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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.

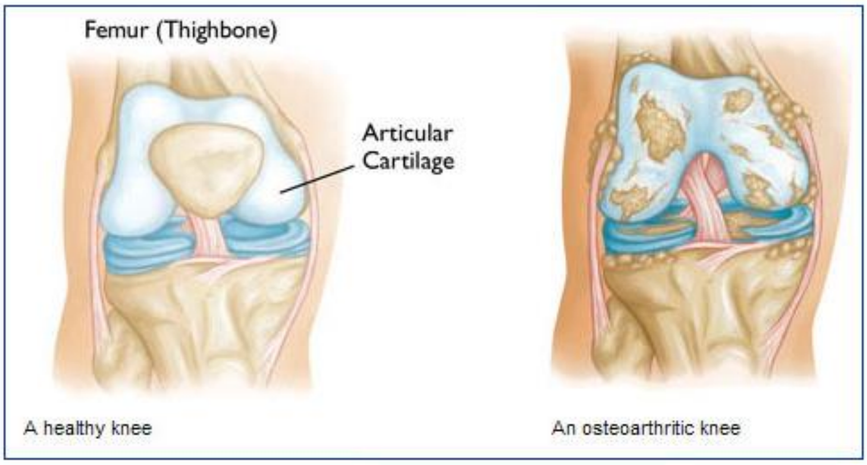

Figure 1. Normal knee anatomy and severe knee osteoarthritis (16)

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. follow-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).

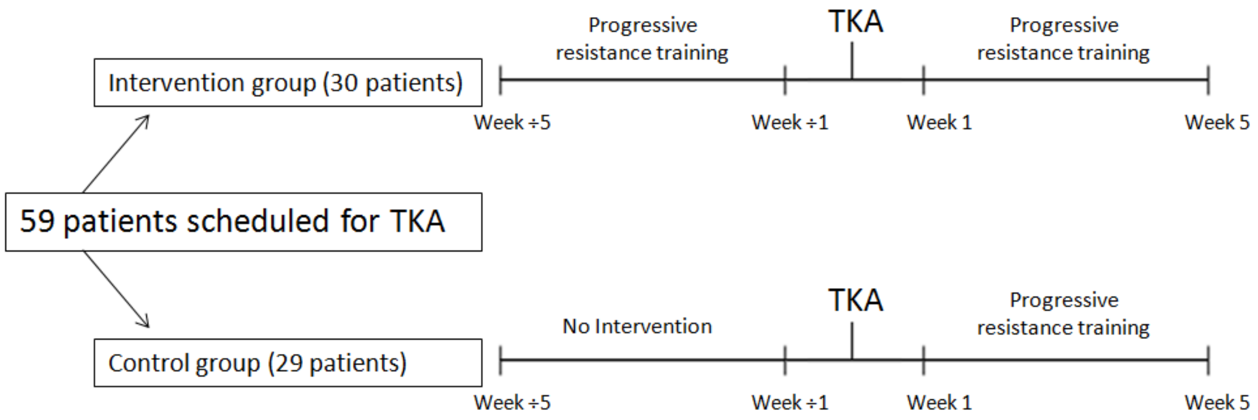

Figure 3: Study design

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.

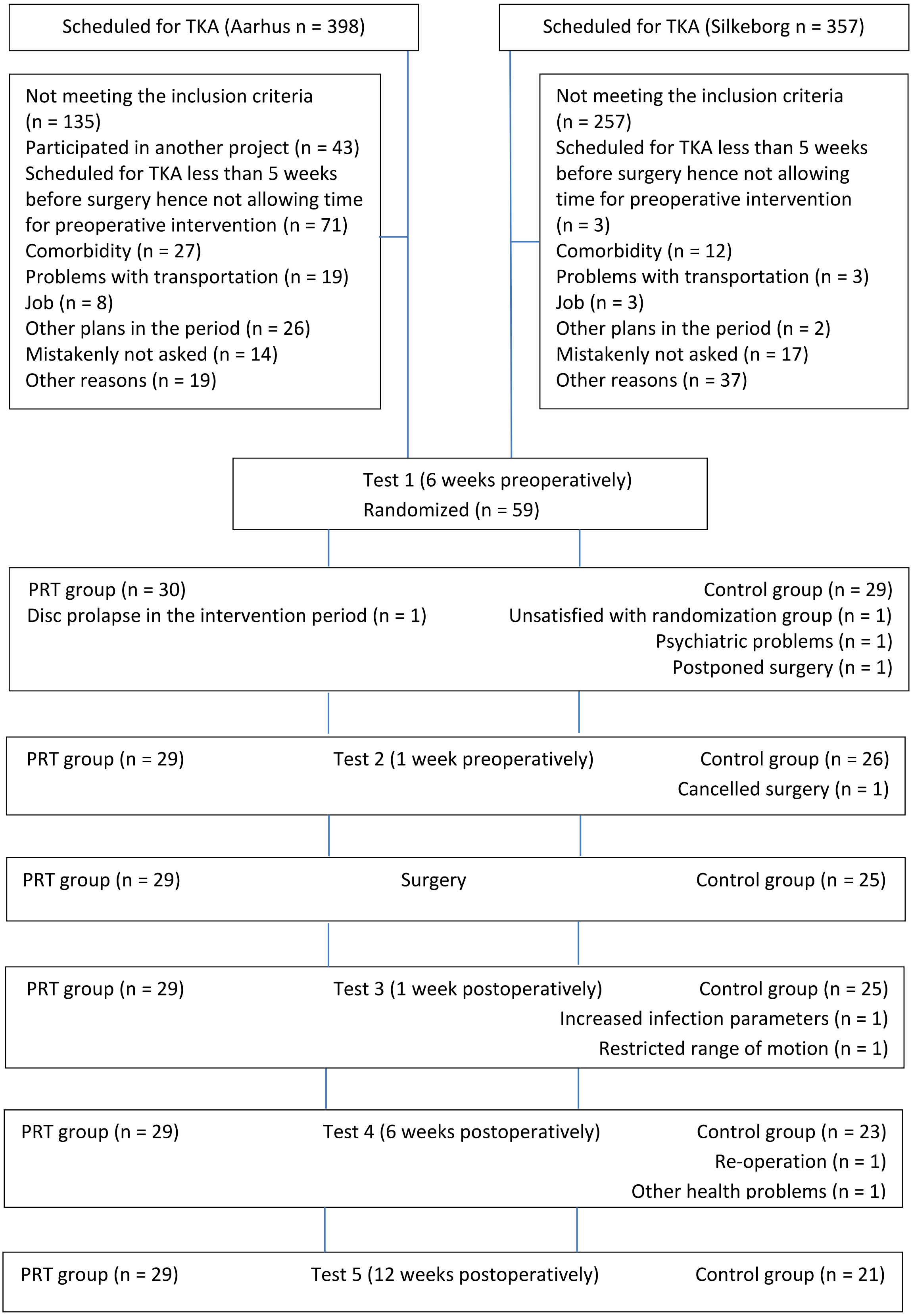

Figure 4. Flow diagram

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.

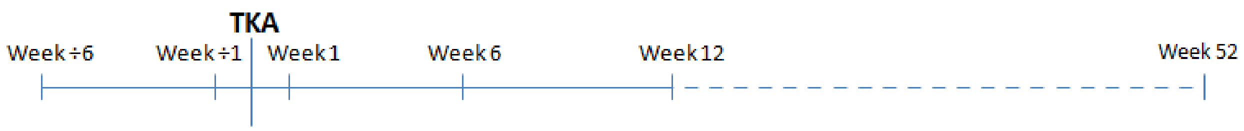

Figure 6. Test points and time for TKA

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

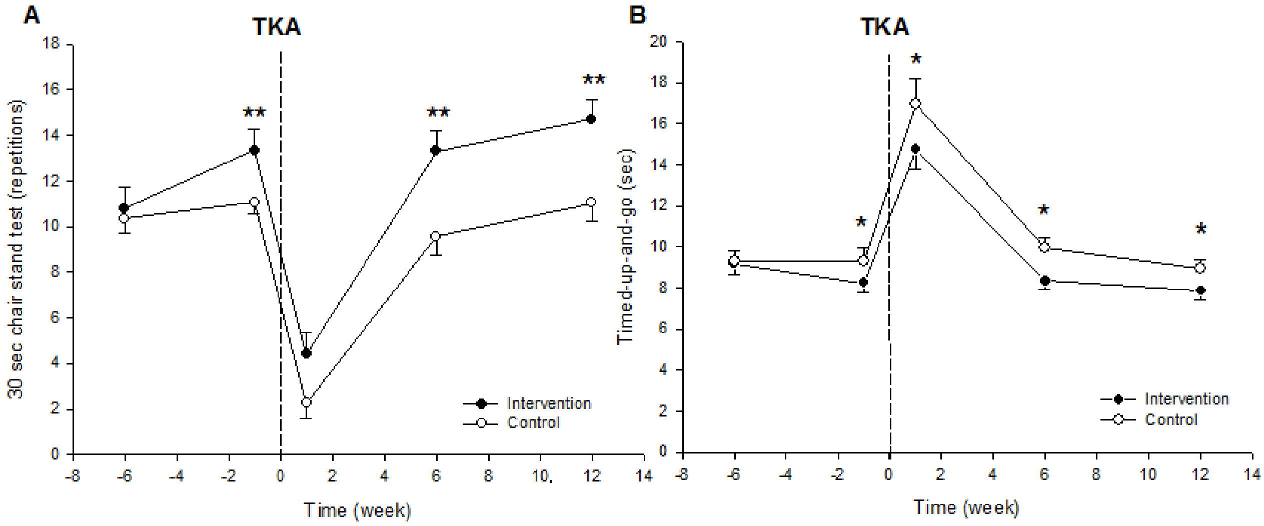

Figure 6 A. 30-s chair stand test between groups (mean (standard error of the mean (SEM))) B. Timed-up-and-go between groups (mean (SEM)). * *p* $\leq$ *0.05; ** p < 0.01.*

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.

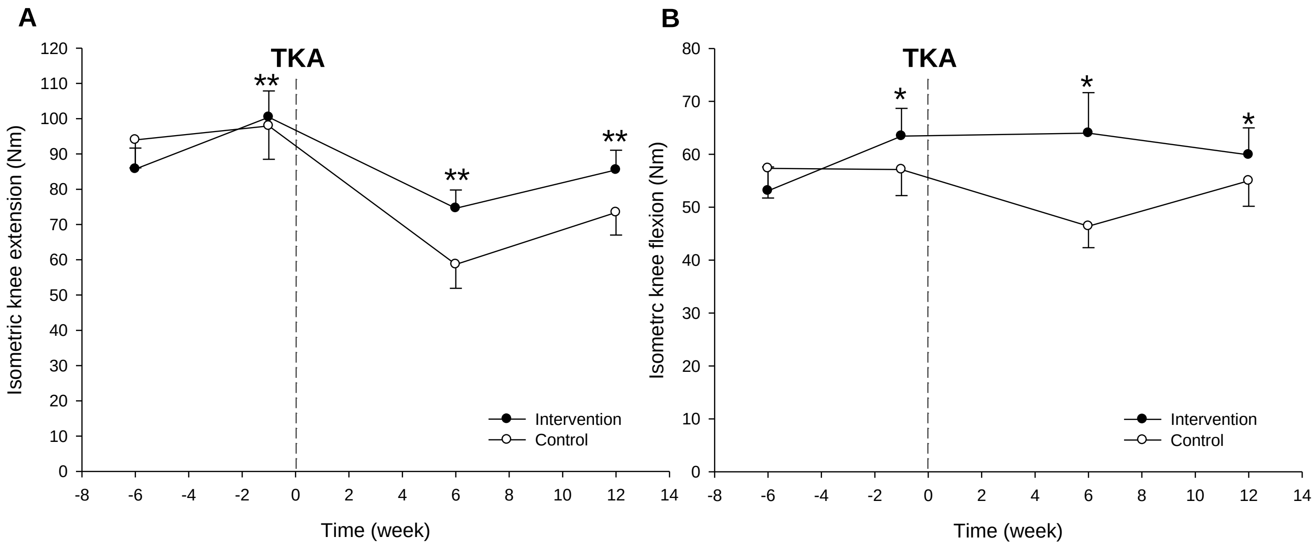

Figure 7 A. Isometric extension between groups (mean (SEM)) B. Isometric flexion between groups (mean (SEM)).
** p ≤ 0.05; ** p < 0.01.*

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 *($p = 0.99$).*

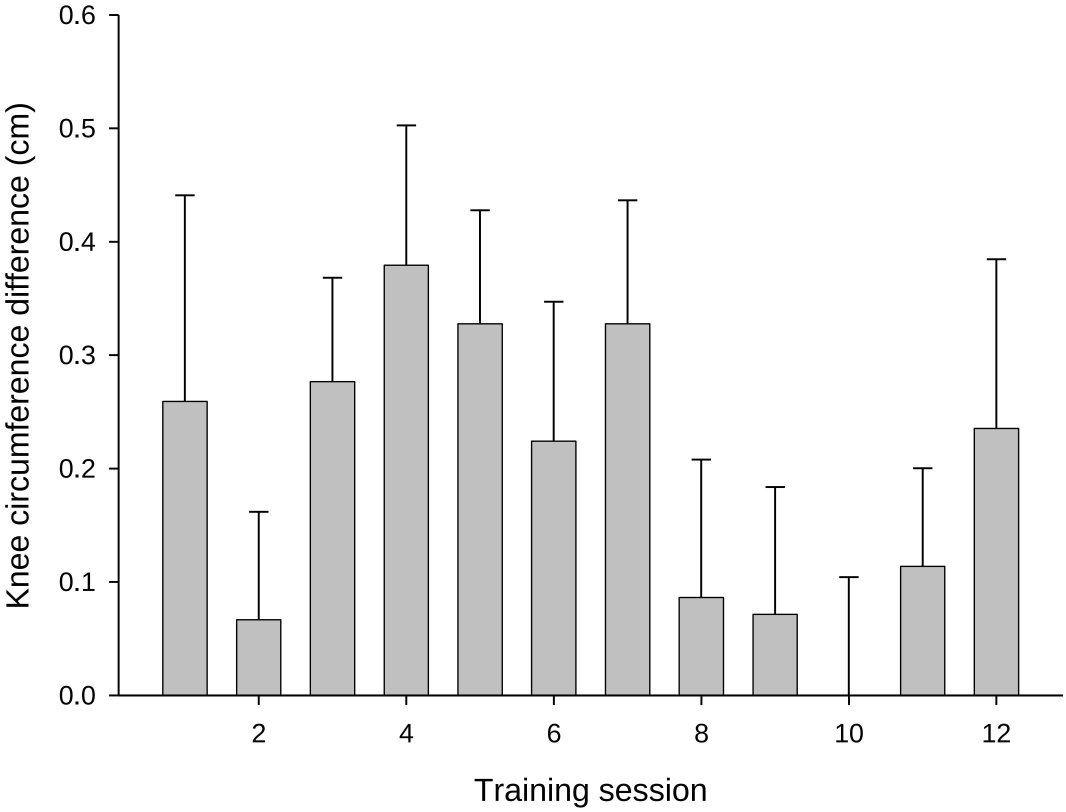

Figure 8 Difference in knee circumference from before to after each training sessions. Bars indicate (means (SEM)). At training session 10, the mean difference is 0. Effusion after training was unchanged over time, $p = 0.99$ (repeated measures (ANOVA)).

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