The power calculation indicated that 31 patients should be needed in each study arm to demonstrate a treatment effect. Due to possible drop-out, it was planned to include 70 patients total.

Statistical analyses

Descriptive statistics were calculated with mean and standard deviation for normally distributed data and median and range for non-normally distributed data. Normal distribution of data was checked by q-q plots and histograms.

Change scores from baseline to all other test points were compared between intervention and control group by repeated-measure analysis of variance, multilevel mixed-effects linear regression. To ensure that the underlying assumptions of the applied statistical model were met, the residuals of the analyses were checked for normal distribution. This was the case for all the performed analyses. The statistical analyses followed the intention-to-treat principle and statistical analyses were performed in Stata 12.1 (StataCorp, College Station, TX). The significance level was set at $p \leq 0.05$.

RESULTS

In total 59 patients were included during the inclusion period (Figure 1, Table 1). In total one patient (3.3%) dropped out of the intervention group while six patients (23%) dropped out of the control group before the primary outcome time point (Figure 1). None of the patients missed training sessions or were discontinued from the study due to adverse events related to the intervention. The adherence was 94.0% (SD 8.4) preoperatively and 100% postoperatively in the intervention group and 94.2% (SD 21.2) postoperatively in the control group.

Comparison of changes from baseline to six weeks post-TKA

Primary outcome

An overall time*group interaction was found. At the primary time-point of interest, a significant difference between changes of the 30sCST performance from baseline to 6 weeks postoperatively in the intervention group versus the control group was found, *2.5 (0.9;4.1)* and *-1.1 (-2.8;0.7)*, respectively, $p < 0.004$ (Table 2 and figure 2).

Secondary outcomes

An overall time*group interaction was found for the TUG. At the primary time-point of interest, the TUG showed a significant difference between changes from baseline to six weeks post-TKA between groups, whereas the walking tests did not (Table 2). At the time-point six weeks post-TKA all muscle strength parameters showed significant improvements in the intervention group compared to the control group of the involved leg, which also was the case in the knee extensors in the non-involved leg (Table 2). No differences were found between the groups in any patient-reported outcomes, except for the KOOS sport subscale (Table 3).

Comparison of changes from baseline to other test time-points

Functional performance measures

Generally, improvements of the 30sCST and the TUG in the intervention group were found at all test points when compared to the control group (Figure 2).

Muscle strength

Generally, improvements of muscle strength of the involved leg were seen in the intervention group at all test points when compared to the control group, while no group differences were apparent for the non-involved leg (Table 2, Figure 2).

Knee joint effusion, range of motion and health related quality of life

No statistically significant differences between groups were found at any test points, except for higher knee joint effusion in the intervention group at test two (Table 4).

Knee pain, medication and walking aids

Improvement of "current pain", "worst pain" and "average pain" within the past 14 days, were found at test two in the intervention group compared to the control group, while no differences between groups were seen at all other test points (Table 3). No differences between groups with respect to the intake of non-prescribed medications or prescribed medications were found at any time point. Also, no statistical differences between PRT and controls in the use of walking aids were seen at any time point.

LOS

Patients in the intervention group had a mean stay of *2.2 days (SD 0.5)* and the control group a mean stay of *2.4 days (SD 0.6), p = 0.133.*

DISCUSSION

The present study demonstrated a significant effect of pre- and postoperative PRT on functional performance and knee extensor and knee flexor muscle strength when compared to postoperative PRT alone at six weeks postoperatively. The improvements were achieved without increasing pain or causing knee effusion. However, in contrast to our hypothesis, no significant improvement was found of preoperative PRT in patient-reported functional performance and health related quality of life except for the KOOS sport subscale (Table 3). PRT was safe when performed both preoperatively and postoperatively in terms of no observed adverse events and an excellent adherence rate.

Only two studies have specifically investigated the effect of preoperative PRT [13,40]. In the study by McKay et al., a six week bilateral lower-body PRT intervention was compared to an upper-body PRT intervention, and findings demonstrated a significant time*group effect on the SF-36 mental component score and non-significant improvements of quadriceps strength and walking speed immediately before TKA. However, six weeks postoperatively the improvements were lost as compared to the control group [13]. In the study by Leeuwen et al., a six week standard training program with additional PRT was not found more efficacious than standard training alone, when assessed on muscle strength and functional performance immediately before TKA and six and 12 weeks after TKA [40]. The significant improvements in our study may be caused by a higher training intensity, application of unilateral versus bilateral training, involvement of more muscle groups around the knee or caused by a larger sample size increasing the power of the study.

A recent systematic review and meta-analysis identified 7 studies of preoperative rehabilitation before TKA. It was concluded that no outcome was consistently improved following preoperative interventions as compared to controls, with the exception of a trend toward the length of hospital stay being shorter [41]. Another systematic review concluded that there is low-to-moderate evidence from mostly small randomized controlled trials demonstrating that pre-operative exercise interventions may reduce pain in TKA patients [42]. However, none of the studies included in the reviews have applied high-intensity resistance training programs.

The impact of the preoperative PRT intervention on the postoperative recovery in our study opposed to previous exercise studies may be attributed to several factors. The training protocol in our study differs from previous studies by the application of very high exercise intensity. The training physiotherapist supervised and ensured that patients continually trained close to the maximum of their capability and followed the plan of progression. The patients trained unilaterally and the training volume of each muscle group within each training session was high compared to previous studies. Since the training took place in small groups; the competitive element might also have optimized the training intensity.

In a recent review by Hoogeboom et al., studies investigating the effects of preoperative exercises on functional performance after TKA and total hip arthroplasty were evaluated on a therapeutic validity scale [43]. It was concluded, that studies had low scores on the therapeutic validity scale evaluated in terms of e.g. if the exercise programs were in line with the latest research, had sufficient volume, and was tailored to the potential of the participants. Hence, the poor therapeutic validity of the exercise programs may have hampered potentially beneficial effects. Regarding

therapeutic validity, we consider our study to have a high therapeutic validity as the training protocol was designed according to the principles recommended by the American College of Sports Medicine [27], e.g. high training intensity and volume of all weak muscles around the involved knee, plan for progression ensured by specially trained physiotherapists and a high training frequency.

No data exists on the minimal clinically relevant change of the 30sCST, but the substantial change of 35.2% between the intervention group and the control group from baseline to 6 weeks post TKA suggest that the improvement could be of clinical relevance.

The observed discrepancy between the results of measured functional performance and patient-reported functional performance is in accordance with other studies concluding that measured functional performance is associated to muscle strength and patient-reported functional performance is associated to pain [44,45]. It could be argued that this would limit the clinical relevance of the intervention, but it could also reflect poor responsiveness of the patient-reported scales.

Interestingly, a recent systematic review including 48 studies investigated the effect of exercise programs on pain and patient-reported disability in knee OA. It was concluded that exercise programs focusing on a single type of exercise were more efficacious in reducing pain and patient-reported disability than those mixing several types of exercise with different goals within the same session [44]. This needs to be taken into account when planning exercise interventions before and after TKA.

Improvements of functional performance, muscle strength and pain were achieved after the preoperative intervention immediately before surgery, indicating that patients with end-stage knee OA profit from high-intensity training. Furthermore, correlations between changes in functional performance and muscle strength from baseline to six weeks postoperatively were found (data not shown). In this study only a relatively short intervention was applied, a longer intervention period may result in greater improvements and further pain reduction. However, the short intervention applied in the current study may be easier to implement in current practice, due to lower associated costs. Moreover, when the preoperative PRT both improved functional performance and muscle strength, and reduced pain levels, we speculate whether the training intervention could postpone the surgery.

It was not the purpose of this current study to reduce the length of hospital stay; as the hospital stay was pre-planned to last two days for all patients.

Limitations

This study has several limitations that should be kept in mind when interpreting the results. First, we failed to include the planned number of patients increasing the risk of type II errors.

Second, only the assessor was blinded in relation to the patient's group affinities. It is, however, very difficult to blind patients and training physiotherapists to an exercise intervention because a placebo intervention is easily revealed by both patients and physiotherapists.

Third, selection bias may have occurred because the patients must be able to transport themselves to the training site.

Fourth, it was not possible to test the muscle strength of the operated leg in the dynamometer at the test 1 week after the operation due to pain and limited range of motion.

CONCLUSION

Supervised preoperative PRT is an efficacious and safe intervention for improving postoperative functional performance and muscle strength, but not for improving patient-reported functional performance and health related quality of life.

Key messages

Progressive resistance training is feasible and increase muscle strength and improve functional capacity in end-stage osteoarthritis.

Progressive resistance training decreases pain in patients with end-stage osteoarthritis.

Preoperative progressive resistance training accelerates recovery following total knee arthroplasty.

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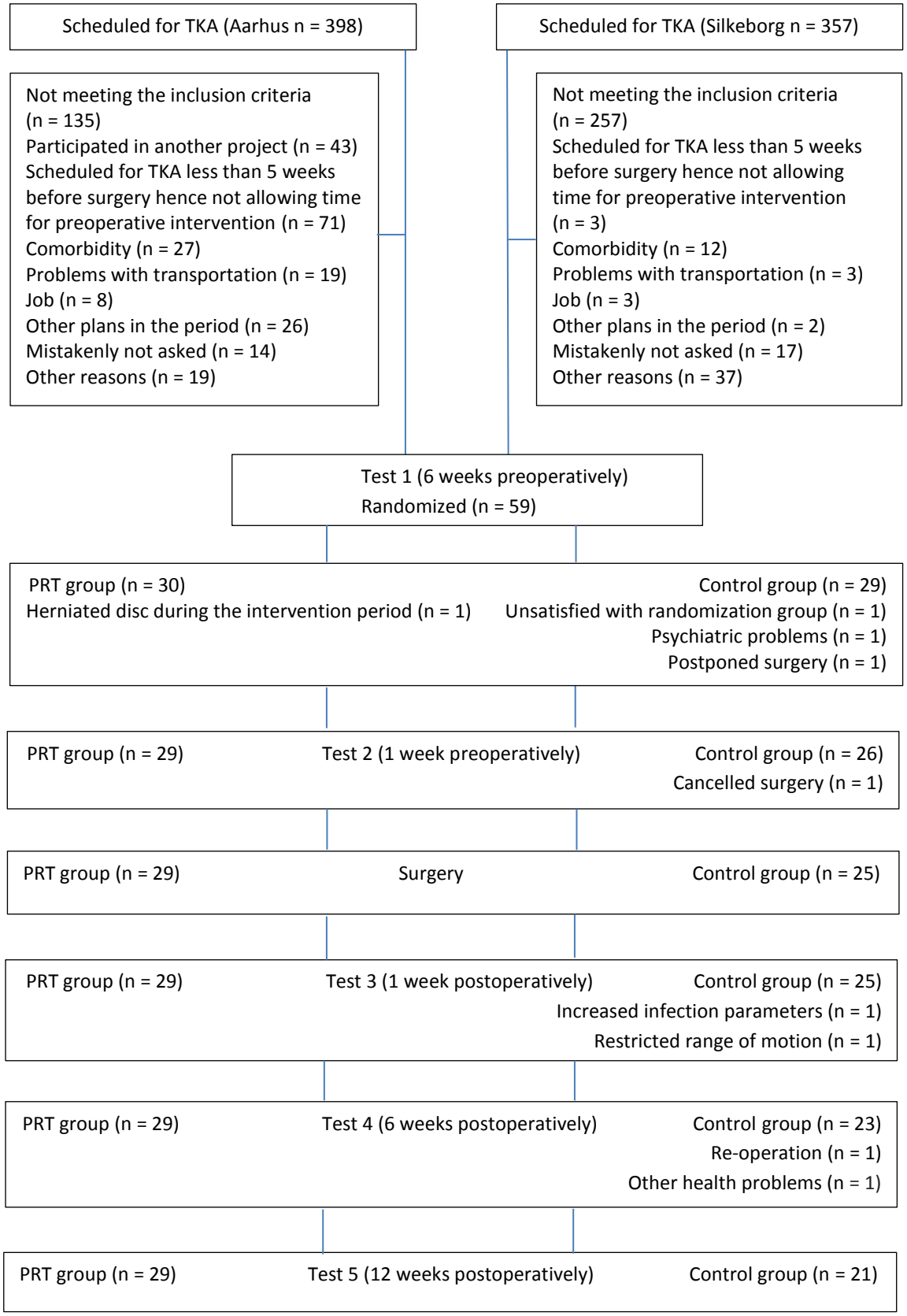
Figure 1. Flow diagram



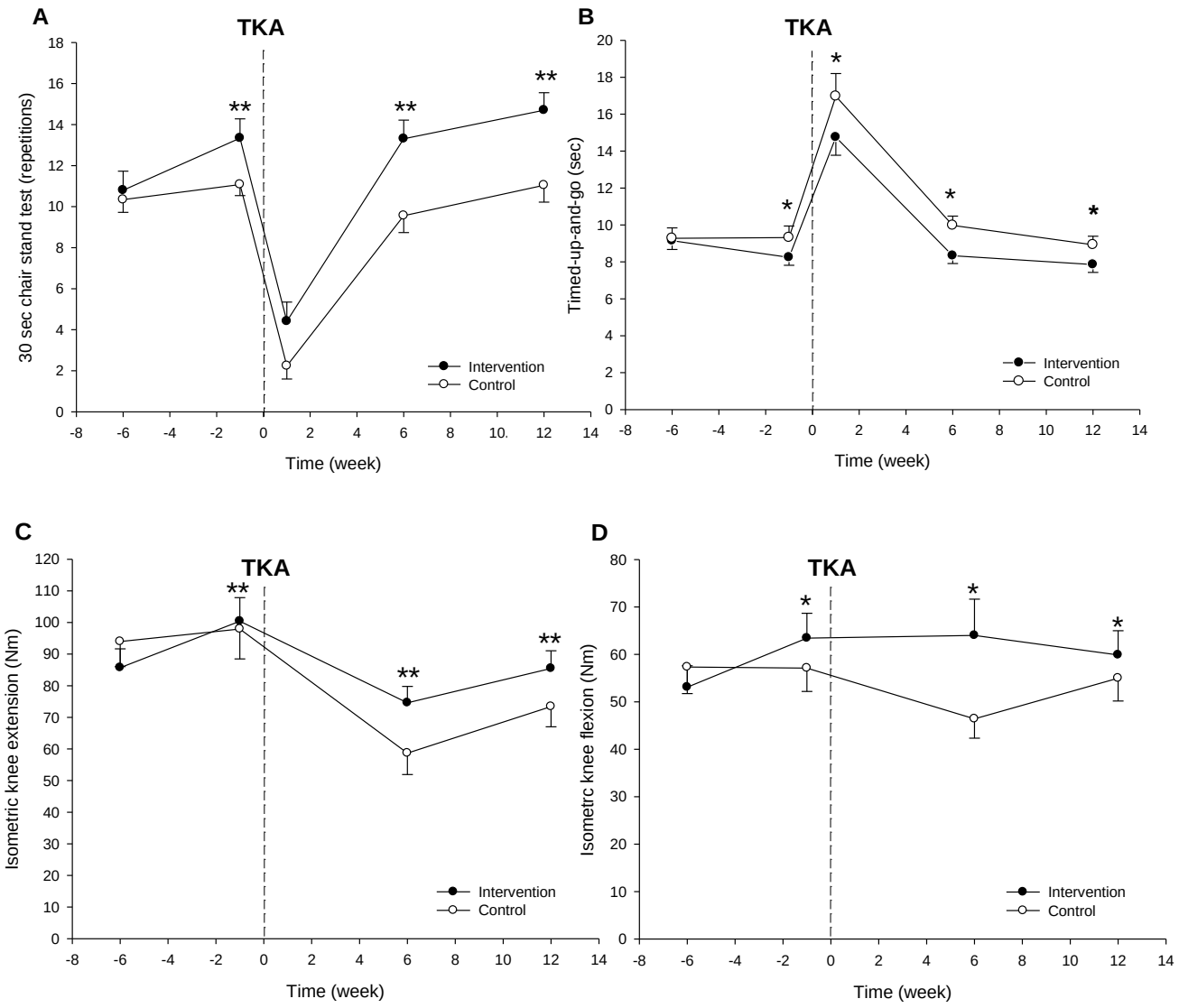


Figure 2. A. 30s chair stand test between groups (mean (standard error of the mean (SEM)) B. Timed-up-and-go between groups (mean (SEM)). C. Isometric extension between groups (mean (SEM)) D. Isometric flexion between groups (mean (SEM)). ** $p \leq 0.05$; ** $p < 0.01$.*

Table 1. Baseline characteristics of the intervention and control group

Characteristics	**PRT group**	**Control group**
Sex (female/male) (n)	19/11	17/12
Age (years)	70.7 (7.3)	70.1 (6.4)
Height (m)*	1.67 [1.45-1.84]	170.0 [1.46-1.97]
Weight (kg)*	83.6 [56.8-117.2]	91.9 [66.2-137.4]
Body mass index (kg/m^2)*	30.0 [22.6-42.5]	31.8 [24.3-42.2]
Pain medication (non-prescribed)		
0 days/1-4 days/5-7 days per week (n)	8/6/16	11/7/11
Pain medication (prescribed)		
0 days/1-4 days/5-7 days per week (n)	22/1/7	18/2/9
Knee arthroplasty of opposite leg (n)	3	4
Smoker (n)	3	4
Job (n)	4	4

Values are means (standard deviation) or * median [range]
† Measured on 11-point numerical rating scale. £ Measured 1 cm above basis of patella
Abbreviation: PRT, progressive resistance training

Table 2. Mean and differences between intervention and control group at each test points in functional performance and muscle strength outcomes

Outcome	**Baseline Mean (SD)**	**Test 2 Mean (SD)**	**Δ test 2 Mean (CI) *p***	**Test 3 Mean (SD)**	**Δ test 3 Mean (CI) *p***	**Test 4 Mean (SD)**	**Δ test 4 Mean (CI) *p***	**Test 5 Mean (SD)**	**Δ test 5 Mean (CI) *P***
Functional performance									
30sCST (rep)									
Intervention	10.8 (5.1)	13.3 (5.1)	2.5 (1.6;3.4)	4.4 (5.1)	-6.4 (-8.0;-4.9)	13.3 (5.0)	2.5 (0.9;4.1)	14.7 (4.7)	3.9 (2.5;5.3)
Control	10.4 (3.3)	11.1 (2.9)	0.3 (-0.6;1.3)	2.2 (3.5)	-8.2 (-9.9;-6.6)	9.6 (4.4)	-1.1 (-2.8;0.7)	11.0 (4.4)	0.2 (-1.4;1.7)
			0.001		*0.116*		***0.004***		***0.001***
TUG (sec)									
Intervention	9.1 (2.6)	9.1 (2.6)	-0.8 (-1.4;-0.2)	14.8 (5.2)	5.8 (4.2;7.4)	8.3 (2.3)	-0.7 (-1.6;0.1)	7.9 (2.3)	-1.2 (-1.9;-0.5)
Control	9.3 (3.0)	9.3 (3.0)	0.2 (-0.5;0.9)	17.0 (5.6)	8.3 (6.4;10.1)	10.0 (2.4)	0.8 (-0.1;1.7)	8.9 (2.1)	-0.1 (-0.9;0.7)
			0.034		***0.044***		***0.015***		***0.050***
10mWT (sec)									
Intervention	7.7 (1.8)	7.3 (1.6)	-0.3 (-0.7;0.1)	12.5 (4.9)	5.0 (3.3;6.7)	7.6 (1.8)	<0.01 (0.6;0.6)	7.1 (1.5)	-0.6 (-1.1;-0.1)
Control	7.9 (1.5)	8.0 (2.0)	0.2 (-0.2;0.7)	14.4 (5.6)	6.6 (4.6;8,5)	8.6 (1.6)	0.7 (0.1;1.4)	7.7 (1.2)	-0.1 (-0.6;0.5)
			0.114		*0.225*		*0.119*		*0.216*
6MWT (m)									
Intervention	404 (119)	434 (101)	23.2 (4.7;41.6)	258 (93)	-156.5 (-194.5;-118.5)	424 (103)	16.8 (-20.4;54.0)	449 (94)	41.2 (7.1;75.3)
Control	408 (63)	427 (76)	9.4 (-11.1;30.0)	226 (82)	-183.1 (-222.6;-143.7)	376 (83)	-33.5 (-74.1;7.1)	433 (74)	8.4 (-29.5;46.3)
			0.330		*0.341*		*0.074*		*0.208*
Muscle strength Involved leg									
Isokinetic ext. (Nm)									
Intervention	71.0 (35.4)	80.0 (40.7)	8.5 (2.7;14.3)	---	---	61.6 (23.5)	-10.5 (-19.1;-1.9)	71.6 (26.8)	0.3 (-8.1;8.7)
Control	80.9 (37.0)	87.6 (40.8)	3.5 (-3.0;10.1)			53.6 (25.6)	-29.8 (-39.0;-20.6)	64.1 (25.3)	-21.1 (-30.3;-11.8)
			0.267				***0.003***		***0.001***

Isokinetic flex. (Nm)									
Intervention	37.9 (25.3)	47.0 (25.3)	8.8 (3.5;14.1)	---	---	41.2 (22.2)	2.3 (-5.0;5.7)	45.7 (21.2)	7.7 (0.6;14.8)
Control	45.5 (23.9)	51.0 (26.4)	4.1 (-1.8;9.9)			33.5 (22.6)	-13.7 (-21.8;-5.7)	38.6 (19.9)	-9.9 (-17.7;-2.1)
			0.241				***0.004***		***0.001***
Isometric ext. (Nm)									
Intervention	85.7 (32.6)	100.4 (40.1)	14.3 (8.1;20.5)	---	---	74.6 (26.4)	-15.2 (-24.4;-6.0)	85.5 (29.5)	0.3 (-8.3;8.9)
Control	94.0 (41.8)	97.9 (46.2)	-3.7 (-10.5;3.0)			58.7 (30.2)	-38.0 (-48.3;-27.7)	73.4 (28.6)	-25.7 (-35.5;-16.0)
			<0.001				***0.001***		***<0.001***
Isometric flex. (Nm)									
Intervention	53.1 (24.4)	63.4 (27.7)	10.4 (3.9;16.9)	---	---	64.0 (39.0)	8.7 (-3.6;21.0)	60.0 (27.0)	8.4 (-0.6;17.5)
Control	57.34 (29.7)	57.1 (24.1)	-1.5 (-8.3;5.4)			46.4 (17.8)	-12.1 (-26.2;1.9)	55.0 (20.4)	-5.8 (-16.3;4.6)
			0.014				***0.029***		***0.043***
Non-involved leg									
Isometric ext. (Nm)									
Intervention	103.8 (43.6)	116.2 (39.5)	11.2 (3.0;19.4)	117.7 (39.3)	12.8 (5.7;19.8)	122.0 (40.9)	13.0 (4.7;21.4)	113.9 (44.2)	9.5 (2.1;16.9)
Control	108.0 (50.6)	117.8 (50.8)	2.9 (-6.0;11.8)	116.6 (46.3)	3.9 (-4.0;11.7)	114.7 (46.0)	0.1 (-9.0;9.3)	120.1 (54.5)	-1.6 (-10.2;7.1)
			0.178		*0.100*		***0.041***		*0.058*
Isometric flex. (Nm)									
Intervention	52.6 (21.9)	61.8 (28.1)	8.6 (1.6;15.7)	60.0 (22.7)	6.3 (-2.2;14.8)	59.9 (20.3)	5.7 (-1.1;12.6)	60.0 (23.4)	7.0 (1.0;12.9)
Control	55.3 (23.0)	62.3 (28.6)	6.7 (-1.0;14.5)	61.7 (35.2)	7.0 (-2.6;16.7)	54.5 (22.2)	0.2 (-7.4;7.8)	61.0 (27.7)	2.9 (-4.1;9.8)
			0.721		*0.912*		*0.293*		*0.381*

Δ, Difference between changes from baseline to; 30sCST, 30s chair stand test; TUG, Timed-up-and-go; 10MWT, 10 m walk test; 6MWT, 6 minute walk test; ext., extension; flex., flexion.

Table 3. Mean and difference between intervention and control group at each time points on pain and KOOS subscales

Outcome	**Baseline Mean (SD)**	**Test 2 Mean (SD)**	**Δ test 2 Mean (CI) *p***	**Test 3 Mean (SD)**	**Δ test 3 Mean (CI) *p***	**Test 4 Mean (SD)**	**Δ test 4 Mean (CI) *p***	**Test 5 Mean (SD)**	**Δ test 5 Mean (CI) *P***
Current pain									
Intervention	4.3 (2.7)	1.8 (2.0)	-2.5 (-3.4;-1.7)	3.3 (2.3)	-1.0 (-2.3;0.3)	1.2 (1.7)	-3.1 (-4.1;-2.0)	1.0 (1.7)	-3.4 (-4.5;-2.2)
Control	4.2 (2.9)	4.2 (2.7)	0.1 (-0.8;1.0)	4.5 (2.6)	0.3 (-1.1;1.6)	1.2 (1.1)	-3.0 (-4.1;-1.9)	1.1 (1.3)	-3.0 (-4.2;-1.8)
			<0.001		*0.166*		*0.878*		*0.655*
Worst pain[#]									
Intervention	6.5 (2.0)	5.4 (2.9)	-1.1 (-1.9;-0.3)	6.7 (2.6)	0.1 (-0.8;1.1)	3.9 (2.7)	-2.7 (-3.7;-1.6)	2.6 (2.6)	-3.9 (-4.9;-3.0)
Control	6.9 (2.0)	6.9 (2.3)	0.1 (-0.8;0.9)	7.6 (2.0)	0.7 (-0.3;1.8)	3.5 (2.0)	-3.4 (-4.6;-2.3)	2.4 (1.9)	-4.3 (-5.4;-3.2)
			0.047		*0.389*		*0.248*		*0.605*
Average pain[#]									
Intervention	5.6 (2.1)	3.4 (2.5)	-2.1 (-2.8;-1.4)	4.2 (2.5)	-1.3 (-2.3;-0.4)	2.3 (1.7)	-3.3 (-4.1;-2.5)	1.4 (1.6)	-4.1 (-5.0;-3.3)
Control	5.3 (1.9)	5.0 (1.9)	-0.2 (-1.0;0.6)	5.3 (2.2)	-0.1 (-1.1;1.0)	2.1 (1.2)	-3.2 (-4.1;-2.4)	1.5 (1.1)	-3.8 (-4.7;-3.0)
			0.001		*0.082*		*0.938*		*0.629*
KOOS_PAIN									
Intervention	53.0 (13.3)	59.2 (15.7)	5.7 (1.0;10.5)	53.9 (15.2)	0.8 (-5.9;7.5)	70.9 (16.7)	17.8 (11.3;24.2)	78.1 (16.3)	24.9 (18.4;31.5)
Control	53.4 (13.5)	55.2 (18.5)	3.7 (-1.5;8.9)	47.7 (16.8)	-4.7 (-11.9;2.5)	67.3 (13.0)	13.9 (6.9;20.9)	79.9 (14.2)	25.8 (18.5;33.2)
			0.566		*0.273*		*0.431*		*0.857*
KOOS_SYMP									
Intervention	60.1 (17.7)	66.0 (14.9)	5.5 (0.7;10.2)	52.5 (17.9)	-7.8 (-15.5;-0.1)	66.7 (16.7)	6.6 (-1.9;15.2)	72.8 (16.4)	12.6 (4.5;20.7)
Control	59.0 (18.7)	59.2 (21.2)	1.1 (-4.1;6.3)	48.1 (12.5)	-10.1 (-18.4;-1.8)	64.0 (12.3)	4.7 (-4.4;13.7)	71.9 (11.4)	12.0 (3.3;20.7)
			0.224		*0.687*		*0.755*		*0.911*
KOOS_ADL									
Intervention	58.8 (13.9)	64.1 (16.1)	5.0 (0.3;9.7)	56.2 (16.1)	-2.7 (-10.3;5.0)	76.1 (13.8)	17.2 (10.7;23.7)	82.9 (11.7)	24.1 (17.5;30.6)
Control	56.7 (14.8)	60.6 (15.9)	5.0 (-0.1;10.0)	50.1 (21.1)	-6.0 (-14.3;2.3)	70.6 (11.4)	14.0 (7.1;21.0)	78.2 (12.9)	21.1 (14.1;28.1)
			0.987		*0.568*		*0.517*		*0.548*

KOOS_SPORT									
Intervention	23.7 (16.7)	29.5 (17.4)	5.9 (1.6;10.1)	18.4 (17.1)	-5.2 (-14.0;3.5)	36.4 (24.3)	12.7 (3.9;21.5)	50.2 (28.4)	26.5 (16.9;36:1)
Control	20.2 (19.9)	19.8 (19.5)	0.2 (-4.4;4.8)	11.7 (22.3)	-7.6 (-17.1;1.8)	18.9 (19.2)	-0.9 (-10.5;8.7)	40.0 (22.5)	19.6 (8.8;30.4)
			0.077		*0.714*		***0.040***		*0.347*
KOOS_QOL									
Intervention	39.6 (14.8)	38.2 (15.0)	-1.4 (-6.6;3.8)	38.4 (15.6)	-1.2 (-7.6;5.3)	56.3 (20.6)	16.7 (10.3;23.2)	66.2 (18.9)	26.6 (19.0;34.2)
Control	33.8 (14.4)	34.1 (17.1)	1.0 (-4.6;6.5)	35.3 (16.8)	2.3 (-4.7;9.4)	50.0 (13.3)	16.8 (9.6;23.9)	61.9 (16.6)	27.6 (19.2;36.1)
			0.546		*0.471*		*0.996*		*0.862*
HRQOL									
Intervention	70.7 (16.7)	71.6 (20.7)	0.4 (-5.4;6.3)	69.7 (18.6)	-1.4 (-8.0;5.1)	83.2 (14.0)	12.2 (4.7;19.7)	86.7 (10.5)	15.7 (9.4;22.0)
Control	63.3 (15.7)	64.9 (15.7)	1.2 (-5.2;7.6)	59.2 (19.6)	-3.6 (-10.7;3.6)	67.2 (23.8)	2.2 (-6.0;10.3)	76.4 (20.1)	11.2 (4.3;18.1)
			0.869		*0.664*		*0.075*		*0.348*

Δ, differences between changes from baseline to; [#], during the past 14 days; KOOS_SYMP, other symptoms; KOOS_ADL, function of daily living; KOOS_SPORT, sport and recreation; KOOS_QOL, quality of life; HRQOL, health-related quality of life measured on a rating scale from 0-100 mm.

Table 4 Mean and differences between groups of intervention and control group on range of motion and knee joint effusion

Outcome	**Baseline Mean (SD)**	**Test 2 Mean (SD)**	**Δ test 2 Mean (CI) *p***	**Test 3 Mean (SD)**	**Δ test 3 Mean (CI) *p***	**Test 4 Mean (SD)**	**Δ test 4 Mean (CI) *p***	**Test 5 Mean (SD)**	**Δ test 5 Mean (CI) *p***
Active flexion (deg.)									
Intervention	120.6 (10.5)	120.7 (10.8)	0.1 (-2.0;2.2)	85.1 (13.2)	-35.5 (-41.7;-29.3)	108.6 (11.0)	-12.0 (-16.7;-7.4)	113.0 (14.8)	-7.7 (-12.6;-2.8)
Control	118.7 (9.9)	120.8 (8.8)	1.1 (-1.2;3.4)	86.4 (19.9)	-32.6 (-39.3;-25.9)	106.1 (13.8)	-12.3 (-17.4;-7.3)	112.5 (7.81)	-7.7 (-13.2;-2.2)
			0.541		*0.536*		*0.928*		*0.995*
Passive flexion (deg.)									
Intervention	125.5 (9.1)	125.0 (10.7)	-0.4 (-2.6;1.8)	88.7 (13.2)	-36.8 (-42.7;-30.9)	115.0 (10.8)	-10.5 (-15.1;-5.9)	118.7 (15.7)	-6.7 (-11.7;-1.8)
Control	122.9 (10.2)	124.8 (9.1)	1.0 (-1.4;3.4)	88.9 (18.9)	-34.3 (-40.7;-27.9)	112.8 (11.6)	-10.1 (-15.0;-5.1)	118.3 (8.0)	-5.2 (-10.7;0.4)
			0.392		*0.568*		*0.906*		*0.678*
Active extension (deg.)									
Intervention	6.1 (3.6)	5.7 (3.8)	0.3 (-1.3;0.6)	7.7 (3.2)	1.6 (0.2;3.1)	5.2 (2.9)	-0.9 (-2.4;0.5)	3.3 (2.8)	-2.8 (-4.0;-1.6)
Control	5.7 (2.6)	6.6 (3.2)	0.8 (-0.3;1.8)	7.2 (3.4)	1.7 (0.2;3.3)	5.2 (3.2)	-0.2 (-1.8;1.3)	4.3 (2.4)	-1.3 (-2.6;<0.1)
			0.116		*0.941*		*0.506*		*0.089*
Passive extension (deg.)									
Intervention	4.4 (4.1)	3.9 (3.9)	-0.4 (-1.3;0.5)	5.6 (3.0)	1.2 (-0.3;2.7)	2.0 (2.9)	-2.4 (-3.9;-0.9)	1.2 (2.3)	-3.2 (-4.3;-2.0)
Control	3.8 (2.6)	4.8 (3.1)	0.8 (-0.2;1.7)	5.6 (3.6)	1.9 (0.3;3.5)	2.2 (3.2)	-1.4 (-3.0;0.2)	1.7 (2.4)	-2.1 (-3.3;-0.9)
			0.090		*0.533*		*0.397*		*0.207*
Knee joint effusion (cm)									
Intervention	44.9 (4.7)	45.1 (4.9)	0.2 (<-0.1;0.5)	49.3 (4.7)	4.4 (3.9;5.0)	46.7 (4.6)	1.8 (1.4;2.2)	46.3 (4.8)	1.5 (1.0;1.9)
Control	46.5 (4.6)	46.4 (4.9)	-0.3 (-0.6;<0.1)	51.2 (4.4)	4.1 (3.5;4.7)	48.5 (5.1)	1.4 (1.0;1.8)	48.1 (5.4)	1.1 (0.6;1.7)
			0.009		*0.376*		*0.158*		*0.344*

Δ, differences between changes from baseline to; deg., degrees.

Appendix 4: Paper 4

No exacerbation of knee joint pain and effusion following preoperative progressive resistance training in patients scheduled for total knee arthroplasty

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Abstract

Background: Preoperative progressive resistance training (PRT) is controversial in patients scheduled for total knee arthroplasty (TKA), since critics are concerned that it may exacerbate knee joint pain and effusion.

Aim: To examine if PRT initiated 5 weeks prior to TKA 1) would exacerbate pain and knee effusion and 2) would allow an increased training load throughout the training period and subsequently increase muscle strength.

Methods: Thirty patients with end-stage osteoarthritis scheduled for TKA underwent unilateral PRT (3 sessions/week) starting 5 weeks before surgery. Exercise loading was 12 repetition maximum (RM) with progression towards 8RM. The training program consisted of 6 exercises performed unilaterally. Before and after each training session, knee joint pain, effusion, and training load were recorded. The first and last training session were initiated by 1RM testing of unilateral leg press, knee extension and knee flexion.

Results: Median differences of the knee pain at rest from before to after each training session varied from 0-2. Knee joint pain after the training session was unchanged over time during the training sessions, $p = 0.99$. Mean differences of the knee joint circumference from before to after each training session varied from 0-0.4 cm. Knee joint circumference was unchanged over time during the training sessions, $p = 0.99$. Maximal muscle strength improved; unilateral leg press mean 18% ± 30 $(p = 0.03)$, knee extension mean 81% ± 156 $(p < 0.0001)$ and knee flexion mean 53% ± 57 $(p < 0.001)$.

Conclusion: PRT of the affected leg initiated shortly before TKA does not exacerbate knee joint pain and effusion despite a substantial increase in muscle strength.

Background

Preoperative progressive resistance training is controversial in patients scheduled for total knee arthroplasty, since critics are concerned that it may exacerbate knee joint pain and effusion. However, no literature has been identified on this assertion. Generally, high-intensity exercise programs have been avoided in end-stage knee osteoarthritis as well as during the early post-operative phase after total knee arthroplasty due to fear of exacerbation of knee joint pain and effusion, and clinicians are commonly reluctant to apply high-intensity exercises in patients with painful and swollen knee. At the same time impaired muscle strength of the involved leg in knee osteoarthritis has been demonstrated (1). Moreover, knee extensor muscle strength is substantially reduced compared to age-matched healthy controls, and this strength deficit is associated with impaired functional performance (1-3). Furthermore, an additional surgery-induced loss of knee extensor muscle strength of 60-80% has been demonstrated at discharge following total knee arthroplasty (4-6). Thus, it seems relevant to initiate a preoperative progressive resistance training intervention with the purpose of improving muscle strength before surgery, hereby potentially reducing the major strength loss immediately after surgery. Nevertheless, no studies could be identified that have investigated how progressive resistance training affects patients scheduled for total knee arthroplasty in terms of knee pain and effusion before and after each training session.

Consequently, the purpose of this study was to examine if progressive resistance training initiated 5 weeks prior to total knee arthroplasty 1) would exacerbate pain and knee effusion and 2) would allow an increase of the training load throughout the training period and subsequently increase muscle strength.

We hypothesized that progressive resistance training before total knee arthroplasty 1) would not exacerbate knee joint pain and effusion, and 2) would increase the training load and subsequently the muscle strength.

Methods

Study design and patients

The present study is a part of an assessor-blinded, randomized controlled trial. Patients scheduled for total knee arthroplasty from January 2012 to December 2013 were recruited from the orthopedic department at Aarhus University Hospital and Silkeborg Regional Hospital. ClinicalTrials.gov (NCT01647243).

The patients were randomly assigned to 4 weeks of preoperative progressive resistance training (intervention group) or were instructed to "live as usual" (control group) in 4 weeks before surgery. In this paper, data on the intervention group during each training session in the training period are evaluated.

Included patients were: 1) scheduled for primary unilateral total knee arthroplasty; 2) diagnosed with osteoarthritis; 3) resident in the Aarhus municipality; 4) able to transport them-selves to training; and 5) willing to give informed consent. Excluded patients were: 1) age < 18 years; 2) suffering from heart disease or uncontrolled hypertension; 3) suffering from neuromuscular or neurodegenerative conditions; and 4) unable to comprehend the protocol instructions. In total 30 patients (63.3% women) were assigned to the training group. Mean age was 70.7 ± 7.3 years and the body mass index was median 30.0 [range 22.6-42.5] kg/m^2.

Progressive resistance training intervention

Patients exercised in groups of 3 at Aarhus University Hospital. Patients performed 3 training sessions per week for 4 weeks initiated 5 weeks before total knee arthroplasty. The duration of each session was approximately 1 hour. The training intensity initiated aimed at a load of 12 repetition maximum (RM) with progression towards 8 RM throughout the intervention period. Three sets of each exercise were performed with a rest length of 2 minutes between sets and exercises. Following a 10 minutes warm up on a stationary bike, 6 exercises were executed unilaterally in standard resistance training machines during all planned sessions. Exercises included leg press, knee extension, -flexion, hip extension, -abduction and -adduction in resistance training machines (Cybex, Owatonna, USA). The session ended with 3x30 sec. static stretching of knee extensors, -flexors and ankle flexors. Each session was supervised by 1 of 3 physiotherapists specifically trained in progressive resistance training.

Outcome measures

The outcome measures were collected by 1 of the 3 trained physiotherapists. Before and after each training session knee pain ratings at rest and knee joint circumference measures were collected. The first and last preoperative exercise session were initiated by a 1RM testing (7) of unilateral leg press, knee extension and -flexion. Training volume was recorded during each training sessions.

Knee pain ratings at rest were recorded on an 11-point numerical rating scale from 0 (‘no pain’) to 10 (‘worst pain imaginable’). Numerical rank scale is a reliable and valid tool for pain assessment (8). *Knee joint effusion* was assessed measuring the knee joint circumference (9,10). Measurement of the knee joint effusion is reliable in patients with total knee arthroplasty (10). *Training volume* in terms of the applied loading (kg) and the number of repetitions were recorded in each set for leg

press, knee extension, -flexion, hip extension, -abduction and –adduction, during each training session by the physiotherapist (Table 1).

Statistical analyses

Data was presented with mean and standard deviation for normally distributed data and median and interquartile ranges for non-normally distributed data. Knee pain at rest after each training session during the training period was assessed using Kruskal-Wallis test. Changes of knee joint effusion before and after each training session during the training period was assessed using repeated measures analyses of variance (ANOVA). Students paired t-test was applied to evaluate the difference between maximal muscle strength before and after the training period. Spearmans test was applied to calculate the correlation between the change in muscle strength and knee joint pain and effusion.

Results

Of the 30 included patients, one patient dropped out of the study due to a herniated disc during the training period. No drop-outs and adverse events related to the training intervention were recorded.

Table 1 shows knee joint pain at rest before and after each training session. In many test points, the patients stated no pain. Median differences of the pain from before to after each training session varied from 0-2. Pain after training was unchanged over time *(p = 0.99).*

Mean differences of the knee joint circumference from before to after a single session varied from 0-0.4 cm (Figure 1), and was statistically unchanged throughout all training sessions *(p = 0.99).*

Table 2 shows an increase in the training load during the sessions for all exercises. Maximal muscle strength improved; unilateral leg press mean 18% ± 30 *(p = 0.03)*, knee extension mean 81% ± 156 *(p < 0001)* and knee flexion mean 53% ± 57 *(p < 0.001).* There was no significant correlation between maximal muscle strength and knee joint pain and effusion: Leg press and pain *(p = 0.96),* leg press and effusion and *(p = 0.60).* Knee extension and pain and effusion *(p = 0.80)* and *(p = 0.29)*, respectively. Knee flexion and knee pain and effusion *(p = 0.53)* and *(p = 0.07)*, respectively.

Discussion

The present results support the hypothesis that progressive resistance training initiated 5 weeks before total knee arthroplasty does not exacerbate knee joint pain and knee joint effusion when measured at rest immediately after a single training session as well as throughout a 4 week intervention period. The training load increased progressively during training sessions for all 6 exercises, and maximal strength of leg press, knee extension and -flexion increased significantly, when assessed by 1RM testing.

Generally, the patients experienced none to mild knee pain at rest both before and after the training sessions. During most of the sessions, the patients experienced no pain at rest, neither before nor after training, and the pain did not increase over the 4 weeks training period. It is possible that the patients have experienced higher levels of pain during the exercises, but even so the pain sensation is a temporary phenomenon that is normalized when the training stops. Only limited swelling was observed after each training session (from 0 to 0.4 cm), and this did not increase over the training period. We consider this minor increase of knee circumference after training to have no clinical relevance since the patients managed to increase muscle strength substantially. In a pilot study applying progressive resistance training immediately after total knee arthroplasty, it was concluded

that the training did not increase knee joint pain or effusion (11). Thus, it seems that the fear of exacerbation of pain and swelling of progressive resistance training immediately before and/or after total knee replacement is unfounded.

Finally, an excellent improvement of maximal knee extension and -flexor muscle strength was observed despite a short training period of only 4 weeks, indicating that progressive resistance training constitute an effective exercise modality prior to total knee arthroplasty.

Limitations

Medicine consumption due to knee pain before and after each training session was not recorded, which may have influenced the results. Further, the disadvantage of using 1RM for evaluating maximal muscle strength is that the patients were tested on the same equipment, in which the patients had trained. This increases the improvement in strength as a consequence of the learning effect (12-14).

Conclusion

Progressive resistance training of the affected leg initiated shortly before total knee arthroplasty does not exacerbate knee joint pain and effusion despite a substantial increase in muscle strength.

Clinical perspective

- No exacerbation of knee pain and knee effusion at rest after progressive resistance training sessions in patients scheduled for total knee arthroplasty.
- Progressive resistance training shortly before total knee arthroplasty improve muscle strength

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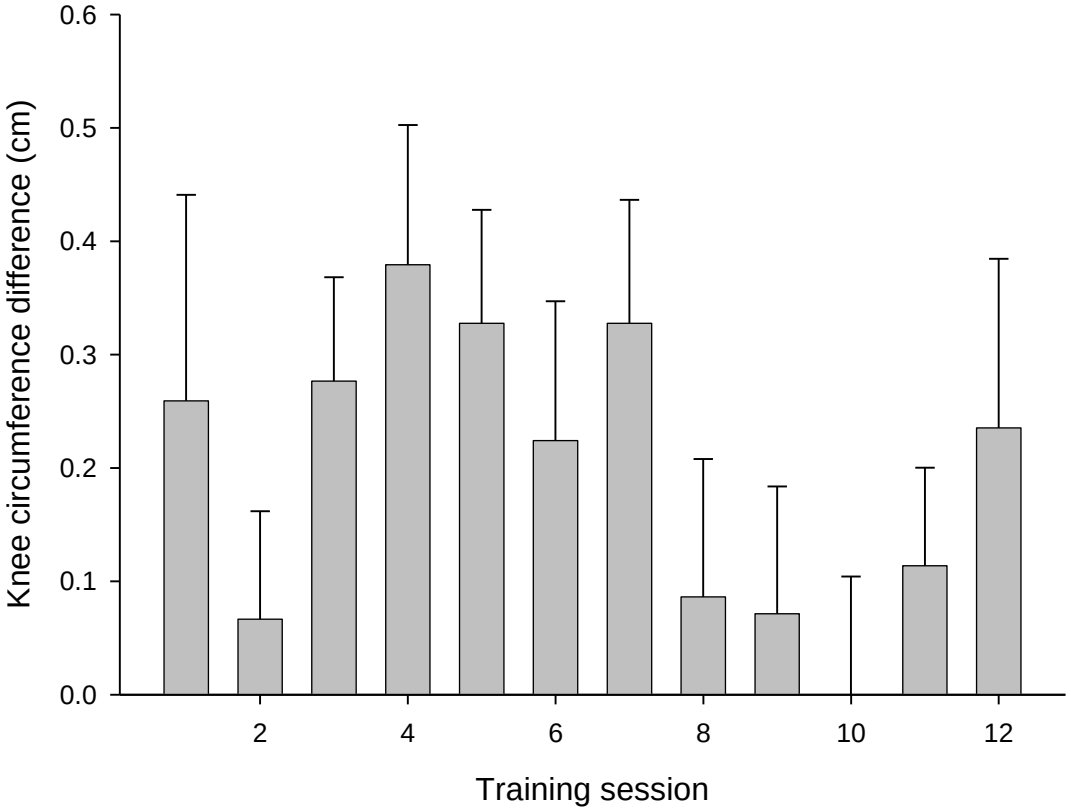

Figure 1. Difference in knee circumference from before to after each training sessions. Bars indicate means and whiskers standard deviation. At training session 10 the mean difference is 0. Effusion after training was unchanged over time, *p = 0.99* (repeated measures (ANOVA)).

Table 1. Pain at rest measured on a numeric rating scale before and after each training session.

	Before training		After training	
Session	**Median**	**IQR[#]**	**Median**	**IQR[#]**
1	0.5	0-2	0	0-2
2	1	0-2	0	0-2
3	0	0-2	0	0-1
4	0	0-1	0	0-1
5	0	0-1	0	0-1
6	0	0-2	0	0-2
7	0	0-1	0	0-2
8	0	0-1	0	0-2
9	0	0-1.5	0.5	0-2
10	1	0-2	0	0-2
11	0	0-1	0	0-1
12	0	0-1	0	0-1

[#]IQR, interquartile range

Table 2. 1RM (kg) before the first and last training session and training load (kg) during each training session

		Leg press		**Knee extension**		**Knee flexion**		**Hip extension**		**Hip abduction**		**Hip adduction**	
Training session	RM	Load Mean	SD	Load Mean	SD	Load Mean	SD	Load Mean	SD	Load Mean	SD	Load Mean	SD
1	1RM	54.3	25.4	22.2	14.0	16.9	7.9	---	---	---	---	---	---
1	12	31.4	13.7	13.0	9.1	8.9	4.6	7.2	2.8	4.8	2.9	6.6	2.1
2	12	34.5	13.9	12.5	8.6	10.2	3.8	7.9	3.6	5.8	2.9	7.0	2.7
3	12	36.4	13.7	14.8	8.6	11.2	4.1	9.3	3.2	6.4	2.9	7.9	2.6
4	10	37.4	13.4	15.3	9.6	12.2	4.4	10.0	3.3	6.8	2.7	8.9	2.8
5	10	39.3	13.5	16.5	10.2	13.5	4.3	11.1	3.7	7.9	2.7	9.7	3.2
6	10	40.6	13.6	17.7	10.4	14.4	4.7	11.8	3.8	8.0	2.9	10.1	3.3
7	8	44.4	14.7	18.5	11.0	15.4	4.9	12.9	3.9	8.9	2.9	11.7	3.7
8	8	45.4	14.4	19.9	11.1	15.9	5.1	13.4	4.1	9.3	3.0	11.8	4.5
9	8	46.4	15.0	21.2	10.7	16.6	5.6	14.0	4.1	9.5	3.2	12.3	4.7
10	8	49.1	14.7	22.2	11.2	16.9	5.4	14.9	4.6	10.1	3.5	13.5	5.0
11	8	51.8	15.5	23.0	11.8	17.8	5.0	15.5	4.8	10.5	3.8	13.9	5.4
12	8	50.6	18.4	23.3	9.6	18.8	6.4	16.5	5.5	11.8	4.1	14.8	6.5
12	1RM	59.7	23.2	27.7	12.9	23.9	8.4	---	---	---	---	---	---

Appendix 5: List of theses from the orthopedic research group

THESES FROM THE ORTHOPAEDIC RESEARCH GROUP

PhD and Doctoral Theses from the Orthopaedic Research Group, www.OrthoResearch.dk, University Hospital of Aarhus, Denmark

PhD Theses

1. In vivo and vitro stimulation of bone formation with local growth factors
   Martin Lind, January 1996
   www.OrthoResearch.dk

2. Gene delivery to articular cartilage
   Michael Ulrich-Vinther, September 2002
   www.OrthoResearch.dk

3. The influence of hydroxyapatite coating on the peri-implant migration of polyethylene particles
   Ole Rahbek, October 2002
   www.OrthoResearch.dk

4. Surgical technique's influence on femoral fracture risk and implant fixation. Compaction versus conventional bone removing techniques
   Søren Kold, January 2003
   www.OrthoResearch.dk

5. Stimulation and substitution of bone allograft around non-cemented implants
   Thomas Bo Jensen, October 2003
   www.OrthoResearch.dk

6. The influence of RGD peptide surface modification on the fixation of orthopaedic implants
   Brian Elmengaard, December 2004
   www.OrthoResearch.dk

7. Biological response to wear debris after total hip arthroplasty using different bearing materials
   Marianne Nygaard, June 2005
   www.OrthoResearch.dk

8. DEXA-scanning in description of bone remodeling and osteolysis around cementless acetabular cups
   Mogens Berg Laursen, November 2005
   www.OrthoResearch.dk

9. Studies based on the Danish Hip Arthroplasty Registry
   Alma B. Pedersen, 2006
   www.OrthoResearch.dk

10. Reaming procedure and migration of the uncemented acetabular component in total hip replacement
    Thomas Baad-Hansen, February 2007
    www.OrthoResearch.dk

11. On the longevity of cemented hip prosthesis and the influence on implant design
    Mette Ørskov Sjøland, April 2007
    www.OrthoResearch.dk

12. Combination of TGF-β1 and IGF-1 in a biodegradable coating. The effect on implant fixation and osseointegration and designing a new in vivo model for testing the osteogenic effect of micro-structures in vivo
    Anders Lamberg, June 2007
    www.OrthoResearch.dk

13. Evaluation of Bernese periacetabular osteotomy; Prospective studies examining projected load-bearing area, bone density, cartilage thickness and migration
    Inger Mechlenburg, August 2007
    Acta Orthopaedica (Suppl 329) 2008;79

14. Rehabilitation of patients aged over 65 years after total hip replacement - based on patients' health status
    Britta Hørdam, February 2008
    www.OrthoResearch.dk

15. Efficacy, effectiveness, and efficiency of accelerated perioperative care and rehabilitation intervention after hip and knee arthroplasty
    Kristian Larsen, May 2008
    www.OrthoResearch.dk

16. Rehabilitation outcome after total hip replacement; prospective randomized studies evaluating two different postoperative regimes and two different types of implants
    Mette Krintel Petersen, June 2008
    www.OrthoResearch.dk

17. CoCrMo alloy, *in vitro* and *in vivo* studies
    Stig Storgaard Jakobsen, June 2008
    www.OrthoResearch.dk

18. Adjuvant therapies of bone graft around non-cemented experimental orthopaedic implants. Stereological methods and experiments in dogs
    Jørgen Baas, July 2008
    Acta Orthopaedica (Suppl 330) 2008;79

19. The Influence of Local Bisphosphonate Treatment on Implant Fixation
    Thomas Vestergaard Jakobsen, December 2008
    www.OrthoResearch.dk

20. Surgical Advances in Periacetabular Osteotomy for Treatment of Hip Dysplasia in Adults
    Anders Troelsen, March 2009
    Acta Orthopaedica (Suppl 332) 2009;80

21. Polyethylene Wear Analysis. Experimental and Clinical Studies in Total Hip Arthroplasty.
    Maiken Stilling, June 2009
    Acta Orthopaedica (Suppl 337) 2009;80

22. Step-by-step development of a novel orthopaedic biomaterial: A nanotechnological approach.
    Thomas H.L. Jensen, September 2009
    www.OrthoResearch.dk

23. Osteoclastic bone resorption in chronic osteomyelitis
    Kirill Gromov, November 2009
    www.OrthoResearch.dk

24. Use of medications and the risk of revision after primary total hip arthroplasty
    Theis Thillemann, December 2009
    www.OrthoResearch.dk

25. Different fixation methods in anterior cruciate ligament reconstruction
    Ole Gade Sørensen, February 2010
    www.OrthoResearch.dk

26. Postoperative pain relief after total hip and knee replacement; prospective randomized studies evaluating two different peri- and postoperative regimes
    Karen V. Andersen, June 2010
    www.OrthoResearch.dk

27. A comparison of two types of osteosynthesis for distal radius fractures using validated Danish outcome measures
    Jesper O. Schønnemann, September 2010
    www.OrthoResearch.dk

28. Optimizing the cementation of femoral component in hip arthroplasty
    Juozas Petruskevicius, September 2010
    www.OrthoResearch.dk

29. The influence of parathyroid hormone treatment on implant fixation
    Henrik Daugaard, December 2010
    www.OrthoResearch.dk

30. Strontium in the bone-implant interface
    Marianne Toft Vestermark, January 2011
    www.OrthoResearch.dk

31. The applicability of metallic gold as orthopaedic implant surfaces – experimental animal studies
    Kasra Zainali, April 2011
    www.OrthoResearch.dk

32. Gene transfer for bone healing using immobilized freeze-dried adeno-associated viral vectors
    Mette Juul Koefoed, June 2011
    www.OrthoResearch.dk

33. Mobile or fixed bearing articulation in TKA? A randomized evaluation of gait analysis, implant migration, and bone mineral density
    Michael Tjørnild, December 2011
    www.OrthoResearch.dk

34. Hip resurfacing arthroplasty. Failures and complications investigated by a meta-analysis of the existing literature, and clinically by microdialysis, laser doppler flowmetry, RSA, DXA and MRI
    Nina Dyrberg Lorenzen, March 2012
    www.OrthoResearch.dk

35. Manipulation of the mevalonate pathway in the bone-implant interface
    Mette Sørensen, September 2012
    www.OrthoResearch.dk

36. Bone allograft and implant fixation tested under influence of bio-burden reduction, periosteal augmentation and topical antibiotics
    Jeppe Barckman, January 2013
    www.OrthoResearch.dk

37. Sternal healing characteristics. Animal and clinical experimental investigation
    Rikke Vestergaard, March 2013
    www.OrthoResearch.dk

38. Assessment of factors influencing the surgical outcome of periacetabular osteotomy for treatment of hip dysplasia in adults
    Charlotte Hartig-Andreasen, June 2013
    www.OrthoResearch.dk

39. Stem cells derived from adipose tissue and umbilical cord blood for cartilage tissue engineering in scaffold cultures
    Samir Munir, December 2013
    www.OrthoResearch.dk

40. Flexor tendon adhesions – a mouse model of flexor tendon injury and repair
    Sys Hasslund Svensson, 2014
    www.OrthoResearch.dk

41. The association between obesity and the effect of total knee – and hip arthroplasty
    Anette Liljensøe, 2014
    www.OrthoResearch.dk

42. Early rehabilitation after fast-track total hip replacement - Effect of early, supervised, progressive resistance training and influence of movement restrictions and assistive devices on functional recovery
    Lone Ramer Mikkelsen, 2014
    www.OrthoResearch.dk

Doctoral Theses

1. Hydroxyapatite ceramic coating for bone implant fixation. Mechanical and histological studies in dogs
    Kjeld Søballe, 1993
    Acta Orthop Scand (Suppl 255) 1993;54

2. Growth factor stimulation of bone healing. Effects on osteoblasts, osteomies, and implants fixation
    Martin Lind, October 1998
    Acta Orthop Scand (Suppl 283) 1998;69

3. Calcium phosphate coatings for fixation of bone implants. Evaluated mechanically and histologically by stereological methods
    Søren Overgaard, 2000
    Acta Orthop Scand (Suppl 297) 2000;71

4. Adult hip dysplasia and osteoarthritis. Studies in radiology and clinical epidemiology
    Steffen Jacobsen, December 2006
    Acta Orthopaedica (Suppl 324) 2006;77

5. Gene therapy methods in bone and joint disorders. Evaluation of the adeno-associated virus vector in experimental models of articular cartilage disorders, periprosthetic osteolysis and bone healing
    Michael Ulrich-Vinther, March 2007
    Acta Orthopaedica (Suppl 325) 2007;78

6. Assessment of adult hip dysplasia and the outcome of surgical treatment
    Anders Troelsen, February 2012
    www.OrthoResearch.dk