

PHYSICAL MEDICINE & REHABILITATION RESEARCH -
COPENHAGEN (PMR-C), CLINICAL RESEARCH
CENTRE, AND LUNDBECK FOUNDATION CENTRE FOR
FAST-TRACK HIP AND KNEE ARTHROPLASTY
COPENHAGEN UNIVERSITY HOSPITAL, HVIDOVRE

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

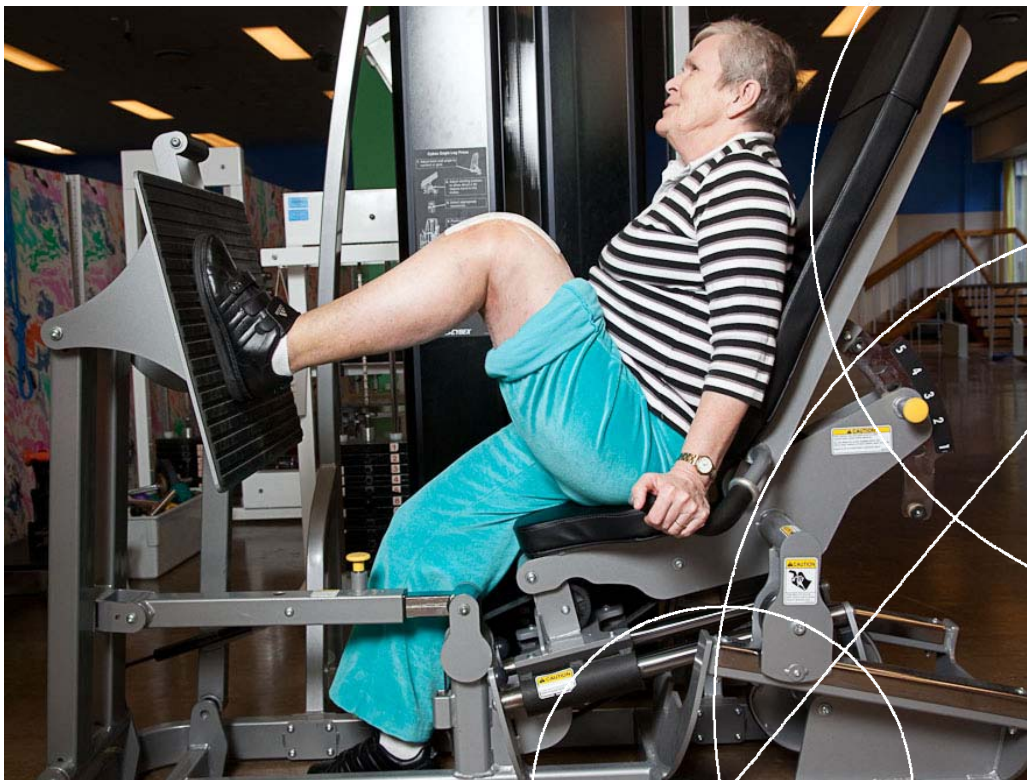


PhD thesis

Thomas Linding Jakobsen

Progressive Strength Training Commenced Early After Fast-Track Total Knee Arthroplasty

Feasibility and Effect



Academic supervisor: Thomas Bandholm

Academic co-supervisor: Henrik Kehlet

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Thomas Linding Jakobsen

Physical Medicine & Rehabilitation Research –
Copenhagen (PMR-C), Clinical Research Centre, and
Lundbeck Foundation Centre For Fast-Track Hip and
Knee Arthroplasty, Copenhagen University Hospital,
Hvidovre, Denmark, 2013



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LIST OF PAPERS

This PhD thesis contains of 3 papers, which will be referred to using roman numerals throughout this thesis.

- I. Jakobsen TL, Husted H, Kehlet, H, Bandholm T. Progressive strength training (10 RM) commenced immediately after fast-track total knee arthroplasty: Is it feasible? *Disability and Rehabilitation* 2012;34(12):1034-40.
- II. Jakobsen TL, Kehlet H, Bandholm T. Reliability of the 6-minute walk test after total knee arthroplasty. *Knee Surgery, Sports Traumatology, Arthroscopy* 2013;21(11):2625-2628.
- III. Jakobsen TL, Kehlet, H, Petersen J. Husted H, Bandholm T. Effect of early rehabilitation with progressive strength training after fast-track total knee arthroplasty: A randomized controlled trial. *Submitted*.

THESIS AT A GLANCE

Paper	Question	Patients	Methods	Results	Conclusion
I	Is PST feasible commenced 1 to 2 days after fast-track TKA, indicated by increasing training loads without exacerbation of knee pain and knee joint effusion?	14 patients with unilateral TKA from a fast-track orthopaedic arthroplasty unit.	Patient received rehabilitation including PST of the operated leg (leg press and knee-extension), using relative loads of 10 (RM) with 3 training sessions per week for 2 weeks. At each training session, training load, knee pain, and knee joint effusion were recorded.	Training load increased progressively. Patients experienced only moderate knee pain during the strength training exercises, but knee pain at rest and knee joint effusion were unchanged or decreased over time.	Rehabilitation with PST commenced immediately after TKA seems feasible indicated by increased training loads without exacerbation of knee joint effusion or knee pain.
II	Is the 6MWT intra-tester reliable with acceptable measurement error to identify a small change of functional performance in patients with TKA?	34 patients with unilateral TKA recruited from different rehabilitation sites.	Patients performed 2 6MWTs the same day, separated by a 1-hour seated rest. To assess reliability, the ICC, SEM ₉₅ , and SRD ₉₅ were calculated.	Patients walked on average 14.1 m longer at the second (397.2 m) compared to the first (383.1 m) test trial. The ICC, SEM ₉₅ , and SRD ₉₅ were 0.97, 25.5 m, and 36.1 m, respectively.	The 6MWT was reliable with an acceptable small error to identify changes in a group of patients (SEM ₉₅) and in an individual patient (SRD ₉₅) early after TKA. A learning effect was observed.
III	Is rehabilitation with PST superior to rehabilitation without PST in improving functional performance early after fast-track TKA?	82 patients with unilateral TKA from a fast-track orthopaedic arthroplasty unit.	Patients were randomized to 7 weeks of supervised rehabilitation with (PST-group) or without PST (CON-group) commenced 1 week after TKA. The primary (6MWT) and secondary outcomes were assessed before (baseline), 4, 8 (primary analysis) and 26 weeks after TKA.	No differences between the PST- and CON-group for the 6MWT were found. No significant or clinically meaningful differences between groups for any secondary outcomes were revealed.	7 weeks of supervised rehabilitation with PST was not superior to 7 weeks of supervised rehabilitation without PST in improving functional performance (6MWT) commenced 1 week after fast-track TKA.

6MWT=6-minute walk test, ICC=Intraclass correlation coefficient, PST=Progressive strength training, TKA=Total knee arthroplasty, RM=Repetition maximum, SEM₉₅=Standard error of measurement with a 95% confidence interval, and SRD₉₅=Smallest real difference with a 95% confidence interval.

ABBREVIATIONS

6MWT	6-minute walk test
ADL	Activity of daily living
AMI	Arthrogenic muscle inhibition
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
CI	Confidence interval
EQ-5D	Euroqol questionnaire
ICC	Intraclass correlation coefficient
ICF	International classification of functioning, disability and health
IQR	Interquartile range
KOOS	Knee injury and osteoarthritis outcome score
OKS	Oxford knee score
PRO	Patient-reported outcome
PST	Progressive strength training
RM	Repetition maximum
ROM	Range of motion
SD	Standard deviation
SEM	Standard error of measurement
SRD	Smallest real difference
TKA	Total knee arthroplasty
VAS	Visual analogue scale

1 INTRODUCTION

1.1 Total knee arthroplasty

Total knee arthroplasty (TKA) is performed to alleviate knee pain and disability related to end-stage knee osteoarthritis. TKA is a common orthopaedic procedure¹ with approximately 8,000 operations per year in Denmark.² The number of TKA operations has increased in the developed countries¹ with over 687,000 operations performed in USA annually,³ and this number has been projected to increase to 3,48 million per year in 2030.⁴ This increase is based on the fact that the predominant risk factors for knee osteoarthritis, age and obesity, are rising.^{1,5} In Denmark, the surgical procedure is primarily performed in women (58.5%), and in a population between 60 to 79 years of age.²

The surgical procedure involves removal of damaged cartilage, correction of joint deformities, and replacement of the worn cartilaginous bearing surfaces (on femur, tibia and patella) with an artificial bearing (prosthesis).⁶ After hospitalization, patients are discharged to a rehabilitation unit or to their own home. The re-admission rate has been reported to be approximately 8-9% within the first 3 months after TKA.^{7,8} Some of the most common complications after TKA are deep vein thrombosis, wound infection, and knee stiffness (limited knee range of motion (ROM) that affects a patient's ability to perform activities of daily living (ADL)).⁹ The TKA is regarded as an effective treatment that promotes substantial self-reported quality of life gains for people with end-stage knee osteoarthritis.¹ Still, some patients experience knee-related symptoms such as persistent pain and stiffness after TKA,^{10,11} and the percentage of patients with TKA, who are dissatisfied with their outcome, varies from 8% to 25%.¹⁰⁻¹²

1.2 Fast-track methodology after total knee arthroplasty

The fast-track methodology is a dynamic concept that focuses on enhancing recovery and reducing morbidity after surgery by implementing evidence-based knowledge within a variety of modalities (fast-track surgery).¹³ These include perioperative pain management, surgical and nursing care principles, reduction of surgical stress responses, prevention of complications in relation to surgery, early mobilisation and oral nutrition, and postoperative rehabilitation. This multimodal approach involves surgeons, anaesthesiologists, nurses, physiotherapists, and strives to optimize clinical, organizational and logistical features to provide the individual patient with the best available treatment.¹⁴ Originally, the fast-track concept was developed around patients undergoing abdominal surgery and hernia-repairs.¹⁴ The concept has since been successfully introduced in patients undergoing total hip and knee arthroplasty, and the first pilot study was carried out in the beginning of 1990's at Copenhagen University Hospital, Hvidovre.¹⁵ In recent years, the fast-track surgery has

gradually reduced the median length of stay after TKA from 11 days¹⁶ to about 2 to 4 days, without increasing morbidity and readmissions.^{7;8;13;17}

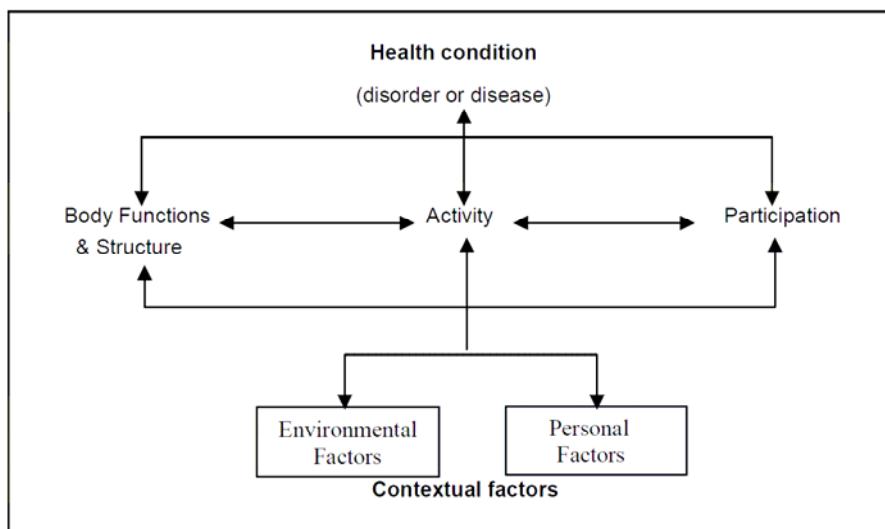
Early postoperative mobilization and rehabilitation is considered important to achieve rapid functional recovery in fast-track TKA.^{13;18;19} To enhance functional recovery, effective pain management is a prerequisite for early mobilization after fast-track TKA. Pain has had a limiting role in the achievement of functional recovery, consequently pain relief allows an early rehabilitation after TKA.¹⁸ With fast-track surgery, which includes the use of spinal anaesthesia, intraoperative, high-volume local anaesthetic wound infiltration and optimized multi-opioid-sparing analgesia, patients were able to transfer independently 1 to 2 days post-TKA.^{18;20}

1.3 Impairments and deficits after total knee arthroplasty

The international classification of functioning, disability and health (ICF) model provides a unified framework for evaluating health and health-related states of populations.^{21;22} The ICF model is predominantly divided into functioning and disability, and contextual factors (Figure 1).

Functioning and disability includes the components of body functions and structures (impairment), activity (activity limitation) and participation (participant limitation). Contextual factors include environmental and personal factors. Within this framework, attention has been focussed on several common impairments early after TKA, such as lower extremity muscle strength, knee joint ROM, knee joint effusion, and knee pain. This interest seems justified, as these impairments have been reported to be associated with limitations in activity (e.g walking and stair climbing)²³⁻²⁶ and participation.²⁷

Figure 1. ICF model²²



1.3.1 Muscle strength

One of the key impairments after TKA is early loss of knee-extension strength, in so far as decreases of 64% to 83% compared to pre-surgery levels have been reported.^{27;28} This loss in knee-extension strength may be regained if rehabilitation with progressive strength training (PST) is provided.^{26;29;30} However, knee-extension strength seldom reaches the strength-levels of age-matched healthy adults.³¹⁻³³ This may pose a functional problem, as decreased knee-extension strength is associated with impaired functional performance in, for example walking and stair climbing after TKA.²⁶⁻²⁸

The loss of knee extension strength after TKA is closely related to atrophy and neural inhibition of the quadriceps muscle.³⁴ The neural inhibition prevents the quadriceps muscle from being fully activated, a process known as arthrogenic muscle inhibition (AMI).³⁴⁻³⁶ It has been suggested that AMI contributes almost twice as much as muscle atrophy to the observed weakness examined 1 month after TKA.^{34;37} After 3 months, this pattern seems to change as muscle atrophy contributed more than AMI to the observed knee-extension weakness.³⁷

Finally, loss of muscle strength after TKA has been reported for other muscle groups as well. These include strength losses in knee flexion,³⁸ hip abduction,³⁹ ankle plantarflexors and ankle dorsiflexors⁴⁰ that may limit functional performance.

1.3.2 Knee joint effusion

Knee joint effusion after TKA is probably caused by intraarticular bleeding and inflammation of the periarticular tissues,⁴¹ and has been reported to persist at least 1 month after TKA.^{27;28;42} More importantly, knee joint effusion (circumference increase) is associated with decreased knee-extension strength early after TKA.²⁸ These findings correspond well with observations from other experimental studies that have demonstrated knee-extension losses by infusing even small amount of fluid (10 ml) into healthy knee joints.^{35;43}

1.3.3 Knee joint range of motion

Numerous studies have investigated knee joint ROM after TKA.^{23;26;28;33;42;44;45} Notably, knee flexion has been examined, as approximately 90°-100° knee flexion is required to perform daily living activities such as stair climbing and rising from a normal-sized chair.^{46;47} In the majority of patients, knee flexion increases with time from around 70° at 3 days to around 115° at 6 months postoperatively.^{23;26;33;42;48} Despite the increased knee flexion, several studies have found that patients with TKA do not often reach levels of either preoperative^{23;33;45} or age-matched healthy

adults ROM-values.^{33;49} Furthermore, a frustrating complication for the individual patient and the involved health professionals is knee stiffness primarily due to arthrofibrosis.⁴⁶ Knee stiffness reaches 5% within the first 7 months after TKA.⁴⁶ However, reports have stated knee stiffness as high as 10% within the first 7 months after TKA.⁵⁰

Knee extension ROM seems not to be as affected as knee flexion with mean values ranging from 1° to 3.6° (Positive knee extension scores indicate ROM limitation (inability to reach the 0-degree starting position)).^{27;51} at 6 months after TKA, approaching ROM-levels of age-matched healthy peers.⁴⁹ However, some patients experience a ROM loss. One large retrospective study found that 3.6% of the patients studied had a knee extension limitation greater than 6° 3 or more years after TKA.⁵²

1.3.4 Knee pain

Postoperative knee pain is common following TKA. Despite the implementation of an enhanced peri-operative recovery program including a multimodal analgesic regimen, patients have experienced mild (Visual Analog Scale (VAS) <30 mm) to moderate (30<VAS<59 mm) knee pain 1 month after TKA.⁵³ These pain-levels seemed to decrease over time, as studies have reported none to mild knee pain at rest 3 months after TKA.^{30;45} Despite the overall success of TKA in reliably reducing pain in most cases,⁵⁴ up to 18% of patients may endure persistent postoperative knee pain (VAS>40 mm) 6 months postoperatively.⁵⁵ However, at the 5-year follow-up many of these patients had improved their pain scores (mean VAS=29 mm).⁵⁶

1.3.5 Functional performance

Functional performance after TKA can be assessed by the use of an objective functional performance-based outcome measure (e.g. 6-minute walk test (6MWT), stair-climbing test and timed up and go test), which is defined as an activity within the ICF framework.^{57;58} Assessed 2 to 3 days post-TKA, patients' functional performance was substantially worsened evidenced by up to a 133% increase in the time to perform the timed up and go test compared to pre-surgery.²⁸ After hospital discharge, research has shown that functional performance may recover and reach the pre-surgical level 8 weeks postoperatively.^{23;26;30} In concordance with the loss of knee-extensor strength, the majority of patients with TKA, assessed by functional performance-based tests, rarely reached the level of age-matched healthy adults.^{32;33;59}

1.3.6 Patient-reported outcome

Several patient-reported outcomes (PROs) such as the Oxford knee score (OKS) and the knee injury and osteoarthritis outcome score (KOOS) have been developed and utilized to document and evaluate patients' self-perceived health condition in relation to TKA.⁶⁰⁻⁶³ Commonly, PROs are linked to the ICF framework by the components of body structure and function, activity and participation.⁶⁴ Generally, patient-perceived disability and quality of health measured with PROs improves rapidly and reaches pre-surgery levels 1 to 2 months after TKA.^{23;27;42;54} Conflicting results exist as to whether patients with TKA reach the same level as their age-matched healthy peers. A systematic review consisting of 12 studies reported OKSs ranging from 30.5 to 40.0 one year after TKA (0=worst score; 48=best score).⁶⁵ These scores seem far from the OKSs of 45.6 to 47.0, found in an age-matched reference population.⁶⁶ On the contrary, reference-levels of the KOOS ADL-subscale⁶⁷ were met 2 years post-TKA in a prospective longitudinal study, while reference levels for the remaining subscales (symptoms, quality of life, pain, sports and recreation) were not.⁶⁸

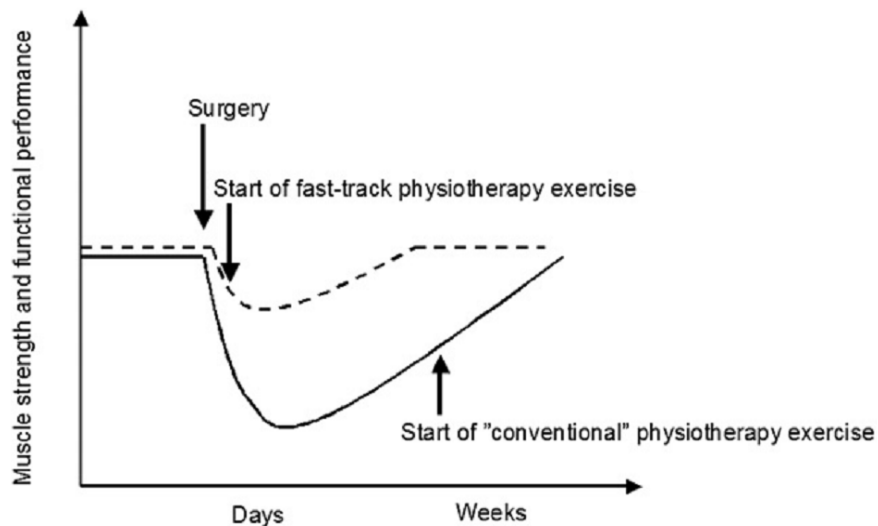
1.4 Assessment of functional performance after total knee arthroplasty

Assessment of functional performance is considered a core outcome in patients with knee osteoarthritis and, subsequently, TKA.⁶⁹ Both PROs and functional performance-based outcome measures have been used to assess functional performance.^{27;57} Lately, PROs have become more popular, because they are patient-administered, cost-efficient, and attendance at a clinic or a rehabilitation unit is not necessary.^{1;27} However, growing evidence has revealed that PROs fail to capture an actual change in functional performance assessed by functional performance-based outcome measures, especially within the first 3 months after TKA.^{27;54;70} This discrepancy between what patients can do rather than what they perceive they can do may have multiple explanations. Firstly, patients' perceived functional performance was influenced more by their pain level than their actual ability to perform the functions^{54;71;72} and, secondly, the potential occurrence of response shift bias (as patients tend to remember their pre-TKA condition worse than it actual was).⁷³ Therefore, assessment of functional performance should not solely rely on PROs as these outcome scores presumably overestimate the patients' actual ability to move around after TKA.⁷⁰ As a consequence, both functional performance-based outcome measures and PROs with necessary psychometric properties (e.g. population-specific reliability, validity, responsiveness) have been recommended in the overall assessment of functional performance after TKA.⁵⁷ This seems especially important in the early stage after TKA where impairments and activity limitations are most pronounced.

1.5 Rehabilitation after total knee arthroplasty

It has been reported to be common practice to treat impairments and functional limitations after TKA.⁷⁴⁻⁷⁶ Surveys, investigating physiotherapy provisions in Denmark and UK, found large variability in the indication for physiotherapy, and the type of physiotherapy offered after TKA.^{76;77} The effectiveness of physiotherapy exercise after TKA was evaluated in a meta-analysis including only 6 studies (Total N=614).⁷⁸ The authors found that physiotherapy exercise had limited short-term effect on functional performance after TKA. The lack of evidence supporting rehabilitation may relate to limited high quality research. Another reason could be that rehabilitation programs after TKA did not incorporate the right exercise modality and/or intensity to enhance functional performance.^{3;79;80} Furthermore, it has been argued that rehabilitation programs may have been instituted too late (weeks) after TKA, when the largest muscle strength and functional performance losses have occurred (Figure 2).^{3;79}

Figure 2. Principles of fast-track physiotherapy exercise after total knee and hip arthroplasty. Modified after Bandholm & Kehlet⁷⁹



In the last decade, a number of studies have investigated a variety of rehabilitation modalities such as progressive strengthening/strength training,^{26;29;30;81} flexibility training,⁸²⁻⁸⁴ balance training,^{85;86} functional task-orientated training,^{80;87} ergometer cycling,⁸⁸ aquatic/water-based therapy,^{74;89} and adjuncts to a rehabilitation program such as continuous passive motion machine/device,^{83;90-95} biofeedback,⁹⁶ and neuromuscular electrical stimulation device.^{26;97-99}

Lately, interest has been focussed on PST as it makes sense from an exercise physiology point-of-view, the rationale being that PST counteracts the acute loss of lower extremity muscle strength after TKA.^{3;29;100;101} The strengthening of the quadriceps muscle has been prioritized, as knee-extension strength is required to accomplish ADL tasks such as walking, chair rise and stair

climbing after TKA.^{27;28} The idea of using PST as rehabilitation modality after orthopaedic surgery is not new. In 1945, Thomas Delorme showed that PST with heavy training loads increased muscle force production in patients with orthopaedic injury or post-surgery. The main principle of PST was to continually increase the stress placed on the muscle as it became stronger.^{102;103} As a consequence of the findings of Delorme, PST has been incorporated successfully in rehabilitation programs, which have improved muscle strength and functional performance in patients following a variety of orthopaedic procedures,¹⁰⁴⁻¹⁰⁶ and in old adults.¹⁰⁷

Clinicians as well as researchers have been reluctant to implement early PST in TKA rehabilitation programs. This reluctance may be based on the understanding that *“training intensity is unlikely ...to achieve meaningful changes in muscle strength in the first few weeks after TKA when patients are still experiencing the anaemia, pain and oedema”*.¹⁰⁸ Additionally, physicians have recommended a delay in the initiation of PST due to fear of exacerbating postoperative symptoms and delaying recovery of knee joint ROM.²³ However, a number of studies have explored the effect of PST or strengthening interventions on muscle strength and functional performance after TKA (Table 1).^{26;29;30;81;109} The evidence must be considered preliminary due to study limitations. Firstly, none of the studies used a randomized controlled trial design with an adequate sample size for a pre-specified primary outcome to determine the effect of rehabilitation with PST compared to a control group after TKA. Secondly, it may be argued whether the effect of PST was fully explored to achieve the optimal training effects. That is, the suggested principles of PST, performing a small number of repetitions (8-12) until failure and increasing the resistance as the ability to generate force develops might not have been followed.¹⁰⁶ Thirdly, the description of the content of the therapeutic exercise in both intervention arms is often lacking due to insufficient reporting of e.g. intensity, frequency, progression and duration.^{110;111} Rehabilitation with PST has been commenced as early as 1 to 2 weeks postoperative^{29;30} and was not reported to increase knee pain assessed 3½ weeks postoperatively.³⁰

In summary, encouraging preliminary evidence supported rehabilitation with PST after TKA. However, the feasibility of rehabilitation with PST performed immediately after TKA, without exacerbating pre-defined post-operative knee symptoms such as knee pain and knee joint effusion, needed to be investigated. If implementation of rehabilitation with PST was feasible early after TKA (proof of concept), further research was needed to investigate the effect of rehabilitation with PST commenced early after TKA in a large assessor-blinded randomized controlled trial.

Table 1. Description of studies investigating rehabilitation with (progressive) strength training after unilateral total knee arthroplasty.

				Exercise group		Control group				Supervised exercise group						
Study, year	Study location	Age, years	Women, %	No. of subjects	Exercise intervention	No. of subjects	Control intervention	Trial design	Deliverer	Type of exercise	No. of times/wk	No. of wk	Intensity	Wk postop.	Primary outcome	Key results
Perhonen (1992)	Finland	70 (5)	69	11: Training group 1 (TG1) 10: Training group 2 (TG2)	Home-exercise program with strength training. TG1: Low volume. TG2: High volume	9	Control group (CG): Home-exercise program consisted of isometric strength knee ext. ex. and knee ROM ex. Not controlled	RCT	PT, instruction in strength training ex. the 1 st wk postop. in TG1 and TG2	TG1=TG2: 5 isometric strength ex.: flex. (2) and ext. (3) and 1 dynamic ext./flex.	3	52	TG1: 1-2 sets, isometric ex.: 5-6 rep., dynamic ex.: max. rep. TG2 slightly higher training volume than TG1 (approx. 50% more rep.). Progressed rep., and sets every 3 rd month. Duration: 30-50 min.	3	Not defined	1RM knee-extension test: TG1>CG from pre to 52 wk postop. (p<0.05). Max. torque: TG2>TG1+CT. Max. RTD: TG2>CT. Both between 6 th and 12 th wk postop. (p<0.05)
Rossi (2005)	USA	72 (5)	50	38	Strength training	N/A	N/A	Observational	PT, supervised	PST targeting lower extremity muscles. Knee ROM, transfer, and stair climbing	3	8	PST: 3 sets, 10 rep. Progressed with 10% if 3x10 rep were performed. After 2 wk, isokinetic training in isokinetic testing system	2	Not defined	Knee-extensor strength: Pre-TKA>post-TKA 30 d, (p<0.002). Post-30 d.<Post 60 d (p<0.002)
Petterson (2009)	USA	66 (9)	62	41	RCT: Strength training and strength training + NMES	41	CT: Standard of care (23 visits)	Cohort comparison	PT, supervised	PST targeting lower extremity muscles, NMES, knee ROM, gait, pain control	2-3	6 (minimum 12 visits)	PST: 2-3 sets, 10 rep. Progressed when 3x10 rep. were performed. Ex. targeting lower limb muscles. NMES: 10 contractions of quadriceps (progressed to the patient's maximum tolerance)	3-4	Not defined in cohort comparison	Knee-extensor strength: RCT>CT (p<0.007), SCT: RCT>CT (p<0.001), TUG: RCT>CT (p<0.004), and 6MWT: RCT>CT (p<0.003) at 12 months postop.
Johnson (2010)	USA	68 (8)	38	11	WBW: Whole-Body Vibration strengthening performed on a WBV platform	10	TPRE: Traditional PST (12 visit)	Pre-test – post-test study	PT, supervised	WBW, stationary cycling, pain and oedema control, and knee ROM.	3	4 (12 visits)	WBT: 2 min. (4 ex., 1 rep. 30 s each) and progressed to 18 min. (6 ex., 3 rep. for 60 s).	3-6	Not defined	Knee-extensor strength and TUG: Post-test>Pre-test (p>0.01). No difference between groups (p=0.66-0.80)
Bade (2011)	USA	65 (12)	63	8	HI: High-intensity strength training	8	CT: Low-intensity strength training (8 wk, 16 visits)	Cohort with a comparable control group	PT, supervised	PST of lower extremity muscles, Balance training, and task-orientated functional training	2-3	12 (25 visits)	PST: 2 sets, 8-10 rep., Progressed if 2x8-10 rep. without fatigue are performed. Balance training: Single-limb stance progression	0 (1 st wk at home)	Stair-climbing test (SCT). Primary analysis 12 wk	SCT: HI>CT (Mean: 5.8 s 95% CI: 1.3-10.4, p = 0.01) at 12 wk

Abbreviations: 6MWT=6-minute walk test, CI=Confidence interval, D=Days, Ex.=Exercise, Ext.=Extension, Flex.=Flexion, Min.=Minutes, N/A=Not Applicable, NMES=Neuromuscular electrical stimulation, PST=Progressive strength training, RCT=Randomized controlled trial, Rep.=Repetitions, ROM=Range of motion, RM=Repetition maximum, RTD=Rate of torque development, S=seconds, SCT=Stair climbing test, TUG=Timed up and go, and Wk=Weeks

2 OBJECTIVES AND HYPOTHESES

The main objective of this PhD thesis was to investigate the feasibility and effect of rehabilitation with PST on functional performance commenced early in patients undergoing fast-track unilateral primary TKA.

2.1 Paper I

Objective

To explore the feasibility of rehabilitation with PST commenced immediately after fast-track TKA.

Hypothesis

Rehabilitation with PST is feasible indicated by progressively increasing absolute training loads with no exacerbation of knee symptoms, such as knee pain and knee joint effusion, after fast-track TKA.

2.2 Paper II

Objective

To assess the intra-tester reliability of the 6MWT in patients early after TKA.

Hypothesis

The 6MWT is reliable with acceptable measurement error to identify a small change of functional performance in a group of patients (research) and in an individual patient (clinical setting) early after TKA.

2.3 Paper III

Objective

To compare 7 weeks of supervised rehabilitation with or without PST commenced early after fast-track TKA on functional performance.

Hypothesis

Seven weeks of supervised rehabilitation with PST is superior to 7 weeks of supervised rehabilitation without PST in improving functional performance commenced early after fast-track TKA.

3 METHODS

In the feasibility study (paper I) and the randomized controlled trial (paper III), patients followed a standardized, optimized fast-track rehabilitation program for unilateral primary TKA at a specialized orthopaedic ward with well-defined discharge criteria at Copenhagen University Hospital, Hvidovre.^{18;112} In the reliability study (paper II), patients were recruited 4-8 weeks post-TKA from various outpatient rehabilitation sites in the Copenhagen area and underwent surgery at different hospitals with unknown perioperative care. Overall inclusion criteria were: (1) age 18 to 80 years (paper II and paper III) but no upper age limit was applied in the feasibility study (paper I), (2) able to understand and speak Danish, (3) resided in counties in the Copenhagen area, and (4) able to participate in rehabilitation with PST early after TKA without having musculoskeletal disorders, that required a special rehabilitation program (paper I and paper III). Exclusion criteria were: (1) alcohol and medicine abuse and (2) experienced knee pain at rest of more than 50 mm on a VAS (paper II). All patients (paper I, II and III) were provided with written information about the procedures of the study and informed consent was obtained in strict accordance with the Declaration of Helsinki. The Research Ethics Committees in the Capital Region of Denmark approved all studies.

3.1 Paper I

Fourteen patients (8 women) having a TKA with mean age of 70 (Standard deviation (SD) 10) years were included by convenience sampling in this explorative study examining the feasibility of early rehabilitation with PST (3 training sessions per week). Patients received rehabilitation with PST starting 1-2 days after surgery and ending 2 weeks after TKA. The principal investigator (Thomas Linding Jakobsen) supervised the rehabilitation and performed all outcome measurements at the outpatient training facility at Copenhagen University Hospital, Hvidovre.

Each rehabilitation session lasted approximately 60 minutes and consisted of gait, active-assisted ROM, balance, stretching, functional task-orientated, and progressive strength exercises. The PST consisted of unilateral (operated leg) knee-extension with ankle weights (Figure 3) and closed chain leg press in training equipment. For each strength training exercise, 2 sets of 10 repetitions with a relative load of 10 RM (repetition maximum) were performed. The absolute training load (kilograms lifted) was adjusted after each set to reflect the intended relative load of 10RM (muscular exhaustion).

Figure 3. Patient performing progressive strength training with ankle weights.



Training load, knee pain and knee joint effusion were recorded at all 6 training sessions, using kilograms lifted, standard mechanical VAS,¹¹³ and knee circumference,^{114;115} respectively. Before the 1st and 6th training session, isometric knee-extension strength and functional performance, were evaluated using a fixed hand-held dynamometer^{116;117} and 10-metre walking test,¹¹⁸ respectively. Additionally, knee joint ROM, PROs and the presence of an intact medial knee joint capsule were assessed, using goniometry,¹¹⁴ KOOS⁶² and Euroqol questionnaire (EQ-5D),¹¹⁹ and clinical and radiographic evaluation.^{120;121} For further details about outcome measures, see paper I.

3.2 Paper II

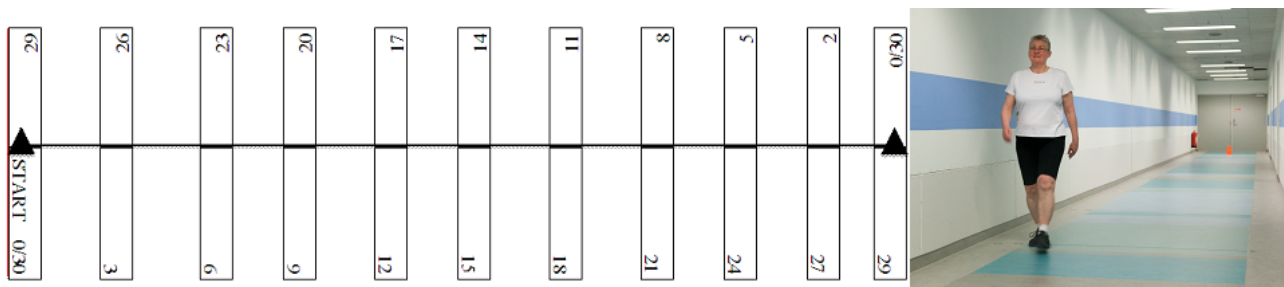
Thirty-four patients (17 women) with a mean age of 66 (SD 8) years were included by convenience sampling into this intra-tester, intra-day reliability study of the performance-based outcome measure, the 6MWT. Patients had undergone TKA surgery 6.2 (SD 1.3) weeks earlier. The assessments were carried out at different training facilities in the Copenhagen area, but each patient's test and retest took place at the same facility.

Patients performed the 6MWT twice the same day separated by a 1-hour seated rest period. Within the week prior to the actual test day, patient were asked to practice walking 6 minutes twice at home to prevent a possible learning effect.^{122;123}

The 6MWT was performed according to guidelines provided by the American Thoracic Society.¹²⁴ In a long corridor, we placed 2 cones 29 m apart with the rationale being that the patients needed 1 metre to turn around the cone to ensure a 30-m-long course (Figure 4). Patients received standardized verbal instructions on how to perform the 6MWT. They were instructed to walk the longest possible distance in 6 minutes without running or jogging (Figure 4). Verbal

encouragements were called out each minute. Patients were allowed to pause during the test trial, but the timer was not stopped. To ensure safety, patients were permitted to use assistive walking aids (e.g. crutches). After 6 minutes, the patients were told to stop promptly, and a piece of tape was placed in front of the tip of the shoes. Subsequently, the total distance walked in 6 minutes was recorded to the nearest centimetre and used in the data analysis. One assessor administered the 6MWT, while another assessor measured and calculated the distance walked during the 6 minutes (assessor blinding).

Figure 4. Patient performing the 6-minute walk test.



3.3 Paper III

Eighty-two patients (52 women) scheduled for a TKA having a mean age of 64 (SD 8) years were included by consecutive sampling in this prospective, randomized controlled trial. Patients were randomly allocated to 2 different interventions: 7 weeks (2 training sessions per week) of supervised rehabilitation with PST (PST-group) or 7 weeks (2 training sessions per week) of supervised rehabilitation without PST (CON-group). Patients were assessed before surgery (baseline), 4, 8 (end of intervention) and 26 weeks postoperatively. The blinded principal investigator (Thomas Linding Jakobsen) assessed all patients at Copenhagen University Hospital, Hvidovre. We attempted to blind patients by not mentioning PST in the information material, and arranging that patients from the 2 different interventions did not meet. The interventions took place at 3 different rehabilitation sites in the counties close to the hospital. Prior to study start, 2 to 3 physiotherapists at each rehabilitation site were thoroughly trained in both interventions. After study start, the principal and senior investigator (Thomas Bandholm) supervised the physiotherapists at least 2 times per year to ensure that the prescribed interventions were executed in the same way at the 3 rehabilitation sites.

Patients were discharge to home approximately 2 days after surgery.¹⁷ They started their intervention as soon as possible at the rehabilitation site. Patients trained alone or with another patient from the same intervention group, with each training session lasting 60 minutes. The PST-group performed warm-up, stretching and ROM exercises, PST, balance training, icing and

elevation of the knee, and functional exercises including gait training, stair climbing, and repeated sit-to-stands from a chair. As in the feasibility study (paper I), the PST exercises were unilateral (operated leg) leg press and knee-extension. At each training session, patients performed 2 sets of each exercise, using relative loads of 12 RM (week 1), 10 RM (week 2-5), and 8 RM (week 6-7). Training load was adjusted after each set to reflect the specific relative load (RM). The CON-group performed the same exercises as the PST-group, but the PST modality was replaced by warming up, ROM exercise, knee-extensor stretches and one-legged balance exercises.

The primary outcome was the maximal distance walked in 6 minutes (6MWT), representing functional performance. The 6MWT was performed twice with a 30-minute pause between test trials. The longest distance walked in 6 minutes was used in the data analysis (see details in paper II).

The secondary outcomes, isometric knee-extension and knee-flexion strength, leg press power, knee pain during walking and at rest, knee joint effusion, active and passive knee ROM, and PROs (KOOS,⁶² Oxford Knee Score,^{63;125} and EQ-5D),^{119;126} were assessed, using a stable strength chair (Good Strength, Metitur Ltd, Jyväskylä, Finland),^{127;128} a leg-extension power rig (Medical Physics and Clinical Engineering Department, Nottingham, United Kingdom),¹²⁹ a standard mechanical VAS,¹¹³ knee joint circumference,^{114;115} and goniometry,^{114;130;131} respectively.

3.4 Statistical analysis

Continuous data were examined for normal distribution using Kolmogorov–Smirnov (paper I and II) or Shapiro-Wilk tests and probability plots (paper III). In all papers, normally-distributed data were expressed as means with single standard deviations (SD) and non normally-distributed data as medians with interquartile ranges (IQR).

In the feasibility study (paper I), repeated measures analysis of variance (ANOVA) with an unstructured analysis investigated the changes of knee pain at rest, knee pain and training load during strength training exercises, and knee joint effusion over the 6 training sessions. The paired Student's t-test investigated the changes in maximal walking speed and isometric knee-extension strength. The percentage increase from the 1st to the 6th training session was used to describe the increases in training load, maximal walking speed, isometric knee- extension strength, and knee ROM.

In the reliability study (paper II), the paired Student's t-test investigated any significant systematic change in the mean of the 2 6MWTs. The intraclass correlation coefficient 2,1 formula ($ICC_{2,1}$) assessed the relative reliability. The acceptable level of the $ICC_{2,1}$ was set at 0.80.¹³² The absolute reliability (measurement error) expresses the variability for individuals of repeated measurements in the actual units recorded (metres). Hence, the standard error of measurement (SEM) was determined by taken the square root of the variance error component from the ANOVA output. The SEM_{95} represents SEM with a 95% confidence interval (CI) calculated by $SEM \times 1.96$. The smallest real difference (SRD_{95}) was calculated from the equation $SEM \times 1.96 \times \sqrt{2}$.¹³³ Additionally, Bland and Altman plotting was applied to provide a visual representation of the results.¹³⁴

In the randomized controlled trial (paper III), the estimated sample size for the primary outcome, 6MWT, was based on the results from the reliability study (paper II), where patients walked approximately 400 metres 6 weeks after their TKA, with a within-subjects SD (SEM) of 13 metres. On average, a 15% longer walking distance (60 meters) in the PST-group compared to the CON-group at the 8-week assessment (end of intervention) was considered the smallest effect worth detecting, using a dropout rate of 10%. Hence, 41 patients per intervention group were needed, assuming 80% power and α (type I error) of 5%.

The primary statistical analysis in the randomized controlled trial (paper III) followed the per-protocol principle. Furthermore, we conducted an intention-to-treat analysis for the primary outcome, using a last observation carried forward-approach.¹³⁵ Our primary analysis for the primary outcome was the change in maximal walking distance in 6 minutes (6MWT) from baseline to the 8-week assessment. The general linear models with analysis of variance (ANOVA) were used to determine between-group differences in change scores for the different time points for the primary and secondary outcomes. Between-group (PST, CON) differences in change scores from baseline to different time points were stated as means with 95% confidence intervals (95% CI). To account for baseline imbalances between the PST- and CON-group, we ran an analysis of covariance (ANCOVA) with adjustment for baseline scores (covariates).¹³⁶ Thus, the between-group difference in change scores for both unadjusted and adjusted baseline scores were reported. An exploratory post-hoc analysis using ANCOVA examined group-differences of change scores from baseline to 8-week assessment of the primary outcome adjusted for rehabilitation site as covariate, was examined.

Data analyses were conducted using SPSS Version 12.0 (SPSS, Inc., Chicago, IL, USA), and Statistical Analysis System Version 9.1 (SAS Institute Inc., Cary, NC, USA). Data in the feasibility

study (paper I) and the reliability study (paper II) were entered and validated in Microsoft Excel XP program (Microsoft Corporation, Redmond, WA, USA). Data in the randomized controlled trial (paper III) were double-entered and validated in Epidata entry 3.1. (Epidata Association, Odense, Denmark). The level of significance was set at 0.05.

4 RESULTS

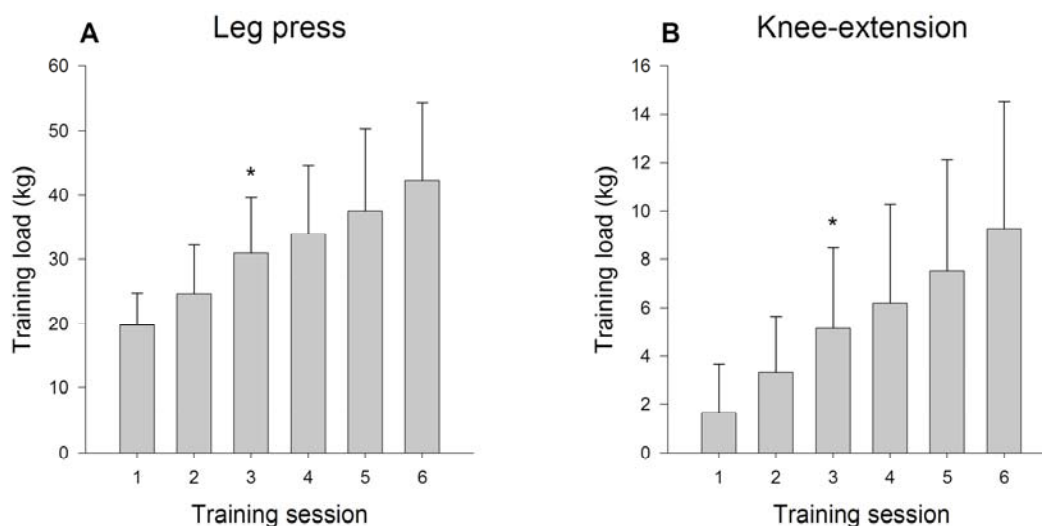
Summary of the main results are presented below. For further details, please see the papers listed.

4.1 Paper I

Progressive strength training (10 RM) commenced immediately after fast-track total knee arthroplasty: Is it feasible?

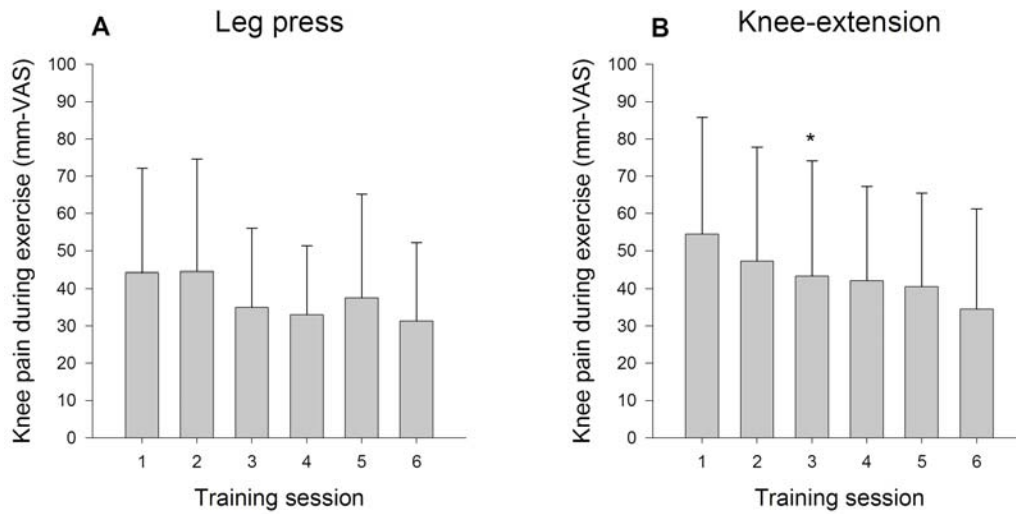
A convenience sample of 16 patients was assessed. Two patients dropped out before the first training session due to postoperative discomfort. As a result, 14 patients were included. The absolute training load for leg press ($P < 0.0001$, Figure 5A) and knee-extension ($P < 0.0001$, Figure 5B) increased progressively. On average, patients experienced mild to moderate knee pain during the strength training exercises. Knee pain was unchanged for leg press ($P < 0.20$, Figure 6A) but decreased significantly for knee extension ($P < 0.03$, Figure 6B) during the 6 training sessions. On average, patients experienced none to mild knee pain at rest pre- and post each training session. Over the 6 training sessions, knee pain at rest was unchanged pre-training session ($P < 0.10$, Figure 7A), while in contrast it decreased significantly post-training session ($P < 0.01$, Figure 7A). Knee joint circumference (knee joint effusion) decreased significantly over the 6 training sessions, which was evident from the 3rd training session ($P < 0.0001$, Figure 7B). From the 1st to the 6th training session, the knee-extension strength and maximal walking speed increased significantly by 147% ($p < 0.0005$) and 112% ($p < 0.003$), respectively.

Figure 5. Absolute training load of (A) leg press and (B) knee-extension over the 6 training sessions.



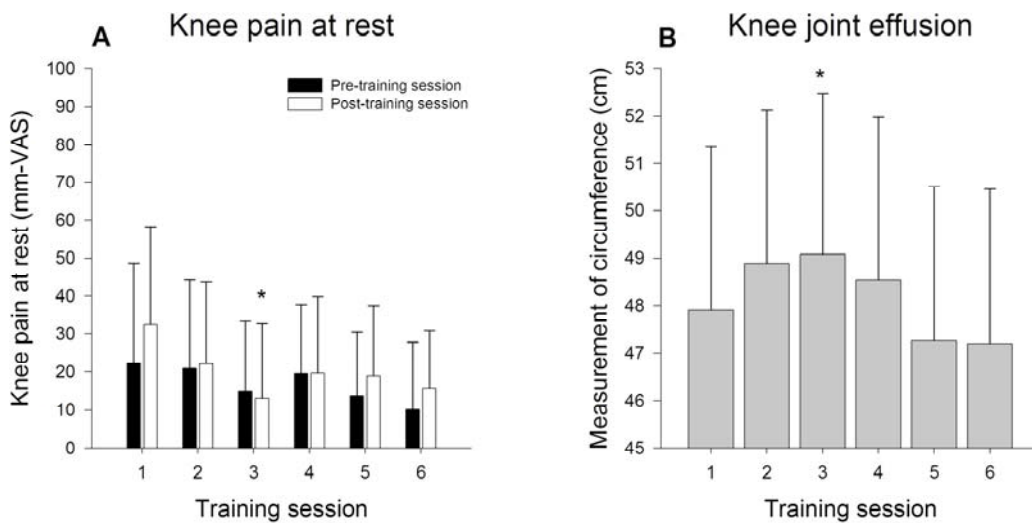
*Systematic change over time (ANOVA main effect) for absolute training load of (A) leg press and (B) knee-extension. From paper I.

Figure 6. Knee pain during (A) leg press and (B) knee-extension over the 6 training sessions.



*Systematic change over time (ANOVA main effect) for knee pain during (B) knee-extension. VAS, Visual Analogue Scale. From paper I.

Figure 7. Knee pain at rest (A) pre- and post-training session and (B) knee joint effusion over the 6 training sessions.



*Systematic change over time (ANOVA main effect) for knee pain at rest (A) post-training session and (B) knee joint effusion. VAS, Visual Analogue Scale. From paper I.

4.2 Paper II

Reliability of the 6-minute walk test after total knee arthroplasty

All patients (n=34) performed both test trials. The 6MWT demonstrated a high relative (ICC) and acceptable absolute reliability, indicating that the test can detect a small real improvement or deterioration in a group of patients (SEM_{95}) or in an individual patient (SRD_{95}) with TKA. On average, patients walked significantly longer during the second (397.2 metres) compared with the first (383.1 metres) test trial. This implied a learning effect (~4%) from the first to the second trial. Results are presented in Table 2 and Figure 8.

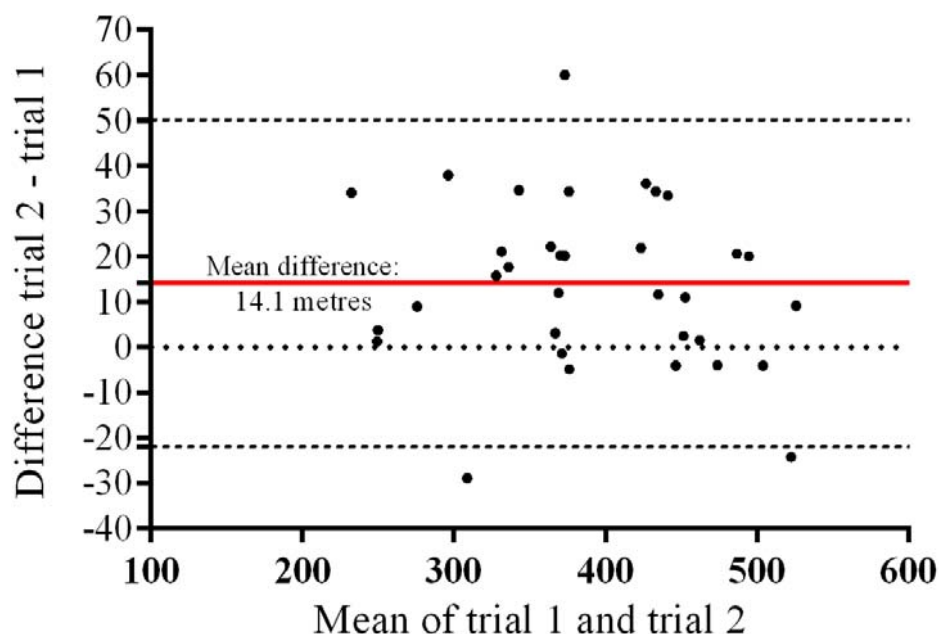
Table 2. The relative (intraclass correlation coefficient) and absolute (standard error of measurement and smallest real difference) intra-tester reliability of the 6-minute walk test (6MWT) in patients with total knee arthroplasty.

	Test (m) [mean \pm 1SD]	Retest (m) [mean \pm 1SD]	Difference \pm 1SD (m)	ICC _{2,1} (LL ₉₅)	SEM (m)	SEM ₉₅ (m)	SRD ₉₅ (m)
6MWT	383.1 \pm 81.9	397.2 \pm 78.6*	14.1 \pm 18.4	0.97 (0.95)	13.0	25.5	36.1

ICC = Intraclass correlation coefficient; LL₉₅ = Lower limit with a 95% confidence interval; SEM = Standard error of measurement; SEM₉₅ = Standard error of measurement with a 95% confidence interval; SRD₉₅ = Smallest real difference with a 95% confidence interval; m = metres.

*Significantly ($p < 0.0001$) different from the first test trial. From paper II.

Figure 8. Bland-Altman plot for the difference of the 2 test trials against the mean of the 2 test trials for each patient. The red line indicates the mean difference between the second and the first test trial (learning effect).



4.3 Paper III

Effect of early rehabilitation with progressive strength training after fast-track total knee arthroplasty: A randomized controlled trial

In this study, 337 patients with TKA were assessed for eligibility. Eighty-two patients were randomized to either the PST-group (n=42) or the CON-group (n=40). We included 72 patients in the primary per-protocol-analysis. In total, ten patients dropped out. Three patients violated the inclusion criteria after randomization but before the start of the intervention, and were therefore excluded from the intention-to-treat analysis (n=79). Patient baseline characteristics were similar in both groups. At the 8-week assessment, patients had attended 14 (IQR: 13-14) and 13 (IQR: 13-14) training sessions in the PST- and CON-group, respectively. Patients started their intervention a median of 7 (IQR: 6-8) days after surgery.

In the primary per-protocol-analysis, there was no significant difference in the 6MWT (primary outcome) between the PST- and CON-group in the mean change score from baseline to the 8-week assessment with unadjusted (-12.1 metres, 95% CI: -46.7 to 22.4; ANOVA, p=0.49) or adjusted baseline scores (-17.2 metres, 95% CI: -49.5 to 15.0; ANCOVA, p=0.29) (Table 3, Figure 9A). Overall, there was no difference between the 2 groups in any of the primary or the secondary outcomes at any time points with unadjusted and adjusted baseline scores (Table 3, Figure 9B). Nevertheless, we found a few trends for a few of the secondary outcomes, but the magnitudes of the differences were considered small. Our intention-to-treat analysis concurred with our primary per-protocol-analysis showing no difference between groups in the 6MWT. Additionally, no significant difference was found at baseline between the patients who did (n=72) and did not (n=7) receive the intervention. In the exploratory post-hoc analysis, no between-group differences were found for change scores from baseline to the 8-week assessment for the primary outcome when adjusted for rehabilitation site (covariate) (-12.1 metres, -46.9 to 22.8; ANCOVA, p=0.49).

Two adverse events occurred during the interventions, and, consequently, patients withdrew from the study. One patient had an episode of angina pectoris during the leg press exercise in the PST-group. One patient felt low back pain after the first training session in the CON-group.

For further details concerning patient flow through the stages of the study (CONSORT diagram), baseline characteristics, and primary and secondary outcome measures for all time points, see paper III.

Figure 9. Values for each patient (solid and dashed lines) as well as mean values for the 2 groups (bold lines) over time for the 6-minute walk test (A) and knee-extension strength (B). Whiskers are 95% confidence intervals. From paper III.

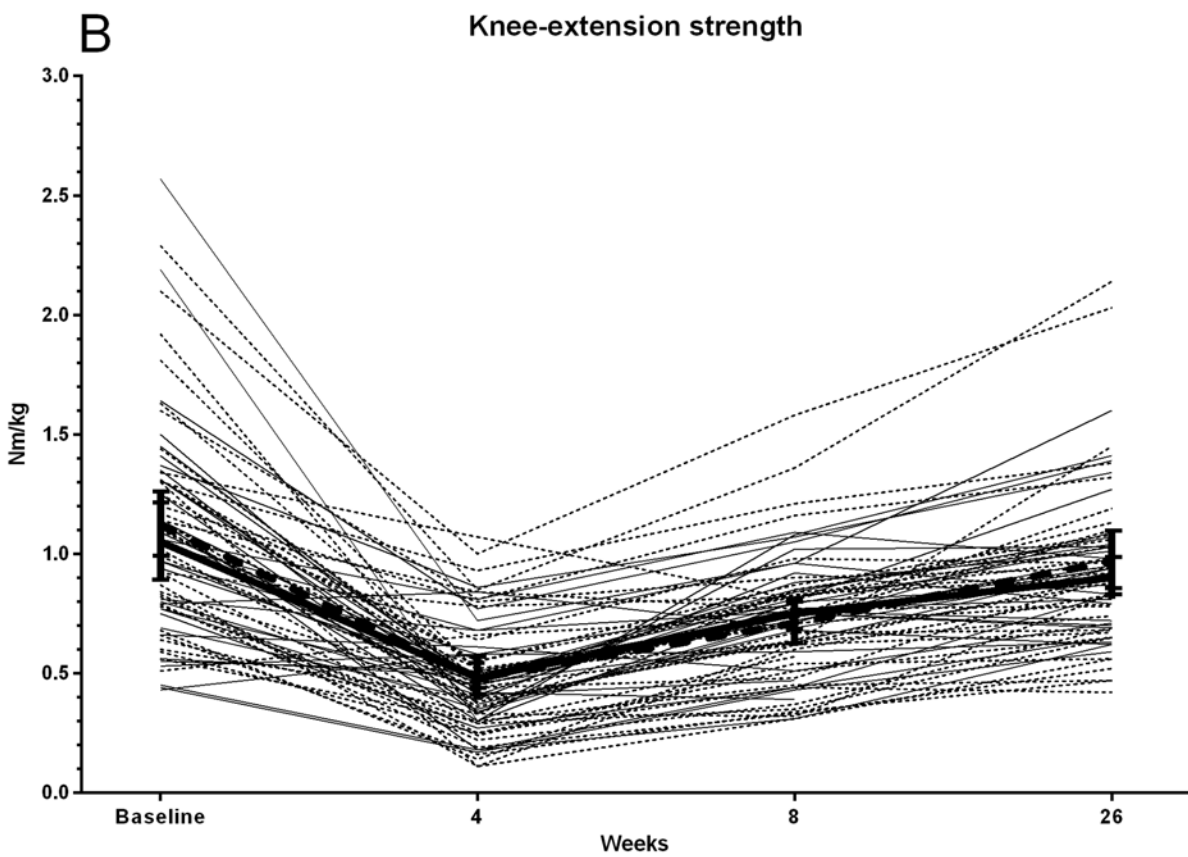
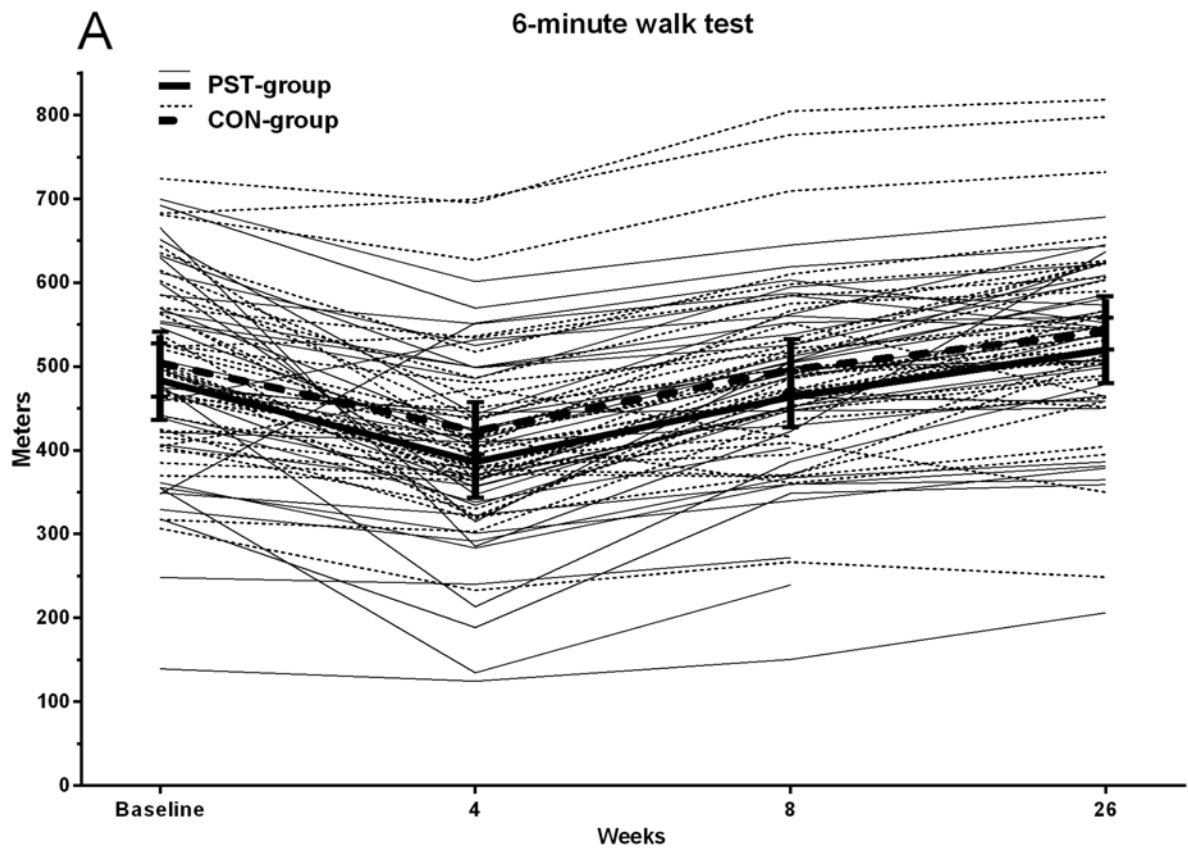


Table 3. Treatment effect. Group-differences of change scores from baseline to the 4-, 8- and 26-week assessments with unadjusted (Un) and adjusted (Ad) baseline scores. From paper III.

From baseline to							
Assessment		4-week	p value	8-week	p value	26-week	p value
6-minute walk test (metres)	Un	-16.2 (-58.6 to 26.1)	0.45	-12.1 (-46.7 to 22.4)	0.49	-13.0 (-44.8 to 17.9)	0.40
6-minute walk test (metres)	Ad	-23.2 (-61.8 to 15.3)	0.23	-17.2 (-49.5 to 15.0)	0.29	-15 (-44 to 14)	0.31
Knee-extension strength (Nm/kg)	Un	0.08 (-0.12 to 0.28)	0.45	0.10 (-0.07 to 0.26)†	0.25	0.05 (-0.10 to 0.22)	0.52
Knee-extension strength (Nm/kg)	Ad	0.02 (-0.08 to 0.12)	0.71	0.06 (-0.03 to 0.16)†	0.20	0.03 (-0.08 to 0.14)	0.63
Knee-flexion strength (Nm/kg)	Un	-0.03 (-0.13 to 0.06)	0.46	-0.00 (-0.09 to 0.09)	0.98	-0.02 (-0.10 to 0.06)	0.63
Knee-flexion strength (Nm/kg)	Ad	-0.05 (-0.12 to 0.02)	0.17	-0.01 (-0.09 to 0.06)	0.69	-0.03 (-0.10 to 0.04)	0.42
Leg-press power (Watt/kg)	Un	-0.07 (-0.34 to 0.21)	0.63	0.02 (-0.21 to 0.24)	0.89	-0.08 (-0.30 to 0.13)	0.44
Leg-press power (Watt/kg)	Ad	-0.07 (-0.23 to 0.10)	0.41	0.02 (-0.16 to 0.19)	0.86	-0.07 (-0.26 to 0.13)	0.51
KOOS subscales							
Symptoms	Un	-2 (-11 to 8)	0.73	-1 (-11 to 9)	0.81	-9 (-19 to 2)	0.13
Symptoms	Ad	-3 (-9 to 4)	0.40	-2 (-9 to 5)	0.55	-8 (-16 to 0)	0.05
Pain	Un	2 (-7 to 10)	0.71	1 (-9 to 10)	0.91	-5 (-14 to 4)	0.32
Pain	Ad	2 (-5 to 9)	0.65	1 (-7 to 8)	0.88	-4 (-11 to 3)	0.30
Activity of daily living	Un	1 (-6 to 9)	0.70	1 (-7 to 9)	0.73	1 (-7 to 9)	0.85
Activity of daily living	Ad	-2 (-9 to 4)	0.51	-3 (-9 to 3)	0.30	3 (-10 to 3)	0.33
Sport/recreation	Un	-3 (-13 to 7)	0.54	-3 (-14 to 8)	0.56	-14 (-26 to -2)	0.02
Sport/recreation	Ad	-4 (-13 to 4)	0.30	-4 (-14 to 5)	0.38	-14 (-25 to -3)	0.02
Quality of life	Un	2 (-6 to 10)	0.63	3 (-6 to 13)	0.46	-4 (-14 to 6)	0.44
Quality of life	Ad	-0 (-7 to 7)	0.98	1 (-7 to 9)	0.82	-5 (-15 to 4)	0.26
Oxford knee score	Un	0 (-4 to 4)	0.92	1 (-3 to 4)	0.79	-3 (-7 to 1)	0.12
Oxford knee score	Ad	-1 (-4 to 3)	0.70	0 (-3 to 3)	0.93	-3 (-7 to 0)	0.06
EQ-5D	Un	0.03 (-0.07 to 0.12)	0.55	-0.01 (-0.10 to 0.08)	0.82	-0.04 (-0.13 to 0.06)	0.43
EQ-5D	Ad	0.03 (-0.05 to 0.11)	0.48	-0.01 (-0.08 to 0.06)	0.79	-0.04 (-0.11 to 0.03)	0.27
Knee pain during walking (mm)	Un	1 (-11 to 13)	0.92	4 (-8 to 16)	0.52	8 (-4 to 19)	0.20
Knee pain during walking (mm)	Ad	-7 (-14 to -0)	0.05	-4 (-12 to 4)	0.37	-2 (-10 to 6)	0.65
Knee pain at rest (mm)	Un	0 (-6 to 6)	0.99	2 (-2 to 6)	0.35	2 (-2 to 6)	0.25
Knee pain at rest (mm)	Ad	-2 (-7 to 4)	0.58	0 (-3 to 3)	0.98	-0 (-1 to 1)	0.85
Knee joint effusion (cm)	Un	-0.2 (-1.2 to 0.8)	0.71	0.1 (-0.6 to 0.7)	0.88	0.4 (-0.6 to 1.4)	0.46
Knee joint effusion (cm)	Ad	0.1 (-0.9 to 1.0)	0.91	0.2 (-0.5 to 0.8)	0.58	0.7 (-0.3 to 1.6)	0.15
Knee AROM flexion (degrees)	Un	-4 (-11 to 3)	0.26	-4 (-11 to 4)	0.33	-6 (-12 to 1)	0.09
Knee AROM flexion (degrees)	Ad	-5 (-11 to 1)	0.08	-5 (-11 to 1)	0.12	-7 (-13 to -2)	0.01
Knee PROM flexion (degrees)	Un	-7 (-14 to 1)	0.09	-5 (-13 to 3)	0.20	-6 (-13 to 2)	0.12
Knee PROM flexion (degrees)	Ad	-7 (-13 to -0)	0.04	-5 (-12 to 1)	0.11	-6 (-12 to -0)	0.04
Knee AROM extension (degrees)	Un	5 (1 to 8)	0.01	3 (-1 to 6)	0.11	4 (0 to 7)	0.04
Knee AROM extension (degrees)	Ad	3 (1 to 6)	0.02	2 (-2 to 5)	0.31	3 (-0 to 6)	0.07
Knee PROM extension (degrees)	Un	5 (2 to 8)	0.00	3 (-1 to 6)	0.12	4 (1 to 8)	0.02
Knee PROM extension (degrees)	Ad	4 (1 to 7)	0.02	1 (-2 to 4)	0.43	3 (-0 to 6)	0.08

Values are means (95% confidence intervals). KOOS=Knee injury and osteoarthritis outcome score; EQ-5D=Euroqol questionnaire; AROM=Active range of motion; PROM=Passive range of motion; Nm/kg=Normalized torque.

Positive scores (and negative knee pain scores, knee joint effusion, and ROM extension) indicate positive treatment effect in favour of the PST-group. Negative scores (and positive knee pain scores, knee joint effusion, and ROM extension) indicate scores positive treatment effect in favour of the CON-group. †=one missed recording.

5 DISCUSSION

This PhD thesis investigated the feasibility (paper I) and effect of rehabilitation with PST (paper III) commenced early after fast-track TKA. Additionally, the reliability of the 6MWT, which was used as the primary outcome in the randomized controlled trial (paper III), was assessed in patients with early TKA (paper II).

5.1 Key findings

The key findings of this PhD thesis were:

- Rehabilitation with PST commenced as early as 1 to 2 days after TKA seems feasible indicated by increased training loads without exacerbating early postoperative knee symptoms such as knee pain and knee joint effusion (paper I). These findings were later confirmed in paper III.
- The 6MWT showed high relative intra-tester reliability with a small measurement error (acceptable absolute reliability). The 6MWT is able to detect a change of more than 25.5 metres in a group of patients (research) and 36.1 metres in an individual patient (clinical setting) after TKA. A learning effect was observed. As a consequence, we recommend that the greatest distance of 2 6MWTs should be used (paper II).
- Seven weeks of supervised rehabilitation with PST (2 training sessions per week) was not superior to 7 weeks of supervised rehabilitation without PST (2 training sessions per week) in improving functional performance (6MWT) commenced early after fast-track TKA (paper III). None of the secondary outcomes (knee-extension and knee-flexion strength, leg press power, knee pain, knee joint effusion, knee joint ROM and PROs) showed any significant or clinically relevant differences between groups at any time point. Knee-extension strength did not reach the pre-surgery values observed at any time point.

5.2 Feasibility

A feasibility study is often carried out prior to a main study. This is done to assess important parameters that are needed to design the main study.¹³⁷ These include, for example, piloting of recruitment rate, allocation procedure and intervention. We conducted a feasibility study to indicate whether PST commenced early after TKA would increase knee symptoms such as knee pain and knee joint effusion (paper I). This was done in an attempt to indicate proof of concept for the subsequent confirmatory randomized controlled trial investigating rehabilitation with PST commenced early after TKA (paper III).

The concern was that implementation of early PST after TKA would increase knee joint effusion and knee pain, in addition to delaying recovery of knee joint ROM.^{23;108} However, that seems not to be the case. Our results are in line with data from other studies.^{29;30} We found that the patients experienced moderate knee pain during the strength training exercises (10RM), but resting knee pain was none to mild before and after each training session, suggesting that such exercises and training loads may be tolerated. Furthermore, these findings are supported by data from the randomized controlled trial (paper III), where none of the secondary outcomes, knee pain at rest and during walking, knee joint ROM, and knee joint effusion, differed significantly or clinically relevant between the PST- and CON-groups at any time point.

In the feasibility study (paper I), we found a large increase in knee-extension strength and maximal walking speed during the first 5 training sessions. These results are supported by preliminary evidence investigating PST that demonstrated an improvement in muscle strength and functional performance within the first 3 months after TKA.^{26;29;30;81;109} Similar improvements have been reported in studies examining PST in patients with total hip arthroplasty^{104;105} and in older adults.¹⁰⁷ The improvement in knee-extension strength and functional performance may be attributable to the content of the PST modality that followed the principles of PST in which patients perform small number of repetitions (8-12) until failure and training loads are increased on a set-by-set basis, as the ability to generate force increases.^{102;103;106} Additionally, the 2 strength training exercises, knee-extension and leg-press, were chosen to restore quadriceps muscle strength, as a substantial loss of knee-extension strength is well-described,^{27;28;33;34} and is related to reduced functional performance after TKA.²⁶⁻²⁸ The seated knee-extension exercise targets the quadriceps muscle specifically,¹³⁸ and performing knee-extensions to failure increases neural activation of the quadriceps muscle during the set in healthy subjects.^{139;140} The leg press exercise involves the activation of several other lower leg muscles with reported strength deficits following TKA⁴⁰ in addition to activating the quadriceps muscle,¹⁴¹ and relates to functional performance early after TKA.¹⁴² With the proof of concept supporting rehabilitation with PST initiated early after TKA (paper I), we planned a confirmatory randomized controlled trial (paper III).

5.3 Reliability of the 6-minute walk test

For the confirmatory randomized controlled study, the 6MWT was selected as the primary outcome to compare rehabilitation with and without PST early after TKA. The arguments were that, firstly, a functional performance-based test (such as the 6MWT) would be more suitable to capture an actual change in functional performance than PROs early after TKA.⁷⁰ Secondly, the 6MWT has been recommended,⁵⁷ commonly used,^{26;27;33;80} and responsive to change over time in the first 4 months

after TKA.^{143;144} As the 6MWT did not possess the necessary psychometric properties such as population-specific reliability, we assessed the intra-tester reliability of the test (paper II) prior to the initiation of the randomized controlled trial (paper III).

We found a high relative intra-tester reliability of the 6MWT after TKA, which is in concordance with that reported in patients with knee osteoarthritis.^{145;146} More importantly, we found a small measurement error (SEM=13.0 metres) that is approximately half of that reported in patients with knee osteoarthritis (SEM=26.3 metres).¹⁴⁶ This indicates that the 6MWT is able to identify small real changes at both individual (clinical setting) and group (research) levels. Even though we encouraged the patients to perform 2 practice trials at home, patients walked significantly longer in the second compared with the first test trial, indicating a learning effect (~4%). Both the presence¹⁴⁵ and absence¹⁴⁶ of a learning effect for the 6MWT has been reported in patients with knee osteoarthritis. The absence of a learning effect may be due to a long time interval between first and second test trials.¹⁴⁷ Still, it is of some concern, as most patients will improve a little, simply by performing the test twice. As a consequence, we recommend patients with TKA to perform 2 6MWTs, with the longest distance walked from the 2 trials used. This approach was subsequently used in the randomized controlled trial (paper III).

5.4 Progressive strength training - explanation of results

Given that the 6MWT has been shown to be both reliable (paper II) and responsive in patients following TKA,^{143;144} one has to consider if the strength training modality provided in the PST-group in the randomized controlled trial (paper III) was designed in a way that elicited the desired physiological response. This is especially an issue, as knee-extension strength was not different between groups, despite the specific targeting of the quadriceps muscle. With this in mind, we still believe that the PST-group program had a high degree of what has lately been termed therapeutic validity.¹⁴⁸ That is, the content of the exercise intervention is based on the latest research and directed to the population of interest. As discussed earlier, the strength training exercises seem justifiable by the encouraging results from the feasibility study (paper I) and the rationale for the choice of the exercises. Furthermore, intensive rehabilitation with PST commenced early after TKA has been recommended,^{3;29;30;79} as it seems a reasonable choice when aiming to enhance functional recovery following TKA. Additionally, similar PST programs performed twice per week have been found effective in increasing muscle strength and functional performance in a population with TKA²⁶ and in older adults.^{107;149} Pertaining to the notion above, rehabilitation with functional or strengthening exercises instituted 4-8 weeks following surgery should be superior in improving functional performance, compared to a control treatment of rehabilitation not including PST.^{26;80}

However, these two studies did not use a well-described treatment control^{26;80} or the control treatment was not randomized.²⁶

So at present, the best explanation for the lack of effect of the PST-group program is that effective strengthening was prevented to some degree by arthrogenic inhibition of the quadriceps muscle following surgery, hereby reducing the normal physiological response to this type of exercise.³⁵ This possible limiting factor is termed arthrogenic muscle inhibition (AMI) and has previously been assessed in patients early after TKA, using the superimposition technique.^{23;26;36} The mechanisms underlying AMI following TKA are still unclear and therefore need further investigation (see Future perspectives).

5.5 Methodological considerations and limitations

In the feasibility study (paper I), there are a few precautions that should be taken when interpreting the results. Firstly, the sample size (n=14) was small, as the study was designed as a feasibility study. Secondly, the same unblinded physiotherapist supervised all training sessions and performed all measurements. To avoid recall bias, measurement results were written down by an assistant and kept inaccessible until the study was completed. Finally, consumption of oral analgesia was not controlled for or monitored.

In the reliability study of the 6MWT (paper II), we did not observe or record whether the patients actually performed the suggested 2 practice trials at home. As we found a small learning effect, practice trials or familiarization sessions should be considered, before valid trials are recorded.

In the randomized controlled trial (paper III), the involved physiotherapists were impossible to blind, as they were an integral part of the intervention.¹¹⁰ However, we made every effort to blind patients by (1) letting them know that we investigated 2 different rehabilitation programs only (and not the content of the 2 intervention programs), and (2) separating the 2 groups, as they trained at different times of the day. The patients trained with different physiotherapists at 3 different rehabilitation sites, which may have increased the risk of inequality of execution of the interventions¹⁵⁰, but, on the other hand, strengthened the generalizability of the results. We tried to avoid this potential inequality by involving the physiotherapists in the planning of the intervention programs, and with regular visits by the principal and senior investigators. Additionally, we performed an exploratory post-hoc analysis that showed that rehabilitation site was not a confounder. Many results of secondary outcomes and time points are presented. We acknowledge that the study was powered to detect a pre-specified difference in the maximal walking distance

(6MWT) at the end of the intervention period only. All secondary analyses were considered exploratory. Finally, this study does not rule out that rehabilitation with PST provided in a different dose (e.g. number of training sessions per week, number of sets per session, or duration of intervention) may be superior to rehabilitation without PST in improving functional performance following TKA.

5.6 Adverse events

In the feasibility study (paper I), no adverse events were recorded related to the rehabilitation with PST. This finding was consolidated further by the indication of an intact medial capsule in all patients assessed by radiographic and clinical evaluation. This was taken to suggest that initiation of early PST did not damage the medial stabilizing soft tissues of the knee. In the reliability study (paper II), no adverse events were recorded. In the randomized controlled study (paper III), 2 patients (3%) (one in each group) withdrew from their treatment due to discomfort. Five patients (7%) had additional knee surgery due to severe knee stiffness (3 in the PST-group and 2 in the CON-group), but seemed unrelated to the interventions provided.

6 CONCLUSION

This PhD thesis provides evidence that:

- (1) In the feasibility study (paper I), rehabilitation with PST commenced as early as 1 to 2 days after TKA seems feasible, indicated by an increase in training loads without exacerbating knee symptoms. These findings were later verified in the randomized controlled trial (paper III).
- (2) In the reliability study (paper II), the 6MWT showed a high relative intra-tester reliability with a small measurement error (acceptable absolute reliability) in patients with early TKA. The 6MWT is able to detect a real small change in a group of patients (research) and in an individual patient (clinical setting) after early TKA.
- (3) In the randomized controlled study (paper III), 7 weeks of supervised rehabilitation with PST was not superior to 7 weeks of supervised rehabilitation without PST in improving functional performance (6MWT) commenced 1 week after fast-track TKA. The secondary outcome, knee-extension strength did not reach the levels recorded before surgery.

7 FUTURE PERSPECTIVES

Based on the findings reported in paper I and III, the reluctance of early commencement of PST after TKA among clinicians and researchers seems to be unjustified and based on traditional beliefs rather than research. We believe that PST can be implemented early after TKA.

The loss of knee-extension strength in the PST-group (paper III) indicates that AMI to some degree is a barrier to effective PST early after TKA. The mechanisms behind AMI after TKA are not clearly understood. After TKA, a combination of knee joint effusion, inflammation, joint laxity, and damage to articular sensory receptors can be found. These clinical features likely alter the afferent discharge from the damaged joint, which affects the central nervous system by changing the excitability of multiple spinal and supraspinal pathways, and thereby prevents the full activation of the quadriceps muscle.³⁵ These aspects call for further research into the understanding of the neural mechanism underlying AMI. Possible treatments (such as PST¹⁵¹ or preoperative glucocorticoids^{35;152}) can then be evaluated.³⁵

We found that 7 weeks of supervised rehabilitation with PST was not superior to 7 weeks of supervised rehabilitation without PST in any of our outcome measures (paper III). Whether another “dose” or another content of the PST program would elicit a greater effect on knee-extension strength and functional performance after early TKA remains unanswered. Thus, dose-finding studies (e.g. duration of rehabilitation, number of training sessions per week, sets per exercise, number of exercises) are warranted to define the most effective PST program to overcome the surgically induced impairment of muscle strength and functional performance after TKA. Furthermore, the characteristics of the patients that may benefit from PST should be identified to help clinicians and researchers in targeting this rehabilitation modality better after TKA (stratified medicine).

The 6MWT was reliable with acceptable measurement error early after TKA. This provides researchers and clinicians with a cost-effective and easy-to-use functional performance-based test that can detect small changes in functional performance over time early after TKA. Hereby, the 6MWT should be a possible choice as a primary outcome in research investigating functional performance after TKA, and enables comparisons of data between studies.

8 SUMMARY

Progressive strength training commenced early after fast-track total knee arthroplasty: feasibility and effect

Total knee arthroplasty (TKA) is a common performed orthopaedic procedure to alleviate knee pain and disability related to end-stage knee osteoarthritis. Early after TKA, patients experience a pronounced loss of muscle strength and functional performance that seldom reaches the levels of age-matched healthy adults. Therefore, rehabilitation with progressive strength training (PST) commenced early after fast-track TKA may be rational to rapidly enhance postoperative recovery.

The main objectives of this PhD thesis were to (1) explore the feasibility of rehabilitation with PST commenced 1-2 days after fast-track TKA (paper I), (2) assess the intra-tester reliability of the functional performance-based outcome measure, 6-minute walk test (6MWT), early after TKA (paper II), and (3) compare 7 weeks of supervised rehabilitation with (PST-group) or without PST (CON-group) commenced early after fast-track TKA on functional performance (6MWT) (paper III).

Fourteen patients with TKA were included by convenience sampling in this explorative study examining the feasibility of early rehabilitation with PST (3 training sessions per week) (paper I). Patients received rehabilitation with PST starting 1-2 days after surgery and ending 2 weeks after fast-track TKA. The principal investigator supervised the rehabilitation and performed all outcome measurements. Rehabilitation with PST commenced early seems feasible indicated by increased absolute training loads without exacerbating knee symptoms such as knee pain and knee joint effusion. Additionally, we found a significant increase in knee-extension strength and maximal walking speed by 147% and 112%, respectively. The feasibility of early commenced rehabilitation with PST was later confirmed by the results from the randomized controlled trial (paper III), where none of the secondary outcomes, knee joint effusion, knee joint range of motion (ROM), knee pain at rest and during walking, showed any significant or clinically relevant differences between the PST- and CON-groups at any time point.

Thirty-four patients were included by convenience sampling into this intra-tester, intra-day reliability study of the functional performance-based outcome measure, the 6MWT, approximately 6 weeks after TKA (paper II). Patients performed the 6MWT twice the same day separated by a 1-hour seated rest period. The 6MWT was performed according to guidelines provided by the American Thoracic Society. The 6MWT showed high relative intra-tester reliability with a small

measurement error (acceptable absolute reliability). The 6MWT is able to detect a real improvement or deterioration of more than 25.5 metres in a group of patients (research) and 36.1 metres in an individual patient (clinical setting) early after TKA. A learning effect was observed. Therefore, we recommend that the greatest distance of 2 6MWTs should be used.

Eighty-two patients were included by consecutive sampling in this prospective, single-blinded randomized controlled trial after fast-track TKA (paper III). Patients were randomly allocated to 7 weeks (2 training sessions per week) of supervised rehabilitation with (PST-group) or without PST (CON-group) commenced early after fast-track TKA. Patients were assessed before surgery (baseline), 4, 8 (end of intervention) and 26 weeks postoperatively. The PST-group was not superior to the CON-group in improving functional performance (6MWT) commenced 1 week after fast-track TKA. None of the secondary outcomes, knee-extension and knee-flexion strength, leg press power, knee pain at rest and during walking, knee joint effusion, knee joint ROM, and patient-reported outcomes, showed any significant or clinically relevant differences between the 2 groups at any time point (4, 8 and 26 weeks). Knee-extension strength values did not reach the levels recorded before surgery.

In conclusion, rehabilitation with PST as early as 1 to 2 days after fast-track TKA seems feasible indicated by increased training loads without exacerbating knee-symptoms such as knee pain and knee joint effusion. The 6MWT showed high intra-tester reliability with a small measurement error, which indicates that the test is able to detect small real changes in a group of patients and in an individual patient after early TKA. Seven weeks of supervised rehabilitation with PST was not superior to 7 weeks of supervised rehabilitation without PST commenced 1 week after fast-track TKA in improving functional performance (6MWT). Knee-extension strength did not reach the pre-surgery values observed at any time point. The best explanation for the lack of effect of the PST-group program is that effective strengthening was partly prevented by arthrogenic inhibition of the quadriceps early after TKA.

9 RESUME (DANISH SUMMARY)

Tidlig progressiv styrketræning efter fast-track total knæalloplastik: Gennemførlighed og effekt

Indsættelse af total knæalloplastik (TKA) er en almindelig ortopædkirurgisk procedure, der skal afhjælpe knæsmærter og forbedre funktionsniveauet hos personer med slidgigt (artrose) i knæet. Efter indsættelse af TKA oplever patienterne et markant tab af muskelstyrke og fysisk funktionsevne, der sjældent når det samme niveau som hos sammenlignelige raske voksne. Derfor vil genoptræning inklusiv progressiv styrketræning (PST) iværksat tidligt efter fast-track TKA være et logisk valg til en hurtig tilbagevenden til et højt funktionsniveau efter en TKA operation.

Hovedformålene med denne PhD-afhandling var at (1) undersøge gennemførligheden af genoptræning med PST med opstart af træning 1 til 2 dage efter fast-track TKA (artikel I), (2) bestemme intratester (samme tester) reliabiliteten af funktionstesten, 6-minutters gangtest (6MWT), tidligt efter TKA (artikel II), (3) sammenligne superviseret 7 ugers genoptræning med (PST-gruppen) eller uden PST (CON-gruppen) iværksat tidligt efter fast-track TKA målt på fysisk funktionsevne (6MWT) (artikel III).

Fjorten patienter med TKA blev inkluderet tilfældigt i dette eksplorative studie, som undersøgte gennemførligheden af tidlig genoptræning med PST (3 gange ugentligt) (artikel I). Patienterne startede deres genoptræning 1 til 2 dage efter operationen og sluttede efter 2 uger. Den projektansvarlige superviserede genoptræningen og udførte alle målingerne. Genoptræning med PST ser ud til at være gennemførlig umiddelbart efter operationen, da den absolutte træningsbelastning steg uden, at patienter oplevede forværring af knæledssymptomer som knæsmærter og knæledshvævelse. Derudover fandt vi en stigning af knæekstensionsstyrken og den maksimale ganghastighed på henholdsvis 147% og 122%. Gennemførligheden af tidligt iværksat genoptræning med PST blev senere bekræftet af vores resultater fra det randomiserede kontrolleret forsøg (artikel III), som viste ingen signifikante eller kliniske relevante forskelle i knæledshvævelse og knæsmærter i hvile og under gang mellem PST- og CON-gruppen.

Fireogtredive patienter med TKA blev inkluderet tilfældigt i et intratester reliabilitetsforsøg af funktionstesten, 6MWT, ca. 6 uger efter operationen (artikel II). Patienterne udførte testen 2 gange den samme dag med 1 times siddende pause imellem testforsøg. Udførelsen af 6MWT fulgte retningslinjerne udstukket af American Thoracic Society. 6MWT viste en høj relativ intratester reliabilitet med en lille målefejl (acceptabel absolut reliabilitet). Derved kan 6MWT registrere en reel forværring eller forbedring på mere en henholdsvis 25,5 meter i en gruppe af patienter og 36,1

meter hos den enkelte patient tidligt efter en TKA operation. En læringseffekt blev observeret. Derfor anbefaler vi, at den længste gangdistance opnået i 2 6MWTs bliver anvendt.

Toogfirs patienter blev inkluderet fortløbende i et prospektivt enkelt-blindet randomiseret kontrolleret forsøg efter fast-track TKA (artikel III). Patienterne blev tilfældigt fordelt til henholdsvis 7 ugers (2 gange ugentligt) superviseret genoptræning med (PST-gruppen) eller uden PST (CON-gruppen) iværksat tidligt efter fast-track TKA. Patienterne blev undersøgt før kirurgi (baseline), 4, 8 (efter interventionen) og 26 uger efter TKA operationen. PST-gruppen viste sig ikke bedre end CON-gruppen til at forbedre den fysiske funktionsevne (6MWT) iværksat 1 uge efter fast-track TKA. Ingen af de sekundære effektmål, knæekstensjons- og fleksionsstyrke, benpresstyrke, aktivitets- og hvilesmerter, knæledshævelse, knæledsbevægelighed, samt patient-rapporteret knæfunktion og helbred, viste signifikante eller klinisk relevante forskelle mellem de 2 grupper på noget undersøgelsestidspunkt (4, 8 eller 26 uger) efter operationen. Patienternes knæekstensjonsstyrke opnåede ikke samme styrke som før operationen.

Konklusivt ser det ud til, at genoptræning med PST iværksat 1 til 2 dage efter fast-track TKA kan gennemføres med stigende træningsbelastning uden forværring af knæledssymptomer. 6MWT viste høj intratester reliabilitet med en lille målefejl. Herved kan 6MWT registrere en lille reel ændring i en gruppe af patienter og hos den enkelte patient tidligt efter en TKA operation. Syv ugers superviseret træning med PST viste ikke en forbedring i den fysiske funktionsevne (6MWT) i forhold til 7 ugers superviseret genoptræning uden PST iværksat 1 uge efter fast-track TKA. Den bedste forklaring på den manglende effekt af PST er, at effektiv styrkelse af quadriceps musklen bliver delvist forhindret af artrogen muskel-inhibition tidligt efter TKA.

10 REFERENCES

- (1) Carr AJ, Robertsson O, Graves S, Price AJ, Arden NK, Judge A, Beard DJ. Knee replacement. *Lancet* 2012; 379(9823):1331-1340.
- (2) Pedersen AB, Mehnert F, Odgaard A, Schroder HM. Existing data sources for clinical epidemiology: The Danish Knee Arthroplasty Register. *Clin Epidemiol* 2012; 4:125-135.
- (3) Bade MJ, Stevens-Lapsley JE. Restoration of physical function in patients following total knee arthroplasty: an update on rehabilitation practices. *Curr Opin Rheumatol* 2012; 24(2):208-214.
- (4) Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am* 2007; 89(4):780-785.
- (5) Arden N, Nevitt MC. Osteoarthritis: epidemiology. *Best Pract Res Clin Rheumatol* 2006; 20(1):3-25.
- (6) Leopold SS. Minimally invasive total knee arthroplasty for osteoarthritis. *N Engl J Med* 2009; 360(17):1749-1758.
- (7) Husted H, Otte KS, Kristensen BB, Orsnes T, Kehlet H. Readmissions after fast-track hip and knee arthroplasty. *Arch Orthop Trauma Surg* 2010; 130(9):1185-1191.
- (8) Jørgensen CC, Kehlet H. Role of patient characteristics for fast-track hip and knee arthroplasty. *Br J Anaesth* 2013; 110(6):972-980.
- (9) Fitzsimmons SE, Vazquez EA, Bronson MJ. How to treat the stiff total knee arthroplasty?: a systematic review. *Clin Orthop Relat Res* 2010; 468(4):1096-1106.
- (10) Bourne RB, Chesworth BM, Davis AM, Mahomed NN, Charron KD. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? *Clin Orthop Relat Res* 2010; 468(1):57-63.
- (11) Lingard EA, Sledge CB, Learmonth ID. Patient expectations regarding total knee arthroplasty: differences among the United States, United kingdom, and Australia. *J Bone Joint Surg Am* 2006; 88(6):1201-1207.

- (12) Robertsson O, Dunbar M, Pehrsson T, Knutson K, Lidgren L. Patient satisfaction after knee arthroplasty: a report on 27,372 knees operated on between 1981 and 1995 in Sweden. *Acta Orthop Scand* 2000; 71(3):262-267.
- (13) Kehlet H. Fast-track hip and knee arthroplasty. *Lancet* 2013; 381(9878):1600-1602.
- (14) Husted H. Fast-track hip and knee arthroplasty: clinical and organizational aspects. *Acta Orthop Suppl* 2012; 83(346):1-39.
- (15) Møiniche S, Hansen BL, Dahl JB, Kehlet H. [Patients' activity and length of stay after hip arthroplasty with balanced analgesia and early mobilization]. *Ugeskr Laeger* 1992; 154(21):1495-1499.
- (16) Husted H, Jensen CM, Solgaard S, Kehlet H. Reduced length of stay following hip and knee arthroplasty in Denmark 2000-2009: from research to implementation. *Arch Orthop Trauma Surg* 2012; 132(1):101-104.
- (17) Husted H, Lunn TH, Troelsen A, Gaarn-Larsen L, Kristensen BB, Kehlet H. Why still in hospital after fast-track hip and knee arthroplasty? *Acta Orthop* 2011; 82(6):679-684.
- (18) Holm B, Kristensen MT, Myhrmann L, Husted H, Andersen LO, Kristensen B, Kehlet H. The role of pain for early rehabilitation in fast track total knee arthroplasty. *Disabil Rehabil* 2010; 32(4):300-306.
- (19) Jans O, Bundgaard-Nielsen M, Solgaard S, Johansson PI, Kehlet H. Orthostatic intolerance during early mobilization after fast-track hip arthroplasty. *Br J Anaesth* 2012; 108(3):436-443.
- (20) Andersen LO, Husted H, Otte KS, Kristensen BB, Kehlet H. High-volume infiltration analgesia in total knee arthroplasty: a randomized, double-blind, placebo-controlled trial. *Acta Anaesthesiol Scand* 2008; 52(10):1331-1335.
- (21) Rastogi R, Chesworth BM, Davis AM. Change in patient concerns following total knee arthroplasty described with the International Classification of Functioning, Disability and Health: a repeated measures design. *Health Qual Life Outcomes* 2008; 6:112.
- (22) World Health Organization (WHO). Towards a Common Language for Functioning, Disability and Health ICF. 2002. <http://www.who.int/classifications/icf/training/icfbeginnersguide.pdf>. (Accessed September 17, 2013).

- (23) Mizner RL, Petterson SC, Snyder-Mackler L. Quadriceps strength and the time course of functional recovery after total knee arthroplasty. *J Orthop Sports Phys Ther* 2005; 35(7):424-436.
- (24) Huang CH, Cheng CK, Lee YT, Lee KS. Muscle strength after successful total knee replacement: a 6- to 13-year followup. *Clin Orthop Relat Res* 1996;(328):147-154.
- (25) Berman AT, Bosacco SJ, Israelite C. Evaluation of total knee arthroplasty using isokinetic testing. *Clin Orthop Relat Res* 1991;(271):106-113.
- (26) Petterson SC, Mizner RL, Stevens JE, Rasis L, Bodenstab A, Newcomb W, Snyder-Mackler L. Improved function from progressive strengthening interventions after total knee arthroplasty: a randomized clinical trial with an imbedded prospective cohort. *Arthritis Rheum* 2009; 61(2):174-183.
- (27) Mizner RL, Petterson SC, Clements KE, Zeni JA, Jr., Irrgang JJ, Snyder-Mackler L. Measuring functional improvement after total knee arthroplasty requires both performance-based and patient-report assessments: a longitudinal analysis of outcomes. *J Arthroplasty* 2011; 26(5):728-737.
- (28) Holm B, Kristensen MT, Bencke J, Husted H, Kehlet H, Bandholm T. Loss of knee-extension strength is related to knee swelling after total knee arthroplasty. *Arch Phys Med Rehabil* 2010; 91(11):1770-1776.
- (29) Rossi MD, Brown LE, Whitehurst M. Early strength response of the knee extensors during eight weeks of resistive training after unilateral total knee arthroplasty. *J Strength Cond Res* 2005; 19(4):944-949.
- (30) Bade MJ, Stevens-Lapsley JE. Early high-intensity rehabilitation following total knee arthroplasty improves outcomes. *J Orthop Sports Phys Ther* 2011; 41(12):932-941.
- (31) Berth A, Urbach D, Awiszus F. Improvement of voluntary quadriceps muscle activation after total knee arthroplasty. *Arch Phys Med Rehabil* 2002; 83(10):1432-1436.
- (32) Walsh M, Woodhouse LJ, Thomas SG, Finch E. Physical impairments and functional limitations: a comparison of individuals 1 year after total knee arthroplasty with control subjects. *Phys Ther* 1998; 78(3):248-258.

- (33) Bade MJ, Kohrt WM, Stevens-Lapsley JE. Outcomes before and after total knee arthroplasty compared to healthy adults. *J Orthop Sports Phys Ther* 2010; 40(9):559-567.
- (34) Mizner RL, Petterson SC, Stevens JE, Vandenborne K, Snyder-Mackler L. Early quadriceps strength loss after total knee arthroplasty. The contributions of muscle atrophy and failure of voluntary muscle activation. *J Bone Joint Surg Am* 2005; 87(5):1047-1053.
- (35) Rice DA, McNair PJ. Quadriceps arthrogenic muscle inhibition: neural mechanisms and treatment perspectives. *Semin Arthritis Rheum* 2010; 40(3):250-266.
- (36) Stevens JE, Mizner RL, Snyder-Mackler L. Quadriceps strength and volitional activation before and after total knee arthroplasty for osteoarthritis. *J Orthop Res* 2003; 21(5):775-779.
- (37) Petterson SC, Barrance P, Marmon AR, Handling T, Buchanan TS, Snyder-Mackler L. Time course of quad strength, area, and activation after knee arthroplasty and strength training. *Med Sci Sports Exerc* 2011; 43(2):225-231.
- (38) Stevens-Lapsley JE, Balter JE, Kohrt WM, Eckhoff DG. Quadriceps and hamstrings muscle dysfunction after total knee arthroplasty. *Clin Orthop Relat Res* 2010; 468(9):2460-2468.
- (39) Piva SR, Teixeira PE, Almeida GJ, Gil AB, DiGioia AM, III, Levison TJ, Fitzgerald GK. Contribution of hip abductor strength to physical function in patients with total knee arthroplasty. *Phys Ther* 2011; 91(2):225-233.
- (40) Judd DL, Eckhoff DG, Stevens-Lapsley JE. Muscle strength loss in the lower limb after total knee arthroplasty. *Am J Phys Med Rehabil* 2012; 91(3):220-226.
- (41) Munk S, Jensen NJ, Andersen I, Kehlet H, Hansen TB. Effect of compression therapy on knee swelling and pain after total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc* 2013; 21(2):388-392.
- (42) Ebert JR, Joss B, Jardine B, Wood DJ. Randomized Trial Investigating the Efficacy of Manual Lymphatic Drainage to Improve Early Outcome After Total Knee Arthroplasty. *Arch Phys Med Rehabil* 2013; [Epub ahead of print].

- (43) Wood L, Ferrell WR, Baxendale RH. Pressures in normal and acutely distended human knee joints and effects on quadriceps maximal voluntary contractions. *Q J Exp Physiol* 1988; 73(3):305-314.
- (44) Lenssen TA, van Steyn MJ, Crijns YH, Waltje EM, Roox GM, Geesink RJ, van den Brandt PA, de Bie RA. Effectiveness of prolonged use of continuous passive motion (CPM), as an adjunct to physiotherapy, after total knee arthroplasty. *BMC Musculoskelet Disord* 2008; 9:60.
- (45) Heiberg K, Bruun-Olsen V, Mengshoel AM. Pain and recovery of physical functioning nine months after total knee arthroplasty. *J Rehabil Med* 2010; 42(7):614-619.
- (46) Ipach I, Schafer R, Lahrmann J, Kluba T. Stiffness after knee arthrotomy: evaluation of prevalence and results after manipulation under anaesthesia. *Orthop Traumatol Surg Res* 2011; 97(3):292-296.
- (47) Jevsevar DS, Riley PO, Hodge WA, Krebs DE. Knee kinematics and kinetics during locomotor activities of daily living in subjects with knee arthroplasty and in healthy control subjects. *Phys Ther* 1993; 73(4):229-239.
- (48) Lenssen AF, Crijns YH, Waltje EM, van Steyn MJ, Geesink RJ, van den Brandt PA, de Bie RA. Efficiency of immediate postoperative inpatient physical therapy following total knee arthroplasty: an RCT. *BMC Musculoskelet Disord* 2006; 7:71.
- (49) Soucie JM, Wang C, Forsyth A, Funk S, Denny M, Roach KE, Boone D. Range of motion measurements: reference values and a database for comparison studies. *Haemophilia* 2011; 17(3):500-507.
- (50) Scranton PE, Jr. Management of knee pain and stiffness after total knee arthroplasty. *J Arthroplasty* 2001; 16(4):428-435.
- (51) Pua YH, Ong PH, Chong HC, Yeo W, Tan CI, Lo NN. Associations of Self-Report Physical Function With Knee Strength and Knee Range-Of-Motion in Total Knee Arthroplasty Possible Nonlinear and Threshold Effects. *J Arthroplasty* 2013; [Epub ahead of print].
- (52) Ritter MA, Lutgring JD, Davis KE, Berend ME, Pierson JL, Meneghini RM. The role of flexion contracture on outcomes in primary total knee arthroplasty. *J Arthroplasty* 2007; 22(8):1092-1096.

- (53) Andersen LO, Gaarn-Larsen L, Kristensen BB, Husted H, Otte KS, Kehlet H. Subacute pain and function after fast-track hip and knee arthroplasty. *Anaesthesia* 2009; 64(5):508-513.
- (54) Stevens-Lapsley JE, Schenkman ML, Dayton MR. Comparison of self-reported knee injury and osteoarthritis outcome score to performance measures in patients after total knee arthroplasty. *PM R* 2011; 3(6):541-549.
- (55) Brander VA, Stulberg SD, Adams AD, Harden RN, Bruehl S, Stanos SP, Houle T. Predicting total knee replacement pain: a prospective, observational study. *Clin Orthop Relat Res* 2003;(416):27-36.
- (56) Brander V, Gondek S, Martin E, Stulberg SD. Pain and depression influence outcome 5 years after knee replacement surgery. *Clin Orthop Relat Res* 2007; 464:21-26.
- (57) Dobson F, Hinman RS, Roos EM, Abbott JH, Stratford P, Davis AM, Buchbinder R, Snyder-Mackler L, Henrotin Y, Thumboo J, Hansen P, Bennell KL. OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. *Osteoarthritis Cartilage* 2013; 21(8):1042-1052.
- (58) Riddle DL, Stratford PW, Bowman DH. Findings of extensive variation in the types of outcome measures used in hip and knee replacement clinical trials: a systematic review. *Arthritis Rheum* 2008; 59(6):876-883.
- (59) Steffen TM, Hacker TA, Mollinger L. Age- and gender-related test performance in community-dwelling elderly people: Six-Minute Walk Test, Berg Balance Scale, Timed Up & Go Test, and gait speeds. *Phys Ther* 2002; 82(2):128-137.
- (60) Collins NJ, Roos EM. Patient-reported outcomes for total hip and knee arthroplasty: commonly used instruments and attributes of a "good" measure. *Clin Geriatr Med* 2012; 28(3):367-394.
- (61) Roos EM, Roos HP, Ekdahl C, Lohmander LS. Knee injury and Osteoarthritis Outcome Score (KOOS)--validation of a Swedish version. *Scand J Med Sci Sports* 1998; 8(6):439-448.
- (62) Roos EM, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS) - validation and comparison to the WOMAC in total knee replacement. *Health Qual Life Outcomes* 2003; 1:17.

- (63) Dawson J, Fitzpatrick R, Murray D, Carr A. Questionnaire on the perceptions of patients about total knee replacement. *J Bone Joint Surg Br* 1998; 80(1):63-69.
- (64) Alviar MJ, Olver J, Brand C, Tropea J, Hale T, Pirpiris M, Khan F. Do patient-reported outcome measures in hip and knee arthroplasty rehabilitation have robust measurement attributes? A systematic review. *J Rehabil Med* 2011; 43(7):572-583.
- (65) Browne JP, Bastaki H, Dawson J. What is the optimal time point to assess patient-reported recovery after hip and knee replacement? A systematic review and analysis of routinely reported outcome data from the English patient-reported outcome measures programme. *Health Qual Life Outcomes* 2013; 11:128.
- (66) Bremner-Smith AT, Ewings P, Weale AE. Knee scores in a 'normal' elderly population. *Knee* 2004; 11(4):279-282.
- (67) Paradowski PT, Bergman S, Sunden-Lundius A, Lohmander LS, Roos EM. Knee complaints vary with age and gender in the adult population. Population-based reference data for the Knee injury and Osteoarthritis Outcome Score (KOOS). *BMC Musculoskelet Disord* 2006; 7:38.
- (68) Nerhus TK, Heir S, Thornes E, Madsen JE, Ekeland A. Time-dependent improvement in functional outcome following LCS rotating platform knee replacement. *Acta Orthop* 2010; 81(6):727-732.
- (69) Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, Simon L, Strand V, Woodworth T, Dougados M. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage* 2004; 12(5):389-399.
- (70) Stratford PW, Kennedy DM, Maly MR, Macintyre NJ. Quantifying self-report measures' overestimation of mobility scores postarthroplasty. *Phys Ther* 2010; 90(9):1288-1296.
- (71) Hamilton DF, Gaston P, Simpson AH. Is patient reporting of physical function accurate following total knee replacement? *J Bone Joint Surg Br* 2012; 94(11):1506-1510.
- (72) Terwee CB, van der Slikke RM, van Lummel RC, Benink RJ, Meijers WG, de Vet HC. Self-reported physical functioning was more influenced by pain than performance-based physical functioning in knee-osteoarthritis patients. *J Clin Epidemiol* 2006; 59(7):724-731.

- (73) Razmjou H, Schwartz CE, Yee A, Finkelstein JA. Traditional assessment of health outcome following total knee arthroplasty was confounded by response shift phenomenon. *J Clin Epidemiol* 2009; 62(1):91-96.
- (74) Harmer AR, Naylor JM, Crosbie J, Russell T. Land-based versus water-based rehabilitation following total knee replacement: a randomized, single-blind trial. *Arthritis Rheum* 2009; 61(2):184-191.
- (75) Minns Lowe CJ, Barker KL, Holder R, Sackley CM. Comparison of postdischarge physiotherapy versus usual care following primary total knee arthroplasty for osteoarthritis: an exploratory pilot randomized clinical trial. *Clin Rehabil* 2012; 26(7):629-641.
- (76) Artz N, Dixon S, Wylde V, Beswick A, Blom A, Gooberman-Hill R. Physiotherapy provision following discharge after total hip and total knee replacement: a survey of current practice at high-volume NHS hospitals in England and Wales. *Musculoskeletal Care* 2013; 11(1):31-38.
- (77) Holm B, Kehlet H. [Rehabilitation after total knee arthroplasty]. *Ugeskr Laeger* 2009; 171(9):691-694.
- (78) Minns Lowe CJ, Barker KL, Dewey M, Sackley CM. Effectiveness of physiotherapy exercise after knee arthroplasty for osteoarthritis: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2007; 335(7624):812.
- (79) Bandholm T, Kehlet H. Physiotherapy exercise after fast-track total hip and knee arthroplasty: time for reconsideration? *Arch Phys Med Rehabil* 2012; 93(7):1292-1294.
- (80) Moffet H, Collet JP, Shapiro SH, Paradis G, Marquis F, Roy L. Effectiveness of intensive rehabilitation on functional ability and quality of life after first total knee arthroplasty: A single-blind randomized controlled trial. *Arch Phys Med Rehabil* 2004; 85(4):546-556.
- (81) Johnson AW, Myrer JW, Hunter I, Feland JB, Hopkins JT, Draper DO, Eggett D. Whole-body vibration strengthening compared to traditional strengthening during physical therapy in individuals with total knee arthroplasty. *Physiother Theory Pract* 2010; 26(4):215-225.

- (82) Chow TP, Ng GY. Active, passive and proprioceptive neuromuscular facilitation stretching are comparable in improving the knee flexion range in people with total knee replacement: a randomized controlled trial. *Clin Rehabil* 2010; 24(10):911-918.
- (83) Denis M, Moffet H, Caron F, Ouellet D, Paquet J, Nolet L. Effectiveness of continuous passive motion and conventional physical therapy after total knee arthroplasty: a randomized clinical trial. *Phys Ther* 2006; 86(2):174-185.
- (84) Bonutti PM, Marulanda GA, McGrath MS, Mont MA, Zywiell MG. Static progressive stretch improves range of motion in arthrofibrosis following total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc* 2010; 18(2):194-199.
- (85) Piva SR, Gil AB, Almeida GJ, DiGioia AM, III, Levison TJ, Fitzgerald GK. A balance exercise program appears to improve function for patients with total knee arthroplasty: a randomized clinical trial. *Phys Ther* 2010; 90(6):880-894.
- (86) Liao CD, Liou TH, Huang YY, Huang YC. Effects of balance training on functional outcome after total knee replacement in patients with knee osteoarthritis: a randomized controlled trial. *Clin Rehabil* 2013; 27(8):697-709.
- (87) Bruun-Olsen V, Heiberg KE, Wahl AK, Mengshoel AM. The immediate and long-term effects of a walking-skill program compared to usual physiotherapy care in patients who have undergone total knee arthroplasty (TKA): a randomized controlled trial. *Disabil Rehabil* 2013.
- (88) Liebs TR, Herzberg W, Ruther W, Haasters J, Russlies M, Hassenpflug J. Ergometer cycling after hip or knee replacement surgery: a randomized controlled trial. *J Bone Joint Surg Am* 2010; 92(4):814-822.
- (89) Liebs TR, Herzberg W, Ruther W, Haasters J, Russlies M, Hassenpflug J. Multicenter randomized controlled trial comparing early versus late aquatic therapy after total hip or knee arthroplasty. *Arch Phys Med Rehabil* 2012; 93(2):192-199.
- (90) Kim TK, Park KK, Yoon SW, Kim SJ, Chang CB, Seong SC. Clinical value of regular passive ROM exercise by a physical therapist after total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc* 2009; 17(10):1152-1158.

- (91) Bruun-Olsen V, Heiberg KE, Mengshoel AM. Continuous passive motion as an adjunct to active exercises in early rehabilitation following total knee arthroplasty - a randomized controlled trial. *Disabil Rehabil* 2009; 31(4):277-283.
- (92) Chiarello CM, Gundersen L, O'Halloran T. The effect of continuous passive motion duration and increment on range of motion in total knee arthroplasty patients. *J Orthop Sports Phys Ther* 1997; 25(2):119-127.
- (93) Leach W, Reid J, Murphy F. Continuous passive motion following total knee replacement: a prospective randomized trial with follow-up to 1 year. *Knee Surg Sports Traumatol Arthrosc* 2006; 14(10):922-926.
- (94) Harvey LA, Brosseau L, Herbert RD. Continuous passive motion following total knee arthroplasty in people with arthritis. *Cochrane Database Syst Rev* 2010;(3):CD004260.
- (95) Beaupre LA, Davies DM, Jones CA, Cinats JG. Exercise combined with continuous passive motion or slider board therapy compared with exercise only: a randomized controlled trial of patients following total knee arthroplasty. *Phys Ther* 2001; 81(4):1029-1037.
- (96) McClelland J, Zeni J, Haley RM, Snyder-Mackler L. Functional and biomechanical outcomes after using biofeedback for retraining symmetrical movement patterns after total knee arthroplasty: a case report. *J Orthop Sports Phys Ther* 2012; 42(2):135-144.
- (97) Avramidis K, Strike PW, Taylor PN, Swain ID. Effectiveness of electric stimulation of the vastus medialis muscle in the rehabilitation of patients after total knee arthroplasty. *Arch Phys Med Rehabil* 2003; 84(12):1850-1853.
- (98) Stevens-Lapsley JE, Balter JE, Wolfe P, Eckhoff DG, Kohrt WM. Early neuromuscular electrical stimulation to improve quadriceps muscle strength after total knee arthroplasty: a randomized controlled trial. *Phys Ther* 2012; 92(2):210-226.
- (99) Mintken PE, Carpenter KJ, Eckhoff D, Kohrt WM, Stevens JE. Early neuromuscular electrical stimulation to optimize quadriceps muscle function following total knee arthroplasty: a case report. *J Orthop Sports Phys Ther* 2007; 37(7):364-371.
- (100) Thomas AC, Stevens-Lapsley JE. Importance of attenuating quadriceps activation deficits after total knee arthroplasty. *Exerc Sport Sci Rev* 2012; 40(2):95-101.

- (101) Meier W, Mizner RL, Marcus RL, Dibble LE, Peters C, Lastayo PC. Total knee arthroplasty: muscle impairments, functional limitations, and recommended rehabilitation approaches. *J Orthop Sports Phys Ther* 2008; 38(5):246-256.
- (102) Delorme TL. Restoration of muscle power by heavy-resistance exercises. *J Bone Joint Surg* 1945; 27(4):645-667.
- (103) Kraemer WJ, Adams K, Cafarelli E, Dudley GA, Dooly C, Feigenbaum MS, Fleck SJ, Franklin B, Fry AC, Hoffman JR, Newton RU, Potteiger J, Stone MH, Ratamess NA, Triplett-McBride T. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc* 2002; 34(2):364-380.
- (104) Husby VS, Helgerud J, Bjorgen S, Husby OS, Benum P, Hoff J. Early maximal strength training is an efficient treatment for patients operated with total hip arthroplasty. *Arch Phys Med Rehabil* 2009; 90(10):1658-1667.
- (105) Suetta C, Magnusson SP, Rosted A, Aagaard P, Jakobsen AK, Larsen LH, Duus B, Kjaer M. Resistance training in the early postoperative phase reduces hospitalization and leads to muscle hypertrophy in elderly hip surgery patients--a controlled, randomized study. *J Am Geriatr Soc* 2004; 52(12):2016-2022.
- (106) Taylor NF, Dodd KJ, Damiano DL. Progressive resistance exercise in physical therapy: a summary of systematic reviews. *Phys Ther* 2005; 85(11):1208-1223.
- (107) Liu CJ, Latham NK. Progressive resistance strength training for improving physical function in older adults. *Cochrane Database Syst Rev* 2009;(3):CD002759.
- (108) Lin CW, March L, Crosbie J, Crawford R, Graves S, Naylor J, Harmer A, Jan S, Bennell K, Harris I, Parker D, Moffet H, Fransen M. Maximum recovery after knee replacement--the MARKER study rationale and protocol. *BMC Musculoskelet Disord* 2009; 10:69.
- (109) Perhonen M, Komi PV, Häkkinen K, von Bonsdorff H, Partio H. Strength training and neuromuscular function in elderly people with total knee endoprosthesis. *Scand J Med Sci Sports* 1992; 2(4):234-243.
- (110) Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med* 2008; 148(4):295-309.

- (111) Herbert RD, Bo K. Analysis of quality of interventions in systematic reviews. *BMJ* 2005; 331(7515):507-509.
- (112) Husted H, Holm G, Jacobsen S. Predictors of length of stay and patient satisfaction after hip and knee replacement surgery: fast-track experience in 712 patients. *Acta Orthop* 2008; 79(2):168-173.
- (113) Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Hals EK, Kvarstein G, Stubhaug A. Assessment of pain. *Br J Anaesth* 2008; 101(1):17-24.
- (114) Jakobsen TL, Christensen M, Christensen SS, Olsen M, Bandholm T. Reliability of knee joint range of motion and circumference measurements after total knee arthroplasty: does tester experience matter? *Physiother Res Int* 2010; 15(3):126-134.
- (115) Gumpel JM, Matthews SA, Altman DG, Spencer JD, Wilkins EA. An objective assessment of synovitis of the knee: measurement of the size of the suprapatellar pouch on xeroradiography. *Ann Rheum Dis* 1980; 39(4):359-366.
- (116) Martin HJ, Yule V, Syddall HE, Dennison EM, Cooper C, Aihie SA. Is hand-held dynamometry useful for the measurement of quadriceps strength in older people? A comparison with the gold standard Biodex dynamometry. *Gerontology* 2006; 52(3):154-159.
- (117) Koblbauer IF, Lambrecht Y, van der Hulst ML, Neeter C, Engelbert RH, Poolman RW, Scholtes VA. Reliability of maximal isometric knee strength testing with modified hand-held dynamometry in patients awaiting total knee arthroplasty: useful in research and individual patient settings? A reliability study. *BMC Musculoskelet Disord* 2011; 12:249.
- (118) Watson MJ. Refining the ten-metre walking test for use with neurologically impaired people. *Physiotherapy* 2002; 88(7):386-397.
- (119) Sørensen J, Davidsen M, Gudex C, Pedersen KM, Bronnum-Hansen H. Danish EQ-5D population norms. *Scand J Public Health* 2009; 37(5):467-474.
- (120) Nagamine R, Otani T, White SE, McCarthy DS, Whiteside LA. Patellar tracking measurement in the normal knee. *J Orthop Res* 1995; 13(1):115-122.
- (121) Engh GA, Holt BT, Parks NL. A midvastus muscle-splitting approach for total knee arthroplasty. *J Arthroplasty* 1997; 12(3):322-331.

- (122) Butland RJ, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six-, and 12-minute walking tests in respiratory disease. *Br Med J (Clin Res Ed)* 1982; 284(6329):1607-1608.
- (123) Gibbons WJ, Fruchter N, Sloan S, Levy RD. Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years. *J Cardiopulm Rehabil* 2001; 21(2):87-93.
- (124) American Thoracic Society. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166(1):111-117.
- (125) Murray DW, Fitzpatrick R, Rogers K, Pandit H, Beard DJ, Carr AJ, Dawson J. The use of the Oxford hip and knee scores. *J Bone Joint Surg Br* 2007; 89(8):1010-1014.
- (126) Lygre SH, Espehaug B, Havelin LI, Vollset SE, Furnes O. Does patella resurfacing really matter? Pain and function in 972 patients after primary total knee arthroplasty. *Acta Orthop* 2010; 81(1):99-107.
- (127) Riddle DL, Stratford PW. Impact of pain reported during isometric quadriceps muscle strength testing in people with knee pain: data from the osteoarthritis initiative. *Phys Ther* 2011; 91(10):1478-1489.
- (128) Curb JD, Ceria-Ulep CD, Rodriguez BL, Grove J, Guralnik J, Willcox BJ, Donlon TA, Masaki KH, Chen R. Performance-based measures of physical function for high-function populations. *J Am Geriatr Soc* 2006; 54(5):737-742.
- (129) Bassej EJ, Short AH. A new method for measuring power output in a single leg extension: feasibility, reliability and validity. *Eur J Appl Physiol Occup Physiol* 1990; 60(5):385-390.
- (130) Brosseau L, Balmer S, Tousignant M, O'Sullivan JP, Goudreault C, Goudreault M, Gringras S. Intra- and intertester reliability and criterion validity of the parallelogram and universal goniometers for measuring maximum active knee flexion and extension of patients with knee restrictions. *Arch Phys Med Rehabil* 2001; 82(3):396-402.
- (131) Edwards JZ, Greene KA, Davis RS, Kovacik MW, Noe DA, Askew MJ. Measuring flexion in knee arthroplasty patients. *J Arthroplasty* 2004; 19(3):369-372.
- (132) Shrout PE. Measurement reliability and agreement in psychiatry. *Stat Methods Med Res* 1998; 7(3):301-317.

- (133) Beckerman H, Roebroeck ME, Lankhorst GJ, Becher JG, Bezemer PD, Verbeek AL. Smallest real difference, a link between reproducibility and responsiveness. *Qual Life Res* 2001; 10(7):571-578.
- (134) Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1(8476):307-310.
- (135) Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol* 2010; 63(8):e1-37.
- (136) Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. *BMJ* 2001; 323(7321):1123-1124.
- (137) Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Med Res Methodol* 2010; 10:67.
- (138) Andersen LL, Magnusson SP, Nielsen M, Haleem J, Poulsen K, Aagaard P. Neuromuscular activation in conventional therapeutic exercises and heavy resistance exercises: implications for rehabilitation. *Phys Ther* 2006; 86(5):683-697.
- (139) Pincivero DM, Gandhi V, Timmons MK, Coelho AJ. Quadriceps femoris electromyogram during concentric, isometric and eccentric phases of fatiguing dynamic knee extensions. *J Biomech* 2006; 39(2):246-254.
- (140) Löscher WN, Cresswell AG, Thorstensson A. Excitatory drive to the alpha-motoneuron pool during a fatiguing submaximal contraction in man. *J Physiol* 1996; 491 (Pt 1):271-280.
- (141) Ashford S, De SL. A comparison of the timing of muscle activity during sitting down compared to standing up. *Physiother Res Int* 2000; 5(2):111-128.
- (142) Aalund PK, Larsen K, Hansen TB, Bandholm T. Normalized knee-extension strength or leg-press power after fast-track total knee arthroplasty: which measure is most closely associated with performance-based and self-reported function? *Arch Phys Med Rehabil* 2013; 94(2):384-390.

- (143) Parent E, Moffet H. Comparative responsiveness of locomotor tests and questionnaires used to follow early recovery after total knee arthroplasty. *Arch Phys Med Rehabil* 2002; 83(1):70-80.
- (144) Kennedy DM, Stratford PW, Riddle DL, Hanna SE, Gollish JD. Assessing recovery and establishing prognosis following total knee arthroplasty. *Phys Ther* 2008; 88(1):22-32.
- (145) Rejeski WJ, Ettinger J, Schumaker S, James P, Burns R, Elam JT. Assessing performance-related disability in patients with knee osteoarthritis. *Osteoarthritis Cartilage* 1995; 3(3):157-167.
- (146) Kennedy DM, Stratford PW, Wessel J, Gollish JD, Penney D. Assessing stability and change of four performance measures: a longitudinal study evaluating outcome following total hip and knee arthroplasty. *BMC Musculoskelet Disord* 2005; 6:3.
- (147) Stillwell KM, Forman DE, McElwain D, Simpson C, Garber CE. The 6 minute walk test for evaluation of functional capacity in elderly adults. *Med Sci Sports Exerc* 1996; 28(5):152.
- (148) Hoozeboom TJ, Oosting E, Vriesekolk JE, Veenhof C, Siemonsma PC, de Bie RA, van den Ende CH, van Meeteren NL. Therapeutic validity and effectiveness of preoperative exercise on functional recovery after joint replacement: a systematic review and meta-analysis. *PLoS One* 2012; 7(5):e38031.
- (149) Rhea MR, Alvar BA, Burkett LN, Ball SD. A meta-analysis to determine the dose response for strength development. *Med Sci Sports Exerc* 2003; 35(3):456-464.
- (150) Devereaux PJ, Bhandari M, Clarke M, Montori VM, Cook DJ, Yusuf S, Sackett DL, Cina CS, Walter SD, Haynes B, Schunemann HJ, Norman GR, Guyatt GH. Need for expertise based randomised controlled trials. *BMJ* 2005; 330(7482):88.
- (151) Weier AT, Pearce AJ, Kidgell DJ. Strength training reduces intracortical inhibition. *Acta Physiol (Oxf)* 2012; 206(2):109-119.
- (152) Lunn TH, Kristensen BB, Andersen LO, Husted H, Otte KS, Gaarn-Larsen L, Kehlet H. Effect of high-dose preoperative methylprednisolone on pain and recovery after total knee arthroplasty: a randomized, placebo-controlled trial. *Br J Anaesth* 2011; 106(2):230-238.