Neuromuscular Exercise prior to Joint Arthroplasty in Patients with Osteoarthritis of the Hip or Knee

Allan Villadsen

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Tutor(s): Ewa Roos, Søren Overgaard & Anders Holsgaard-Larsen

Official opponents: Nadine Foster & Søren Solgaard

Correspondence: Department of Orthopaedics and Traumatology, OUH Svendborg Sygehus, Valdemarsgade 53, 5700 Svendborg, Denmark

E-mail: allan.villadsen@rsyd.dk

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2. Villadsen A, Overgaard S, Holsgaard-Larsen A, Christensen R, Roos EM.Immediate efficacy of neuromuscular exercise in patients with severe osteoarthritis of the hip or knee: a secondary analysis from a randomized controlled trial. J Rheumatol. 2014 Jul;41(7):1385-94

3. Villadsen A, Overgaard S, Holsgaard-Larsen A, Christensen R, Roos EM. Postoperative effects of neuromuscular exercise prior to hip or knee arthroplasty: a randomised controlled trial. Ann Rheum Dis. 2014 Jun;73(6):1130-7

INTRODUCTION

Osteoarthritis (OA) and the diagnosis

OA is a degenerative joint disease which alters the structure of the cartilage. The thickness of the cartilage diminishes and the adjacent structures, i.e. synovial membrane, menisci and underlying bone, are also affected. In time, OA causes pain, lowers physical function and ultimately leads to a reduced quality of life.[2] In OA research, two possibly interacting views govern the field, namely a biomechanical view, where altered loading patterns of the joint are thought to cause additional wear to the cartilage, and a systemic view, where inflammation is the driving factor behind cartilage degeneration.[5-10] For the clinician, however, OA may be better defined by its two cardinal symptoms, i.e. pain and functional loss, or by its pathology such as radiographic changes, Figure 1.

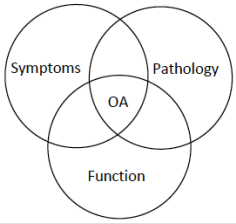

Figure 1. A conceptual model with osteoarthritis defined by symptoms or pathological changes

OA symptoms Traditionally, a medical history of the patient´s symptoms, severity and duration is obtained through a semi-structured interview (anamnesis) led by a health care professional. Through this, an overall, however possibly subjective, idea of the patient´s illness is obtained. To facilitate interpretation of the patient´s response, great focus has been placed on the development of patient self-reported questionnaires over the last two decades. In the clinical setting, symptom severity may be evaluated by disease-specific questionnaires, examples of which include the Oxford Knee Score (OKS) or the Knee Injury and Osteoarthritis Outcome Score (KOOS) and the Oxford Hip Score (OHS) or Hip Osteoarthritis Outcome Score (HOOS) for patients with knee or hip OA respectively. Here, the challenge lies in defining cut points for disease severity based on the score derived from the questionnaire.[11]

OA pathology In the early stages of the degenerative process, pathological changes are detectable by means of biomarkers; i.e. molecular fragments measured in patient's plasma. However, biomarkers have not attained a position in the clinical setting to secure diagnosis. In mild OA, the thinning of joint cartilage and its effect on underlying bone may be visualised by magnetic resonance (MR) scanning. This highly detailed modality is appreciated by many clinicians but is costly and time-consuming. More advanced OA can be seen as radiographic features, i.e. osteophytes, joint space narrowing and sclerosis of subchondral bone. The radiological severity of OA may be evaluated through various classification systems.[12-14] Defining severity of the disease is challenging. Generally, joint space narrowing and subchondral sclerosis are accepted as signs of more progressive disease.[15, 16] Throughout the OA literature, the Kellgren & Lawrence method (KL) is most commonly used. Radiographic changes are graded from 1 to 4 with severe joint space narrowing and marked subchondral sclerosis being present in grade 4.[12]

As illustrated in Figure 1, the diagnosis of OA is not always straightforward since patients with symptoms of OA may not necessarily display radiographic features of the disease and vice versa.[17-20] The discrepancy often found between symptom and

radiographic severity may influence and further challenge the decision-making about what treatment to offer the patient.[21] Today, the diagnosis may be based on symptoms and clinical evaluation only.[22]

Magnitude and burden of OA

OA patients not only suffer from pain, physical disability and reduced quality of life, but also display an increased risk of premature death most likely due to the sedentary and inactive lifestyle the disease imposes on the individual.[23] At a societal and worldwide level, OA has major implications. The disease generates a heavy burden equivalent to that of diabetes and ranks eighth in the leading causes of disability worldwide.[24-26] The prevalence of OA increases with age and 10-18% of people aged above 60 years are affected.[27] In the United States (US) alone, 67 million people (25%) are expected to be diagnosed with an arthritic condition by the year 2030 with OA being the major contributor.[28] People who are overweight have a higher prevalence of OA[2, 29]. Furthermore, the risk of symptomatic and radiographic progression is closely related to obesity.[30, 31] With the ageing of the population in combination with life-styles yielding obesity and physical inactivity, the future burden of OA will increase.[26, 32]

Few studies have investigated the economic impact of OA.[33] An estimate from an American population puts the total annual costs of OA in the US at $89.1 billion.[34] This figure is based on both direct costs, e.g. medication, physical therapy and hospitalisation and indirect costs, e.g. home care and absence from work. Although more prevalent in the elderly population, OA also affects younger people still working, with the median age of diagnosis estimated to be 55 years.[35] Work disability is significantly higher in the OA population.[36] In the US, costs are estimated to be $8.3 billion due to job-related OA alone.[34] In general, with the increase in affected individuals, the overall costs associated with the disease will inevitably increase.[37-39]

Treatment options

Currently, there is no cure for OA and the various treatment modalities aim at addressing symptoms, i.e. to reduce pain, to improve physical function and to prevent further progression of the disease. End-stage OA is successfully treated with joint arthroplasty. Treatment falls into one of three categories: first line, pharmacological and surgical, Figure 2.

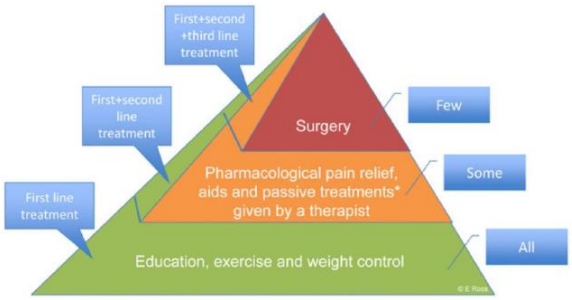

Figure 2. Treatment options in OA

Roos E & Juhl C: Osteoarthritis 2012 year in review: rehabilitation and outcomes

First line treatment for OA

Modalities in this category are various and some multi-faceted. Current guidelines recommend patient education, weight loss, orthoses and exercise.[22, 40-42] Patient education is considered a core element in treating OA and aims at providing basic information about the disease, enhancing empowerment and self-management. A meta-analysis for both hip and knee patients demonstrates small (0.06, 95% CI 0.02, 0.10) but statistically significant effect sizes for patient education in reducing pain and self-reported activity limitation.[41] It can of course be questioned if other outcomes such as improved decision-making and reduced anxiety would be more appropriate outcomes than pain reduction and functional improvement. Patient education can be delivered in different settings[43, 44] and with various content[45, 46], however, no optimal programme has been identified for patients with OA.[47]

In patients with knee OA, the effectiveness of weight loss programmes on body weight, pain and/or physical function has been demonstrated, typically, in programmes delivered weekly as supervised sessions for a range of 8 weeks to 2 years.[48-52] The effects on pain and function from attending weight loss programmes are overall small, but significant (ES pain 0.20, 95% CI 0.00 to 0.39; ES physical function 0.23, 95% CI 0.04 to 0.42).The intervention strategies generally include advice on how to reduce calorie intake and comprise behavioral modification, self-monitoring, goal setting, and some include exercise.

Exercise is proven effective for reducing pain and improving physical function in patients with mild to moderate radiographic knee OA (K+L score 1-2).[53, 54] This association is not as well documented for hip OA.[43, 55-57] For knee OA, the effects of exercise are small to moderate and significant for pain reduction (ES 0.40, 95% CI 0.30 to 0.50) and improvement in physical function (ES 0.37, 95% CI 0.25 to 0.49). The exercise interventions applied in OA research are heterogeneous which makes comparison across studies challenging.[53, 55] These interventions generally fit into one of three categories: strength, aerobic or mixed interventions.[58] The neuromuscular training method applied in this dissertation belongs in the category of mixed interventions with components of aerobic exercise, muscle strength training, functional alignment and core stability.[59] ***Strengthening exercise training*** is exercise that causes muscles to work or hold against an applied force or weight.[60] These may comprise handling of own body weight in various positions or exercises where external loads, e.g. free weights and weight stacks on resistance exercise equipment, are applied. Strengthening exercise aims at improving muscle strength which is a known deficit associated with OA.[61, 62] Resistance training programmes emphasising dynamic exercises involving concentric (shortening) and eccentric (lengthening) movements that recruit multiple muscle groups are recommended.[59] For patients with knee OA, both specific quadriceps strengthening exercises or strength training for the lower limb in general are effective in reducing pain (ES, 95% CI: 0.29, 0.06 to 0.51 and 0.53, 0.27 to 0.79, respectively) and improving physical function (ES, 95% CI: 0.24, 0.06 to 0.42 and 0.58, 0.27 to 0.88, respectively).[63] ***Aerobic exercise training*** refers to exercises in which the body's large muscles move in a rhythmic manner for sustained periods.[60] It generally aims at improving cardiovascular function, e.g. oxygen uptake, and metabolic status such as glycemic control but may furthermore improve range of movement. Various training methods can be used, e.g. cycling, walking, swimming, etc. Most OA studies evaluating aerobic exercise have focused on walking. In patients with knee OA, aerobic training (walking) is effective in reducing pain (ES, 95% CI: 0.48, 0.13 to 0.43) and improving physical function (ES, 95% CI: 0.35, 0.11 to 0.58).[63] ***Neuromuscular exercise*** programmes aim at improving sensorimotor control and achieving compensatory functional stability. Functional, weight-bearing and land-based exercises are

used in various positions, resembling conditions of daily life and more strenuous activities. The quality of the performance in each exercise is emphasised and the level of training and progression is guided by the patient's neuromuscular function evaluated by the supervising physiotherapist.[64] The evidence for mixed exercise programmes including strengthening, aerobic and flexibility components in patients with mild to moderate knee OA is conflicting.[58, 63, 65] However, one meta-analysis demonstrates effect sizes for knee pain (ES,95% CI: 0.4, 0.30 to 0.50) and self-reported physical function (ES,95% CI: 0.37, 0.25 to 0.49).[53] Tailored neuromuscular exercise training programmes have positive effects in younger patients with anterior cruciate ligament injury, they improve cartilage glycosaminoglycan content and physical function in middle-aged people at risk of OA[66, 67]and are found feasible and safe for patients with severe OA.[64] However, no randomised controlled trials in the OA literature evaluating the effects of specified neuromuscular exercise were found.
Today, no one category of exercise has been demonstrated to be superior to another in patients with OA.[58, 63, 65] However, a very recent systematic review suggests that focusing on one category is more effective than mixed interventions and supervised exercise is favorable to unsupervised.[68] Twelve or more directly supervised sessions have been shown to be more effective than less than 12 sessions on pain (ES 0.46, 95% CI 0.32 to 0.60 versus ES 0.28, 95% CI 0.16 to 0.40, p=0.03) and physical function (ES 0.45, 95% CI 0.29 to 0.62 versus ES 0.23, 95% CI 0.09 to 0.37, p=0.02).[63]

Pharmacological treatment

Pain is a cardinal symptom of OA and, together with reduced physical function, is the main reason for this patient group seeking professional health care. Hence, much focus is placed on relieving pain. The effects of pharmacological treatment on OA come from studies evaluating patients with knee OA or studies where hip or knee OA patients were evaluated as one group and no stratified analysis was made on the basis of the affected joint. Pharmacological treatment alongside first line treatment is recommended as optimal management of mild to moderate OA.[40, 41, 69] Acetaminophen (paracetamol) in doses of up to 4 g/day is today considered first-line pharmacological treatment.[41, 70] For knee OA, it demonstrates small effects on pain reduction (ES, 95% CI: 0.13, 0.04 to 0.22) and no effect on physical function (ES, 95% CI: 0.09, -0.03 to 0.22).[71, 72] When acetaminophen does not offer satisfactory pain relief, the use of non-steroidal anti-inflammatory drugs (NSAIDs) is recommended.[41, 42] NSAIDs can be delivered orally or topically with varying effects (ES, 95% CI: 0.29, 0.22 to 0.35 vs. 0.44, 0.27 to 0.62) for knee pain.[41] Although displaying a superior effect to acetaminophen (ES, 95% CI: 0.20, 0.10 to 0.30)[73], oral NSAIDs are associated with serious side effects, e.g. gastro-intestinal (GI) ulcers and bleeding[74], and results in more frequent GI hospitalisation.[75] NSAIDs are available as selective cyclooxygenase (Cox) -2 inhibitors shown to have fewer GI side effects compared with non-selective NSAIDs[75], however, more frequently displaying cardiovascular side effects, e.g. myocardial infarction.[74] No differences in GI side effects are found between selective and non-selective NSAIDs when administered in combination with a proton pump inhibitor.[76] Paracetemol and NSAIDs may be given in combination and a recent randomised trial reported greater short-term pain relief from combined administration than paracetamol and ibuprofen alone.[77] However, the combination seems to increase the risk of GI hospitalisation.[75]
Opioids offer large reduction in pain intensity (ES, 95% CI : 0.78, 0.59 to 0.98), but the effect is outweighed by the numerous side effects, e.g. nausea and dizziness.[41]
As treatment for OA, the use of glucosamin, a natural constituent of cartilage, is thought to stimulate regeneration of cartilage and reduce pain. Although recommended in six of the ten guidelines, evidence is rather conflicting and much debated.[41, 78]

Surgical treatment

Where first line and second line treatment fails to alleviate pain and physical dysfunction, surgery constitutes a viable treatment option. Total joint arthroplasty (TJA) is recognised as an effective pain relief and a relatively safe and cost-effective treatment in patients with severe OA of the hip or knee joint.[79] Millions of TJA procedures are performed annually worldwide. The exact number is unknown but one study reports a crude incidence rate for total hip arthroplasty (THA) of 119 per 100,000 persons per year and a little lower for total knee arthroplasty (TKA).[80] The variation, however, is great between wealthier and poorer countries, e.g. in Austria, the age-standardised incidence rate is 266.2 (95% CI 269.7 to 273.3) per 100,000 and in Romania 35.4 (95% CI 36.3 to 37.1) being the highest and lowest, respectively.[80] The rates are increasing and have been for the past two decades, as illustrated for Denmark in Figure 3.

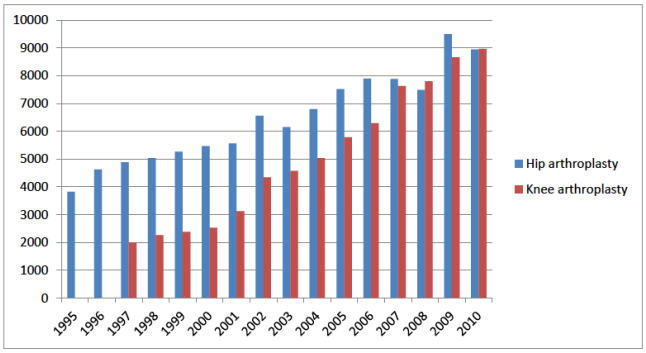

Figure 3. Illustration of trends in primary total hip and knee arthroplasty performed in Denmark.

Data from Danish Hip and Knee Arthroplasty Registers[2,3]

After surgery, patients generally experience significant reduction in pain, and improvement in self-reported physical function and health-related quality of life.[81-83] The greatest improvements are reported at 6-12 months after surgery.[84, 85] As for pharmacological treatment, there seems to be differences in response to THA and TKA.[86]Very few studies have made direct comparison between the two. TKA patients may display faster short-term recovery (6 to 9 weeks post-surgery) in physical function, but this is surpassed by THA patients at 9 to 11 weeks.[87] However, in general, THA patients report higher improvement in pain reduction, physical function, quality of life and tend to be more satisfied with the procedure.[81, 83, 86] Overall, patients report general satisfaction although their pre-operative expectations are not always fulfilled.[81, 85, 88, 89] Various studies have been conducted to evaluate predictors of a successful TJA procedure and patient satisfaction.[84, 90-98] In general, high expectations, high level of pre-operative pain and older age are associated with a poorer outcome. Socioeconomic factors, e.g. years attending school, employment and disability pension, are independent predictors of post-operative outcome.[91] Although regarded as successful procedures, there are still challenges to

overcome in this patient group; some do not respond to treatment[90] and have persistent pain[85] and THA patients never reach the level of physical function of healthy controls[99], Figure 4.

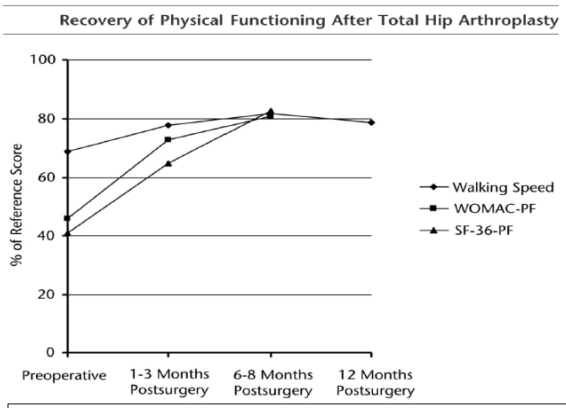

Figure 4. Expected physical function after total hip arthroplasty. Relative improvement normalised to maximum scores of hip function in population reference values.
Vissers et. al. 2011

The decision as to when to offer TJA surgery is influenced by many factors, e.g. pain severity, level of physical disability, age and sex.[100, 101] As of today, no specific cut-off or severity state is found to determine an indication for surgery.[21, 102]

Two other surgical procedures serve as alternative treatment options for a selected group of patients with knee OA, i.e. tibial-osteotomy and uni-compartmental joint arthroplasty. These will not be considered in this dissertation.

PRE-OPERATIVE EXERCISE

Exercise treatment (pre- or post-operative) is incorporated in the umbrella term 'rehabilitation', defined as treatments designed to facilitate the process of recovery from injury, illness, or disease to as normal a condition as possible. In relation to TJA, it has traditionally been practised after surgery with a focus on restoring activities of daily living (ADL) and physical fitness. Reports on the efficacy and feasibility were published in the early years of joint arthroplasty surgery.[103-106] Accelerated perioperative care or Fast Track Surgery, where patient information, procedures and rehabilitation associated with TJA are optimised, has gained ground over the last decade. It has reduced costs and length of hospital stay[107-109] and is now considered standard care. Post-operative rehabilitation is the general approach still recommended and practised.[110-113] However, exercise could be delivered prior to surgery and serve as an adjunct treatment in the accelerated perioperative care. In the 1990s the thought of offering rehabilitation through exercise to OA patients prior to TJA blossomed.[114-116] The idea of getting TJA patients 'into shape' prior to surgery later became popularly referred to as 'prehabilitation'.[117] Hypothetically, pre-operative exercise is associated with improvements in physical function prior to surgery and during in-hospital stay but may also contribute to post-operative recovery.[118, 119] One theoretical model just to justify pre-operative exercise is presented in Figure 5. In theory, by improving physical function prior to surgery and otherwise following the known path with an immediate drop in physical function post-operatively, patients may achieve a higher level of physical function and/or an earlier onset of recovery.[119]

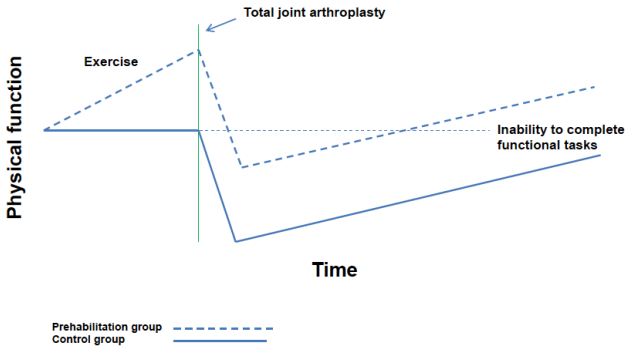

Figure 5. A theoretical model of the effects of pre-operative exercise in patients with severe osteoarthritis undergoing total hip or knee arthroplasty.

Inspired by *Topp et al. 2009*

A systematic review found early studies to include insufficient numbers of patients and one to be confounded by the intervention group receiving both pre- and post-operative exercise therapy.[120] Additionally, the heterogeneity of the interventions applied prevented pooling of the results.[121] However, there was some evidence to suggest clinically important differences between groups and reduced length of in-hospital stay.[120, 121] Since publication of the two systematic reviews, several randomised controlled trials (RCTs) have evaluated the effects of pre-operative exercise.[119, 122-125] In 2011, one meta-analysis concluded there was moderate evidence to show that pre-operative exercise reduces pain prior to total knee arthroplasty (ES, 95% CI: 0.43, 0.13 to 0.73) and improves physical function prior to total hip arthroplasty (ES, 95% CI: 0.47, 0.11 to 0.83) .126 Furthermore, there is moderate evidence that pre-operative exercise and education programmes improves physical function 3 weeks after total hip arthroplasty (ES, 95% CI: 0.53, 0.09 to 0.9).126 A low to moderate effect on pain reduction prior to surgery (hip and knee) and a moderate effect on self-reported physical function (hip) post-operatively may potentially be outweighed by the pain relief from surgery. These beneficial post-operative effects of self-reported physical function are in contrast to the conclusion drawn in the latest review by Hoogeboom et al.[126] where no effect of pre-operative exercise was found on post-operative functional recovery. Potential benefits may have been hampered by poor therapeutic validity of the exercise programmes evaluated in the included trials.[126] In summary, the knowledge of the role of pre-operative exercise in joint arthroplasty is based on a limited number of studies with small numbers of enrolled patients, heterogeneous interventions with low therapeutic validity and few studies evaluating the cost-effectiveness of implementing such interventions.126,127

AIMS OF THIS DISSERTATION

General

The overall aim was to evaluate the efficacy of a well described neuromuscular exercise programme when delivered to patients with severe symptomatic OA prior to joint arthroplasty of the hip or knee.

Specific

To determine the intra-rater reliability and agreement for maximal leg muscle power and several functional performance measures in patients with severe OA of the hip or knee joint. (Paper I)

To evaluate the immediate efficacy of an 8-week neuromuscular exercise programme in patients with severe osteoarthritis of the hip or knee joint. (Paper II)
To study the 3-month post-operative effects of a neuromuscular exercise programme delivered prior to joint arthroplasty in patients with severe OA of the hip or knee joint. (Paper III)
To determine potential differences in treatment effects between patients with hip and knee OA. (Papers II and III)

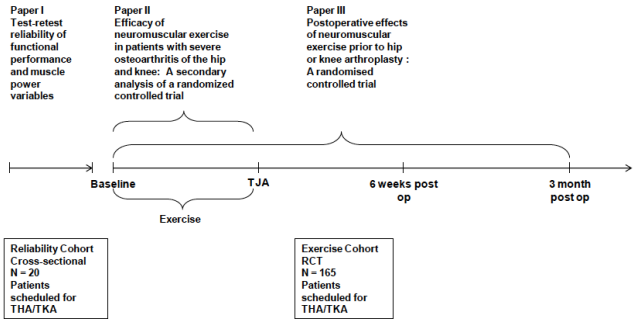

Figure 6. Overview of study populations in Papers I-III. The data collection spans the time period from October 2009 to July 2011.

METHODS

Participants

A total of 185 patients were included in the studies, Figure 6. All had symptomatic and severe radiographic hip or knee OA and were scheduled for joint arthroplasty. Inclusion criteria were kept wide to reflect daily clinical practice and are listed alongside exclusion criteria in Table 1. Patient characteristics for the patients included in the respective papers are listed in Table 2.

Table 1. Inclusion and exclusion criteria for patients with symptomatic OA of the hip or knee joint scheduled for hip or knee arthroplasty

Inclusion criteria	Exclusion criteria
Age over 18 years Symptomatic osteoarthritis Scheduled for hip or knee arthroplasty at Svendborg Hospital, Odense University Hospital, Denmark	Previous fracture in or adjacent to the joint Inflammatory arthritis Co-morbid diseases, e.g. severe heart disease and neurological deficits, making exercise and testing impossible Scheduled for bilateral total joint arthroplasty Not speaking or understanding Danish Living on adjacent islands making frequent attendance unrealistic

Table 2. Characteristics of 185 patients included in Papers I-III

Cohort	N	Age Mean Range	BMI Mean Range	Sex % women	Joint affected No. hip/knee
Paper I	20	69 56-79	29 23-37	50%	9/11
Papers II-III	165	67 43-89	30 19-51	56%	84/81

The recruitment procedure differed for the two cohorts.

The Reliability Cohort (Paper I)

Eligible patients were scheduled for primary unilateral total hip or knee arthroplasty due to symptomatic OA at the Svendborg Hospital, Odense University Hospital, Denmark. A complete list of patients on the waiting list was generated by a secretary. The patients were contacted consecutively (top down) until 20 patients were included. Information on the study aim and procedure was given over the telephone by the author and again on first contact. Informed written consent was obtained on the first test day.
Recruitment took place from 1 November 2010 to 18 December 2010. In total, 32 patients were contacted.

The RCT Cohort (Papers II-III)

Eligible patients were scheduled for primary unilateral total hip or knee arthroplasty due to symptomatic OA at the Svendborg Hospital, Odense University Hospital, Denmark. Patient interest and eligibility were screened by the author via telephone and patient records. Written information about the study was given to the participants in the clinic by the surgeon scheduling the surgery. The surgeon was not otherwise involved in the study. Informed written consent was obtained on the day of baseline testing. Recruitment took place from 4 January 2010 to 21 March 2011. In total, 628 patients were screened and 499 patients met the inclusion criteria. There is a treatment guarantee in the Danish Health Care System that one will be operated on within one month of being scheduled for TJA. Entering this study meant that all patients accepted an additional waiting time of up to 5 weeks in comparison with the treatment guarantee. One hundred and five patients (21% of those eligible) were unwilling to wait longer for surgery and 108 patients (22% of those eligible) were unwilling to participate due to logistical constraints such as travelling distance or lack of transportation. After randomisation, the additional waiting time applied only to patients randomised to the exercise intervention. Of the eligible patients, 165 (33%) (81 with knee OA) were included and underwent randomisation, Figure 11.

Intervention

Participants in the intervention group (Papers II and III) received a basic educational package (described below in detail for the control group) in addition to attending a neuromuscular exercise programme for approximately 8 weeks. Neuromuscular Exercise in Total Joint Replacement (NEMEX-TJR) is a physiotherapist-supervised, individualised and goal-based exercise programme. It has been demonstrated to be feasible in elderly people with severe knee and hip OA in terms of self-reported pain, decreased or unchanged pain during training, and progression in level of training.[64] The exercise programme was adopted in full from the original paper and the author, together with the supervising physiotherapist, participated in a training session and half a day of discussions with the developers of the programme in Lund, Sweden to ensure the programme would be carried out in accordance with the original intentions. The training programme is open access and available online as an additional file to the original publication.[127] Briefly, it consists of a short warm-up (10 minutes) on a stationary bike followed by a circuit programme (40 minutes) and a cooling-down (10 minutes with walking, stretching and mobility exercises). Neutral alignment ('knee over foot') is emphasised throughout the programme. The circuit programme comprises four main focus areas: core stability/postural function, functional alignment of hip/knee, lower limb muscle strength and functional exercises. Each focus area comprises several exercises. The quality of the performance in each exercise is emphasised and the level of training and progression is guided by the patient's neuromuscular function evaluated by the supervising physiotherapist. The programme was delivered twice a week. We stated a priori that attendance at 12 exercise sessions (out of a possible 16 to 18, depending on the week day the patient joined the training) was considered good compliance.
The control group (Papers II and III) received only the educational package, which consisted of written information about the operating procedure, expected postoperative progress and a leaflet on various exercises targeting range of motion and dynamic stability which was handed to them when scheduled for total hip or knee arthroplasty. One week prior to surgery patients participated in a 3-hour in-clinic information session led by health professionals. No limitations were imposed on either group with regard to

changing exercise habits or seeking out other treatment during the study period.
Post-operative rehabilitation was offered to all patients within their municipality. The duration and intensity varied, which is why we stratified for municipality.[128]

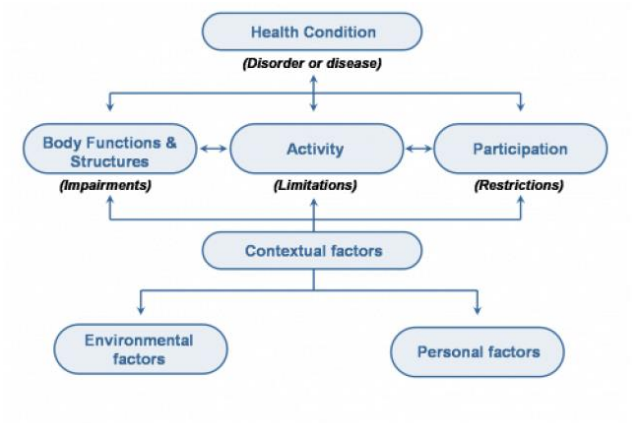

Figure 7. The model of functioning and disability on which the International Classification of Functioning, Disability and Health is founded.[1]

Outcomes
Outcomes were chosen to reflect the impairments experienced by patients with OA. These impairments fit well under the International Classification of Functioning, Disability and Health (ICF).[1] The ICF is a framework to describe the dynamic interaction between the health conditions (body function/structures, activity and participation) and contextual factors (environment and personal), Figure 7. OA can lead to impairments in body function (e.g. muscle weakness and pain), impairments in body structure (e.g. joint space narrowing and mal-alignment), activity limitation (e.g. reduced walking distance and difficulties performing daily activities) and participation restrictions (e.g. difficulties with participating in social activities). For this dissertation, the focus was on body function and activity limitations evaluated by means of self-reported questionnaires, functional performance and muscle function measures.
Self-reported (Primary and secondary outcomes)
The primary outcome in the RCT was the Activity of Daily Living (ADL) subscale on the Hip disability and Osteoarthritis Outcome Score (HOOS) and the Knee Injury and Osteoarthritis Outcome Score (KOOS) for patients with hip and knee OA, respectively.[129-131] The HOOS and KOOS are disease-specific questionnaires and include the Western Ontario and McMasters Osteoarthritis Index (WOMAC) 3.0, a widely used questionnaire within the field of OA.[132] In addition to the subscales of Pain, Symptoms and ADL, which include the WOMAC items, the KOOS and HOOS also hold subscales assessing Sport and Recreation Function and joint-related Quality of Life. The ADL subscale contains 17 items where patients rate the level of difficulty by answering on a 5-point Likert Scale from 'None' to 'Extreme'. Secondary outcomes were the HOOS/KOOS Pain, Symptoms, Sport & Recreation and joint-related Quality of Life subscales. The HOOS and KOOS subscale scores are transformed to scores from 0 to 100 points with higher scores indicating fewer joint-related problems. To assess health-related Quality of Life, the EuroQol 5-Dimension Health Questionnaire (EQ5D), a widely used generic self-administered instrument, was used.[133, 134]. EQ5D consists of two pages: the EQ5D descriptive system and the EQ5D visual analogue scale (VAS). The descriptive system holds 5 dimensions: mobility, self-care, usual activity, pain/discomfort and anxiety/depression, and is scored as the EQ5D index from 0 to 1. '0' represents worse health state and '1' represents full health state in the 5 dimensions. The EQ5D VAS records the respondent's self-rated health on a vertical, visual analogue scale with end-point 'Best imaginable health state' (100) and 'Worst imaginable health state' (0).[135]
Functional performance (exploratory outcomes)
Measures of quantitative physical function are necessary to fully describe the disability experienced by OA patients and are recommended outcome measures in OA trials.[136, 137] We chose to include chair stands (i.e. 5 repeated chair stands timed at maximal velocity) and 20-meter walk tests (both 20-m walk at self-chosen pace and at maximal velocity) to reflect activities performed daily. Furthermore, unilateral knee-bending (i.e. maximal number of knee-bends performed in 30 seconds) was included to reflect unilateral muscle strength and coordination.[138]
Muscle function (exploratory outcomes)
Muscle power (force exerted x velocity of the exertion) describes functional capacity more precisely than isometric and isokinetic variables in older healthy individuals.[139-143] However, little is known of muscle power in patients with OA.[144] We wanted to evaluate both isolated (single-joint) and integrated (multi-joint) muscle function in this patient group by means of dynamic maximal leg muscle power. Specific muscle groups, i.e. knee-extensors, hip-extensors and hip-abductors, were examined by connecting a linear encoder to standard resistance exercise equipment and determination of peak power was subsequently made from the force-velocity relationship by commercial software (MuscleLab Power, Ergotest Technology, Langesund, Norway), Figure 8. Multi-joint leg extension power was measured in the so-called Nottingham Power Rig (NPR) (Nottingham University, Nottingham, UK), a commercially available leg extension press, Figure 9.[145]
The outcomes evaluated in the two cohorts are listed in Table 3.

Specifics for the reliability study (Paper I)
Participants underwent a test-retest setup with testing on two separate occasions with approximately one week in between. Testing conditions were standardised (i.e. time of day, settings on exercise machines). No limitations to the patient's daily activities prior to, or in between, test sessions were imposed. Testing was preceded by a 5-minute warm-up on a stationary exercise bike with low resistance (equal to a self-reported intensity of 3-6 on the Borg-scale). For unilateral tests, the 'unaffected' leg was tested first and the 'affected' leg tested last. The test battery was conducted in the following order: functional performance (20-m walks, chair stands and one-leg knee bends) and leg muscle power (multi-joint leg extension and single-joint knee extension, hip extension and hip abduction).

Table 3. Overview of outcomes used and evaluated in this dissertation

	Paper I* (Reliability)	Paper II-III (RCT)
Patient reported		
HOOS/KOOS ADL		X
HOOS/KOOS Pain		X
HOOS/KOOS Symptoms		X
HOOS/KOOS Sport & recreation		X
HOOS/KOOS Quality of Life		X
EQ5D-index		X
EQ-VAS		X
Functional performance		
Chair stands	X	X
20-m walk self chosen pace	X	X
20-m walk maximal pace	X	X
Max. one-leg knee bends	X	X
Muscle power		
Single-joint knee extension	X	X
Single-joint knee flexion	X	X
Single-joint hip extension	X	X
Single joint hip abduction	X	X
Multi-joint leg extension	X	X

*Outcomes evaluated for reliability and agreement.
HOOS = Hip disability and Osteoarthritis Outcome Score, KOOS = Knee injury and Osteoarthritis Outcome Score. (score 0 to 100 with higher scores indicating fewer joint related problems)
EQ5D-index = European Quality of Life 5 Dimension Index Score (score 0 to 1)
EQ5D-VAS = European Quality of Life 5 Dimension Visual Analog Scale (score 0 to 100 with higher scores indicating better overall quality of life)

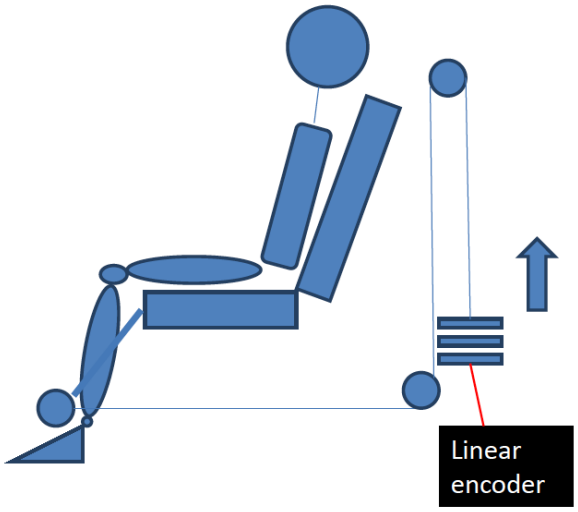

Figure 8. Schematic illustration of muscle power measurement using a linear encoder and a standard resistance exercise machine. The encoder is connected to the weightstack. Software calculates maximal average power.

Figure 9. Multi-joint leg extension power evaluated with the Nottingham Power Rig.

RANDOMISATION AND BLINDING (Papers II-III)

The methodology in the study protocol was inspired by, and the manuscripts written in accordance with, the CONSORT-statement, the generally accepted procedure when reporting RCTs.[146-148] Allocation was conducted by the author after baseline assessment using sequentially numbered, opaque, sealed envelopes. The allocation sequence was stratified by gender and municipality, and blocked in groups of four to allow for similar recruitment rates into both groups. The sequence and envelopes were produced by a person not otherwise affiliated with the trial. The allocation was performed either with the patient present or over the telephone.

We did not consider it realistic to blind the participants to the group allocation. Four assessors conducted the physical testing and all underwent the same laboratory training. Allocation concealment was attempted by instructing the patients not to reveal group allocation to the assessor. The post-intervention assessors had no access to previously obtained data.

ETHICS APPROVAL AND STUDY REGISTRATION

The Regional Ethics Committee of Southern Denmark approved the study protocol, layman study information was sent to the participants along with the written consent form and information on the individual's rights regarding participation; approval number S-20090099. The randomised controlled trial was registered with ClinicalTrials.gov; identifier: NCT01003756.

STATISTICAL ANALYSIS

Reliability study (Paper I)

The chosen sample of 20 participants was based upon recommendations of sample size for reliability studies.[149] coefficient of variation (CVws) was used as a measure of agreement to describe the measurement error[150] and expressed as a percentage of the standard deviation to the group mean difference.[151] Minimal detectable change at the 90% confidence level (MDC90, also a measure of agreement) was calculated according to the following method[152]: MDC90 = SDtest-retest x 1.65 based on MDC90 = SEM x 1.65 x √2, where SEM = SDtest-retest/√2.[150] A change greater than the MDC90 is often interpreted as a true change on a personal level,[153] whereas CVws is unitless and makes variables comparable.

Intraclass correlation coefficients (ICCconsistency) were calculated as a single measure of reliability to reflect between-patient variability.[150] The calculation is based on a mixed effect model with the listed parameter as the response variable and age, sex, weight, number of previous lower limb total joint arthroplasties, and joint operated on (hip or knee) as the exposure variables. A maximum likelihood estimate was used and ICC was calculated as patient variability divided by patient plus the residual variability. No interaction terms were included. There is no consensus on cut-points for ICCs. We applied the cut offs suggested by Landis et al.: no agreement (0), some (0-.20), fair (.21-.40), moderate (.41-.60), good (.61-.80) and excellent (>.81).[154] Graphs of the mean plotted against the difference of test minus retest results with 95% limits of agreement (LOA) (e.g. mean difference (test-retest) ± 1.96xSD) were made for simple evaluation of heteroscedasticity and systematic bias.[153] A conservative approach to describe outliers as more than 3 SD of the mean was chosen[155] and subsequently omitted from further analysis.

Randomised controlled trial (Papers II-III)

Seventy-four patients were needed to detect a clinically relevant change of 10 points on the HOOS/KOOS ADL subscale (SD 15, power = .80 and α = .05). To allow for separate analysis of patients with knee OA and hip OA, 74 patients with knee OA and 74 patients with hip OA were needed. To allow for around 10% loss to follow up, we decided to include 160 patients in total.

A statistical analysis plan including all assessment points was outlined, allowing evaluation at 3 months after surgery and im-

provement from baseline to 3 months after surgery in the same analysis. The plan was developed prior to code-breaking the allocation sequence. Data for primary and secondary outcomes were analysed according to the intention-to-treat principle with the baseline observation carried forward in cases where data were missing.[147] To evaluate the effects of the intervention, HOOS/KOOS subscales were analysed using analysis of covariance (ANCOVA) (Paper II) and a multilevel repeated-measures random effects model with change value as the response variable and baseline value, group, joint and time as covariates (Paper III). All interaction terms of group, joint and time were included and a maximum likelihood estimate was used (Paper III). Data from all assessed time points were included (Paper III). This one statistical model holds all between-group comparisons at all assessment points and allows for evaluation of the average effect over the time period from baseline to 3 months post-operatively. Data for functional performance and maximal muscle power (exploratory outcomes) were analysed as observed (baseline observation not carried forward) by analysis of covariance.

Based on patients who improved 15% or more[156], the number needed to treat was calculated using the formula: 1/(EER - CER) where EER was the event rate in the exercise group and CER in the control group (Paper II).[157] Standardised mean differences (SMD, effect size) were calculated for the subscales ADL and Pain to allow for comparison across studies.

All p-values and 95% confidence intervals (95% CI) are reported as 2-sided; p-values < 0.05 were considered statistically significant. Statistical analyses in Papers II and III were done by the project statistician who was masked to group allocation and the joint affected. The SAS statistical package (version 9.2; SAS institute Inc., Cary, NC, USA) and Stata 11 (Stata Corp., College Station, USA) were used for statistical models.

SUMMARY OF RESULTS

Agreement and Reliability of Functional Performance and Muscle Power (Paper I)

A statistically significantly better retest value (indicating a learning effect) was observed for four of the tests: 20-m walk at maximal pace, chair stands, unilateral knee bending and leg extension press. This learning effect is illustrated in Figure 10 where the confidence interval does not contain the value 0. Furthermore, No heteroscedasticity (tendency towards a greater difference, the larger the mean – 'trumpet shape plot') was observed, Figure 10.

Agreement. For single-joint and multi-joint maximal peak power and functional performance measures, we demonstrated poor (CVws~25%, single-joint hip extension), moderate (CVws~15% , multi-joint leg extension press, single-joint knee extension, chair stands and knee bending) to good (CVws < 10% , single-joint knee flexion, single-joint hip abduction and 20-m walk) agreement. The minimal detectable change ranged from 6.0% to 59.7% for the 20 meter walk at maximal pace and single-joint hip extension, respectively.

Reliability. We demonstrated good (ICC: .61-.80, single-joint hip extension, multi-joint leg extension press and knee bending) to excellent (ICC >.81, single-joint knee extension, knee flexion, hip abduction, 20-m walk and chair stands) reliability.

An increase in VAS pain was reported after performance of the test battery compared with that prior to testing. After the first test session, this increase was insignificant (mean difference 4 mm, p = .2876). A slightly higher increase, of doubtful clinical significance, was observed after the retest session (mean difference 11 mm, p = .0005)

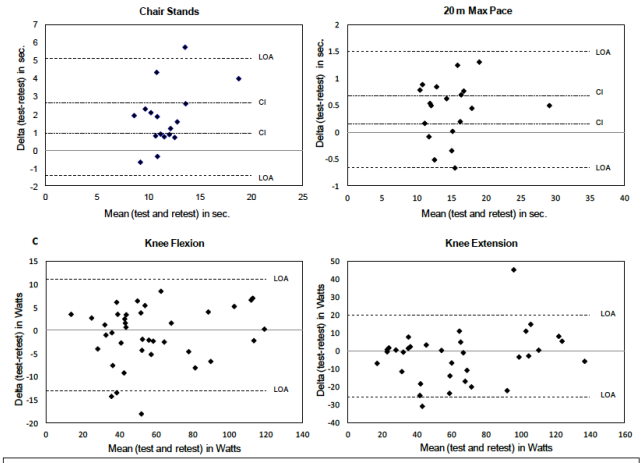

Figure 10. Bland & Altman plots with Limits Of Agreement (LOA).
95% confidence intervals (CI) plotted on A and B to illustrate the 'learning effect'.
A. 5 timed repeated chair stands, B. 20 m walk maximal pace, C. Peak power during single joint unilateral knee flexion, and D. Peak power during single joint unilateral knee extension

Recruitment and patient characteristics in the RCT (Papers II and III)

The 334 patients unwilling to participate were, on average, 4 years older (95% CI 2.3 to 5.6), 58% had hip OA and 60% were women. The 165 patients randomised to the two groups were, on average, 67±8 years, 84 (51%) had hip OA and 92 (56%) were women. The intervention group attended a mean of 13±5 exercise sessions and all patients, in both groups, received the folder containing educational material. Of the 84 patients in the intervention group, 62 attended the pre-specified goal of 12 or more exercise sessions indicating good compliance. One hundred and fifty-three patients attended the pre-operative 3-hour information session and underwent surgery. Of the 81 patients with knee OA, 5 (3 in the exercise group) were re-scheduled and received a uni-compartmental implant. Three patients were diagnosed with cancer, one with polymyalgia and one with a defective heart valve. One patient with both hip and knee OA was re-scheduled from THA to TKA. One patient from the control group was re-evaluated and found to be ineligible for surgery. Finally, one patient felt markedly better after the exercise intervention and postponed surgery and, however regrettably, declined further participation.

Figure 11 depicts recruitment and flow of patients through this trial.

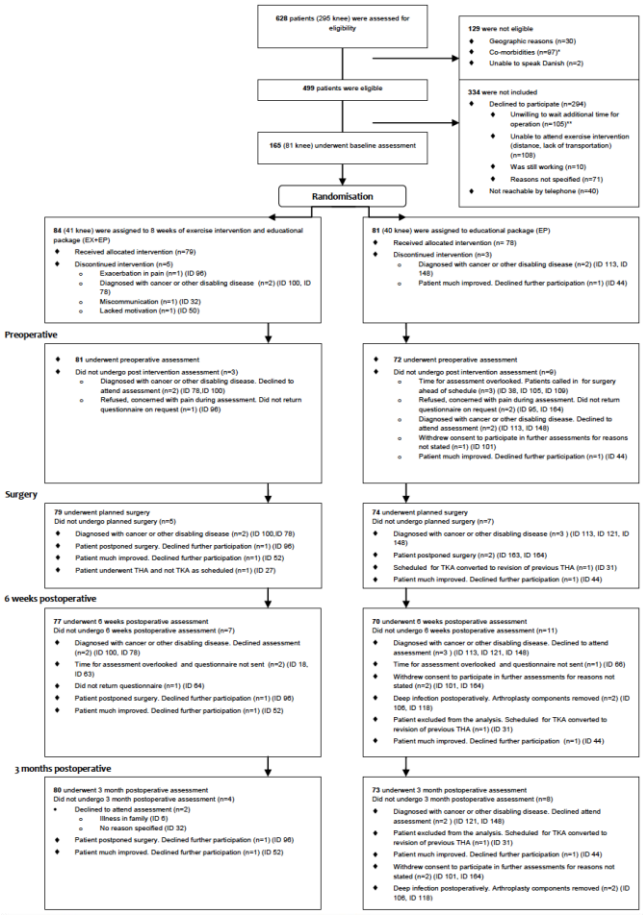

Figure 11. Flow diagram of patients participating in this study

* Co-morbidities (n=97)

- Previous fracture in or adjacent to the joint (n=13) (1 knee)
- Inflammatory arthritis (n=11) (5 knee)
- Revision arthroplasty (n=7) (4 knee)
- Previously enrolled with another joint (n=9) (7 knee)
- Unicompartmental replacement (knee) (n=27)
- Bilateral procedure in same session or within 3 month (n=16)
- Necrosis of the femoral head (hip) (n=6)
- Neurological disorders (n=6), Hemiparesis (n=2), Parkinsons Disorder (n=2), Dementia (n=2)
- Dysplasia of the femoral head (n=1)
- Possible cancer metastasis in proximal femur (n=1)

** The Danish Healthcare System has a one month treatment guarantee. Entering this study meant all patients accepted an additional waiting period of up to 5 weeks in comparison with the treatment guarantee. After randomisation, this additional wait applied only to patients randomised to the 8-week exercise intervention. The control group was operated on when originally scheduled.

Neuromuscular exercise in patients with severe OA of the hip or knee (Paper II)

The median time from baseline to post intervention (pre-operative) assessment was 8.6 weeks (inter-quartile range (IQR) 8.0 to 9.4 weeks) in the intervention group and 5.1 weeks (IQR 3.6 to 6.9 weeks) in the control group.

Primary and secondary outcomes

For the primary outcome, HOOS/KOOS ADL subscale, the difference in mean change between groups was 7.2 points (95% CI 3.5 to 10.9, p = .0002) in favour of NEMEX-TJR compared with the control. Likewise for the secondary outcomes of Pain, Symptoms, Sport and Recreation Function and Joint-Related Quality of Life, the mean differences were 5.3 (95% CI 2.1 to 8.4, p = .0012), 3.8 (95% CI 0.3 to 7.3, p = .0358), 4.5 (95% CI 0.4 to 8.7, p = .0329) and 5.6 (95% CI 1.9 to 9.3, p = .0034) points, respectively, Figure 12.

Patients with hip OA reported greater improvement in physical function and reduction in pain than the patients with knee OA, shown by the significant effect of the interaction term joint × group (p = 0.0497 and p = 0.0544 for the ADL and Pain subscales respectively). The difference between groups in HOOS/KOOS ADL scores showed improvement in favour of the intervention group of 10.9 for the hip OA patients (95 % CI 5.8 to 15.9) and 3.5 for the knee OA patients (95 % CI 1.8 to 8.8).

On the basis of 15% improvement in ADL, the number needed to treat was 7 (4 and 23 for patients with hip and knee OA, respectively. For ADL and Pain, we found moderate effect sizes in patients with hip OA (0.63, 95 % CI 0.26 to 1.00 and 0.57, 95 % CI 0.20 to 0.94) and low effect sizes in patients with knee OA (0.23, 95 % CI -0.14 to 0.60 and 0.15, 95% CI -0.21 to 0.52).

Exploratory outcomes

There was a significant difference between the groups in favour of the intervention group in chair stands (1.9, 95% CI 0.9 to 3.0 seconds), 20-m. walk self-chosen pace (0.9, 95% CI 0.0 to 1.8 seconds) and maximal number of knee bends on the index leg (leg to undergo surgery) (3.3, 95% CI 1.0 to 3.9 seconds). In the leg muscle power variables, we found statistically significant differences in single-joint hip abduction on the index leg (3.9, 95% CI 0.1 to 7.8 Watts) and in multi-joint leg extension on the contra lateral side (10.1, 95% CI 0.8 to 19.3 Watts) in favour of the intervention group.

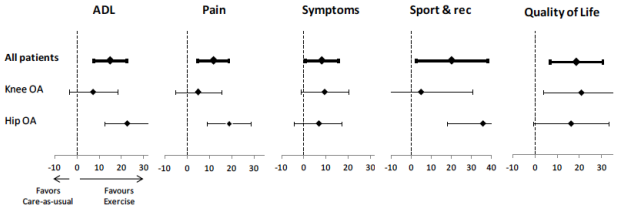

Figure 12. KOOS/HOOS difference between means given as percentages of the overall baseline mean.

Postoperative effects of neuromuscular exercise prior to hip and knee arthroplasty (Paper III)

Median time from baseline to surgery was 9.6 weeks (inter quartile range from 8.9 to 10.7 weeks) in the intervention group and 7.1 weeks (inter quartile range from 6.1 to 8.1 weeks) in the TJA only group.

Hip versus knee OA

We found no effect over time depending on the joint affected (hip or knee) demonstrated by a non-significant value of the interaction term time×joint×group (p-value = 0.4639). That is, the additional effect of exercise seen over the whole time period, baseline to 3 months post-operatively did not differ between patients with hip or knee OA, Figure 13A. However, the main effect of the explanatory variable Group was highly significant (p-value = 0.0029) indicating an effect of exercise seen over the time period. With no interaction of joint×group (p = 0.7370) seen, the approach of ignoring the affected joint is acceptable, Figure 13B. The results are thus given for all patients together, regardless of their having hip or knee OA.

Efficacy analysis

6 weeks after surgery

Both groups improved at 6 weeks post-operatively, Figure 13. The intervention group demonstrated a statistically significant greater improvement in ADL (p = 0.0488) and Pain (p = 0.0472) than did the control group (difference between group means 5.6, 95% CI 0.03 to 10.3 and 5.4, 95% CI 0.1 to 10.8, respectively), Figure 13B.

We found no statistically significant differences between groups in the HOOS/KOOS subscales Symptoms, Sport & Recreation and Joint-related Quality of Life.
Patients in the intervention group reported significantly greater improvement in self-reported general health measured with the EQ5D VAS (difference between group means 7.6, 95% CI 2.1 to 13.0).

Three months after surgery – Primary end-point
For the primary outcome ADL, we found no statistically significant difference between the two groups (4.4, 95% CI -0.8 to 9.5) at 3 months after surgery, Figure 13B. As for the primary outcome, all secondary outcomes displayed a tendency towards favouring exercise over control, e.g. Pain: 4.5, 95% CI -0.8 to 9.9; however, none were statistically significant. Additionally, there was no difference in self-reported general health measured with the EQ5D between the two groups.
Of the exploratory outcomes, i.e. functional performance and maximal muscle power evaluated only at 3 months post-operatively, single-joint hip extension on the non-operated (8.4 W, 95% CI 0.2 to 16.6) and single-joint hip abduction on both the operated and non-operated (8.0 W, 95% CI 2.4 to 13.6 and 7.1 W, 95% 1.6 to 12.7) sides displayed statistically significant differences in favour of the intervention group. For all other exploratory outcomes, no differences were found.

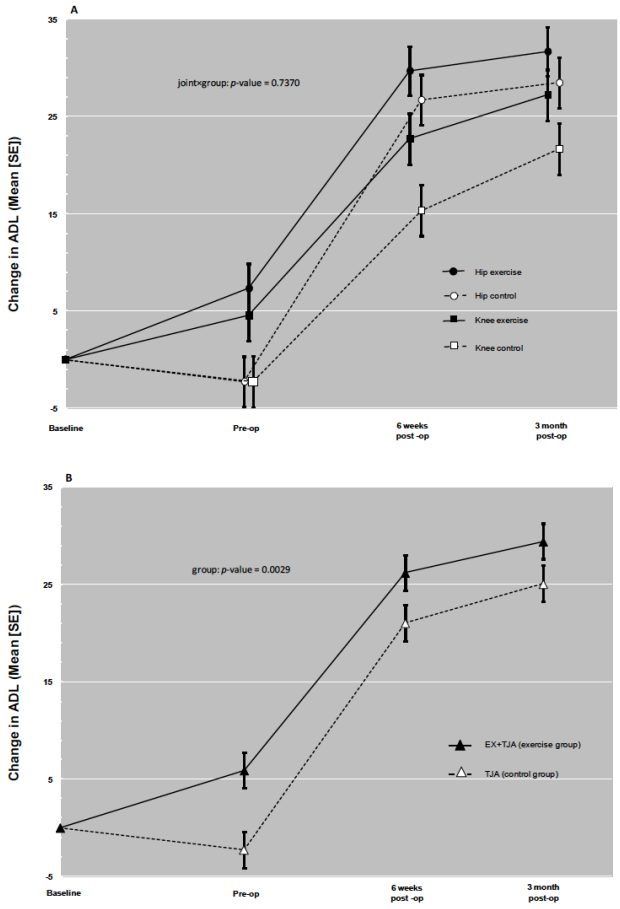

Figure 13. Mean change (SE) in Activities of Daily Living for the intervention and control group stratified for the affected joint (A) and for the two groups when ignoring the affected joint (B) at baseline, prior to surgery, 6 weeks and 3 months after surgery.

Adverse events

Two patients from the control group, one with hip and one with knee OA, developed a deep peri-prosthetic infection and had the prosthetic components removed prior to the 6-week post-operative assessment, Figure 11.

GENERAL DISCUSSION

Main findings

This dissertation is based on the findings from three studies investigating reproducibility of quantitative measures of physical function (Paper I) and the effects of neuromuscular exercise in patients with severe symptomatic OA undergoing total hip or knee arthroplasty (Papers II and III).
The evaluated test-battery comprising functional performance and muscle power measures demonstrated moderate to good agreement (that is, how close repeated measures are, within patient variability) and good to excellent reliability (that is, the parameter's ability to distinguish between patients, between patient variability). To assist clinicians in future interpretations, minimal detectable changes were calculated for the individual tests (Paper I). Attending an 8-week exercise programme, previously found to be feasible, improved self-reported physical function, objective functional performance and reduced pain prior to surgery. The effect seemed greater in patients with hip OA compared with knee OA (Paper II). At 3 months postoperatively (primary endpoint), no additional benefits were seen from the pre-operative exercise. Seen over the entire time period, from baseline to 3 months after surgery, the adjunct of exercise resulted in an earlier onset of postoperative recovery in self-reported activities of daily living (ADL) and pain relief compared with the standard TJA procedure. Although no statistically significant differences were observed at 3 months after surgery, the statistically significant differences in ADL, Pain and QoL at 6 weeks postoperatively support the greater overall improvement seen from baseline to 3 months postoperatively for the intervention group. Overall, the treatment effects of pre-operative exercise in combination with TJA were not more beneficial for THA patients than for TKA patients (Paper III).

Methods and material

Design:
To evaluate the effects of an intervention, a randomised controlled trial is considered the method of choice. We conducted a randomised, controlled trial according to the CONSORT-statement (the gold standard for RCT reporting)[146-148] with a rigorous study design and an adequate sample size to allow for separate analysis for hip and knee OA patients.
Patients:
The inclusion criteria were kept broad to reflect the daily clinical practice as seen by the wide age range (43 to 89 years). The exclusion criteria applied were to ensure a representative group with regard to the disease in question. Of the population scheduled for THA and TKA, only 16% were excluded. Despite succeeding in including a higher proportion of eligible patients than in similar studies, we still only included 30% of those eligible, which diminishes the external validity of the study. The low inclusion rate was mostly due to the one-month treatment guarantee in the Danish Healthcare system and the fact that the intervention was offered at only one location, circumstances that were beyond our control but may nevertheless have introduced a selection

bias. The 334 patients unwilling to participate were, on average, 4 years older and more were of the female sex than the patients included. Unfortunately, little else is known about these patients, e.g. their level of pain experienced and physical function. However, the recruitment rate is higher than similar trials, e.g. Rooks et al. (12%)[123], where the surgical treatment and the surgeons' reputation attract patients from a wide geographic area. Generally, unwillingness to participate may reside in the fact that patients tend to seek out treatment when symptoms are at their worst.

Intervention:

The exercise interventions applied in OA research are heterogeneous which makes comparison across studies challenging.63,126 Furthermore, the interventions may lack therapeutic validity which affects the clinical efficacy.[126] For this dissertation, a feasible and safe intervention was chosen. The neuromuscular exercise intervention is well described, focuses on the quality of the performance in each exercise and is individualised and progressed through therapist supervision.[64] It aims at achieving dynamic stability through coordinated muscle activity, which is essential for everyday voluntary movement. It is therefore encouraging to observe significant effects on the patient's perception of activities of daily living alongside improvement in functional performance (Paper II).

Outcomes:

Outcomes were chosen to reflect the impairments experienced by patients with OA. It is generally recommended to use patient-reported outcomes as primary outcomes in clinical trials.[137, 158, 159] However, it is suggested to include functional performance measures to fully cover the patient's disability.[136, 160] Both the self-reported and the performance measures chosen for this study are easily administered and require little time, making them feasible to use in trials with a larger number of enrolled participants. We included a test-battery of functional performance measures and specific single-joint and multi-joint muscle tests to complement patient reports and possibly serve as explanatory factors for observed differences between groups.162Muscle power (force exerted x velocity of the exertion) has been shown to describe functional capacity more precisely than isometric and isokinetic variables in older healthy individuals.[139-143, 161]. The apparatus and software used in the evaluation of muscle power was easy to handle and demonstrated acceptable reliability and agreement, however the procedure was rather time-consuming and cannot be recommended for large scale RCTs or cohort studies.

Exercise in patients with patients with severe symptomatic OA

Today, it is generally accepted that exercise can reduce pain and improve physical function in patients with mild to moderate symptoms of knee OA[41] and thus constitutes one of the core treatments for OA, Figure 14.[70, 162]

Little, however, is known of the effects in patients with severe OA. I am un-aware of any studies evaluating the effects of exercise in this patient group unless derived from data obtained preoperatively with the exercise intervention as adjunct to surgical treatment. We too used patients scheduled for surgery as a model of severe symptomatic OA (Paper II). The significant improvements in both ADL and Pain were demonstrated alongside improvements in functional performance and muscle power, making the exercise intervention the probable cause. Furthermore, we found indications that the neuromuscular exercise was more effective in patients with hip OA. One could argue that part of the difference between the two groups was caused by a small deterioration in the control group which amplified the potential 'true' difference (Table 2, Paper II). A true deterioration in the control group is unlikely due to the short time awaiting surgery. This was

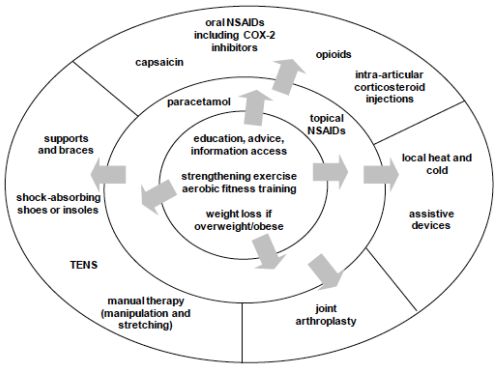

Figure 14. Illustration of core and adjunctive treatment in OA.
From NICE clinical guideline 59. Osteoarthritis: the care and management of osteoarthritis in adults.

supported by previous research which indicates no deterioration in up to 3 months while waiting for surgery.[163] If the deterioration is caused by disappointment at not being allocated to the intervention group, this is unknown. It is possible that the further attention received in the intervention group may have affected the results, but one would expect this to apply to only the self-reported outcomes. Again, we observed concurrent improvements in functional performance which support a true overall improvement.

Preoperative exercise as adjunct treatment to joint arthroplasty

We aimed to improve ADL and reduce pain postoperatively by adding a clinically feasible neuromuscular exercise programme as an adjunct treatment prior to THA and TKA surgery. Despite a greater mean change favouring exercise, our results demonstrated no statistically significant difference in effect for preoperative exercise at 3 months after surgery. However, when considering improvement from baseline to 3 months postoperatively, neuromuscular exercise therapy was associated with greater overall improvement and earlier onset of postoperative recovery. Taking part in a pre-operative exercise programme enabled the participants to reach the level of ADL improvement seen in the surgery only group at 12 weeks some 6 weeks earlier. This earlier improvement may be valued by some patients, their surgeons and other decision-making stakeholders.

The findings in this trial are in line with that of a recent systematic review and meta-analysis demonstrating short-term postoperative effects of exercise undertaken prior to TJA by patients with severe OA.126 In contrast to previous studies with suggested poor therapeutic validity of the exercise interventions[126] and little or no effect post surgery, the neuromuscular exercise intervention used in this study was found to be effective immediately following the intervention (Paper II), indicating good therapeutic validity. The generally favourable effects seen in functional performance and muscle power (Paper II) levelled out at 3 months after surgery. However, for hip abduction and hip extension, the improvements of up to 40% seen in the intervention group were statistically greater than in the control group. These movements were tested in a standing up-right position and it is conceivable that the intervention group felt more confident performing a maximal voluntary contraction. It is of particular note, however, that patients with hip OA from the intervention group, after a

recent surgical trauma and receiving an artificial joint, performed markedly better on the operated side at follow up than did controls. Hip abduction and hip extension are important prerequisites for normal gait.[164-166] For quadriceps muscle function, known to be reduced in THA and TKA patients[167, 168], no effects of neuromuscular exercise were found. This is not surprising since this intervention is specifically targeting dynamic alignment and functional stability and not muscle power per se. This may partly explain the superior results for the exercise group in the tests performed in the standing position, since these require more core and lower limb stability.
One-third of the participants in this study were less than 65 years of age and, hence, potentially still working. It is unknown if earlier onset of recovery was beneficial in terms of faster return to work. In future studies, return to work should be assessed in addition to other possible benefits from pre-operative exercises such as the need for in-patient and out-patient postoperative rehabilitation services.

Differences in treatment effects between patients with hip and knee OA

Previous findings of possible differences in effects of exercise between THA and TKA patients are conflicting. Some have found TKA patients to display a somewhat slower course of physical function and pain recovery than THA patients.[81, 169] In contrast, others argue a faster recovery of physical function after TKA.[87] This study was designed to allow for comparison of hips and knees. We have demonstrated that patients with hip and knee OA respond differently immediately after the exercise intervention, showing greater benefit for the hip patients (Paper II). This pattern shifts postoperatively with knee patients demonstrating a greater and statistically significant short-term effect in ADL (Paper III, Table 2, Figure 2A). The analysis from baseline to 3 months after surgery demonstrated however no difference for hip and knee in the additional effect of exercise. Since all assessment points were included in the longitudinal analysis model, a potentially greater postoperative benefit in TKA patients may be blurred by the favourable effects seen immediately after exercise in THA patients. Furthermore, the postoperative within-group improvements from baseline were generally greater for patients with hip OA. This was particularly clear for short-term (6 weeks) self-reported pain, where the statistically different (p=0.0060) within-group improvement for hip OA patients was above 30 points, and for knee OA patients below 20 points. Also for pharmacological treatment of pain in OA, differences have been demonstrated for hip and knee patients.[170]
Whatever the exact course of recovery after TJA, this study adds to the body of evidence suggesting that different measures may need to be taken to individualise and optimise the treatment for patients with hip and knee OA.[41, 171]

Strengths and limitations

We conducted a randomised, controlled trial that was reported according to the CONSORT statement[146, 147] with a rigorous study design, adequate sample size to allow for separate analysis for hips and knees, and a clinically feasible and therapeutically valid intervention. Our study also has limitations. No measures were taken to comply with the possible risk of attention bias. However, treatments in the two groups did not differ from the day of hospital admission to follow-ups and we believe the potential risk of attention bias introduced during the preoperative exercise intervention to be minimal when outcomes were assessed following surgery. Despite succeeding in including a higher proportion of eligible patients than in similar studies, we still only included 30% of those eligible, which diminishes the external validity of the study. The low inclusion rate was mostly due to the one-month treatment guarantee in the Danish Healthcare system and the fact that the intervention was offered at only one location, circumstances that were beyond our control but may nevertheless have introduced a selection bias.
The exercise intervention was consistent over the entire period, though it is uncertain as to whether or not the same results would be obtainable in a multiple-location setting. Blinding of assessors was attempted through patient discretion and restriction of access to previously obtained data. We did not measure the success of assessor blinding, however the primary and secondary outcomes were self-reported and thus not subjected to possible assessor bias. Delivering a placebo treatment would have been optimal but was not deemed realistic due to the nature of exercise and the difficulty in designing a credible placebo intervention.

CONCLUSION AND FUTURE IMPLICATIONS

Preoperative neuromuscular exercise constitutes a viable adjunct therapy to hip or knee arthroplasty, which may be of interest to individual patients willing to engage in preoperative exercise to achieve an earlier onset of postoperative recovery. At 3 months however, the effects of preoperative exercise were no longer evident.
We have demonstrated an effect from baseline to 3 months after surgery. Future studies will evaluate one-year postoperative efficacy and whether implementation of this new practice is cost-effective. If so, it should be implemented and offered as part of the treatment to all patients undergoing total joint arthroplasty due to severe symptomatic OA of the hip or knee. Although economic evaluations were not a part of this dissertation, it is somewhat thought-provoking that most hospitalisation costs (ambulatory and hospital care) are allocated to hip and knee arthroplasties, and although they constitute a large proportion of total costs, they represent resources used by only 5% of the OA patients.[33] This should be seen in the light of the positive effects of non-pharmacological/non-surgical options in OA, e.g. patient education and exercise, described throughout this dissertation.
The results from this dissertation bring forth new information to decision-making stakeholders and also question whether the clinically unfounded treatment guarantee of one month for total joint arthroplasty after being scheduled is reasonable and desirable. Finally, I propose a more stringent clinical pathway in line with national and international evidence-based recommendations[22, 41, 162] to ensure patients with hip or knee OA receive core treatments and international standards of care prior to surgical options. This clinical pathway should include optimised non-surgical treatment including exercise and be offered 3 months prior to the referral to the orthopaedic surgeon.

SUMMARY

Osteoarthritis (OA) is a degenerative joint disease affecting the whole joint and peri-articular structures like the muscles. The hallmark of OA is cartilage loss. The main symptoms are pain and decreased physical function leading to a reduced quality of life. OA ranks 8th in leading causes of disability worldwide and it generates a heavy economic burden for society. The prevalence of OA increases with age and 10-18% aged above 60 years are affected. Currently there is no cure for OA and the various treat-

ment modalities aim at addressing symptoms, i.e. reducing pain, improving physical function and preventing further progression of the disease. Exercise has proven to be a viable treatment option with regard to reducing pain and improving physical function in patients with mild to moderate knee OA and is today regarded a cornerstone in the treatment. The documentation is less clear for hip OA. Patients with severe OA of the hip or knee are treated with total joint arthroplasty (TJA). Although, in general, it is a very successful procedure, there are still challenges to overcome in this patient group, as approximately 10% of those having hip arthroplasty and 20% of those having knee arthroplasty have persistent symptoms. The evidence on the efficacy of exercise prior to TJA is sparse. It is based on insufficiently powered trials and with interventions of questionable validity. Two recent systematic reviews and meta-analyses reach conflicting conclusions and highlight the need for high quality trials with sufficient sample sizes.

In this dissertation, I wanted to evaluate the effects of an individualised neuromuscular exercise programme (NEMEX-TJR) when administered prior to joint arthroplasty in patients with severe OA of the hip or knee joint. This intervention was previously found to be feasible with regard to pain level during exercise and it was possible to progress the training level in this patient group. The main question asked was: Does the addition of neuromuscular exercise prior to TJA result in further improvement in self-reported outcomes during the first 3 months? To answer this, a randomised controlled trial (RCT) enrolling patients with severe symptomatic OA scheduled for TJA was conducted. Self-reported ADL was the primary outcome of the trial and self-reported pain and quality of life were the main secondary outcomes. A test battery of three functional performance measures and four lower extremity muscle power tests was chosen to complement the questionnaires and to explore the physical function in these patients.
In the first study, the test battery was evaluated with regard to agreement and reliability. Identification of the smallest detectable differences in the tests was needed to assist in the interpretation of the RCT results and aid clinicians in future evaluation of patients in their daily clinical practice. A cohort of 20 patients with severe symptomatic OA of the hip or knee (56-79 years, 50% women) was evaluated in the test battery on two occasions separated by one week. We found that muscle power can safely be evaluated with poor to good agreement and good to excellent reliability. Hence, some measures (20 m walk, chair stands) are more reliable to detect change over time, e.g. longitudinal research, whereas others may be useful in a daily clinical setting to evaluate to what extend the patient's muscle function is affected (single- and multi-joint muscle power). Seen as a whole, the entire test battery is time-consuming (1½-2 hours) and not suited for evaluation of larger cohorts.
The enrollment of patients in the RCT began in January 2010. A cohort of 165 hip and knee OA patients (43-89 years, 56% women, 84 hip OA) was enrolled after approximately one year. This sample size would also allow stratified analysis, e.g. evaluation of possible differences in the treatment effect between hip or knee OA patients. The intervention group participated in an 8-week neuromuscular exercise programme prior to TJA in addition to the usual care (information leaflets and a 3-hour information session by health professionals) provided in Svendborg Hospital, Odense University Hospital, Denmark. Patients were assessed at baseline, one week prior to surgery, 6 weeks and 3 months after surgery (primary end-point). Two essential questions of interest were identified prior the development of the statistical analysis plan. Firstly: Does the addition of neuromuscular exercise prior to TJA improve the postoperative outcome? The initiation of rehabilitation prior to surgery was thought to be of general interest to the health community. Secondly: What are the effects of neuromuscular exercise when evaluated as a treatment option for patients with severe osteoarthritis? This question is most likely to be of interest to health professionals with a specific interest in exercise rehabilitation and OA research.
In the second study, the cohort served as a model for patients with severe OA (regardless of the following operation). Patients were evaluated immediately after the intervention (one week). We found that participation in neuromuscular exercise for 8 weeks according to the NEMEX-TJR programme improves activities of daily living, objective functional performance, and quality of life and reduces pain in patients with severe osteoarthritis (OA). The effect is greater in patients with hip OA than in patients with knee OA. The study confirms previous findings from non-randomised studies that neuromuscular exercise is feasible and safe for patients with severe OA
In the third study, the efficacy of NEMEX-TJR as an adjunct treatment to TJA was evaluated. At the primary end-point 3 months after surgery, there was no additional effect of an 8-week preoperative neuromuscular exercise programme in combination with total joint arthroplasty compared with total joint arthroplasty alone. However, from baseline to 3 months after surgery the overall longitudinal improvements seen in physical function and pain were statistically significantly greater and occurred earlier after surgery in the intervention group receiving preoperative neuromuscular exercise compared with the control group receiving care-as-usual only.

From this dissertation, I conclude that neuromuscular exercise according to NEMEX-TJR can serve as adjunct therapy to hip or knee arthroplasty of interest to individual OA patients willing to engage in preoperative exercise to achieve an earlier onset of postoperative recovery. At 3 months however, the effects of preoperative exercise are no longer evident. Furthermore, for patients with severe OA of the hip joint, neuromuscular exercise may serve as a safe and viable treatment option with improvement in ADL, functional performance and a reduction in pain. Whether implementation of this adjunct therapy in clinical practice is feasible and cost-effective remains to be evaluated.

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